GMP Advisor

The GMP Questions & Answers Guide

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About this document

Searching for concrete answers to GMP questions is a time-consuming activity. This document is intended to provide a single source of information.

We have summarized GMP questions and answers from Regulators around the world.

In addition to EMA, FDA, Health Canada, MHRA (UK), TGA (Australia) and ICH we have also used Q&As from ECA. The subject index contains some of the "GMP Key Words" and allows to find Q&As addressing the relevant topic.

It is the intension to update this comprehensive collection and to also add new Q&As once they are available.

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1. General GMPs

1.1 EMA Europe

1.1.1 General

1. What are the differences between EU and World Health Organization (WHO) requirements for GMP? H July 2006

EU GMP principles and guidelines are laid down in Directive 2003/94/EC (human medicines) and Directive 91/412/EEC (veterinary products). These principles and guidelines are subject to further detailed guidance in the form of the EU GMP guideline with its annexes.
WHO publishes its own GMP guidance documents.
Although EU and WHO GMP guidance documents do differ in some details, the main principles remain the same. EU requirements fulfil all the recommendations of WHO.

GMP certificates
1. What is a GMP certificate and what is the difference between GMP certificates, certificates of medicinal product (CMPs, also called certificates of pharmaceutical products, CPPs) and certificates of suitability to the monographs of the European Pharmacopoeia (CEPs)? H+V July 2006
A **GMP certificate** is a certificate issued following a GMP inspection, by the competent authority responsible for carrying out the inspection, to confirm the GMP compliance status of the inspected site.
GMP certificates are site-specific, but can be restricted to particular activities depending on the scope of the inspection (e.g., manufacturing activities related to a specific product). Directives 2001/82/EC and 2001/83/EC, as amended state that after every GMP inspection, and within 90 days of the inspection, a GMP certificate shall be issued to a manufacturer, if the outcome of the inspection shows that the manufacturer complies with GMP.
CMPs are product-specific certificates issued by the competent authority that granted the marketing authorisation. The European Medicines Agency issues CMPs on behalf of the European Commission for centrally authorised products.
CMPs are issued in the context of the World Health Organization certification scheme on the quality of pharmaceutical products moving in international commerce, to confirm the marketing-authorisation status of the products. These certificates also confirm the GMP compliance status of the manufacturing sites. CMPs are mainly used by companies to support applications to export their pharmaceutical products to countries with less-developed regulatory systems.
CEPs are certificates issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) to confirm that a certain active substance is produced according to the requirements of the relevant monograph of the European Pharmacopoeia or of the monograph on transmission spongiform encephalopathies.
CEPs can be used by companies when submitting an application for marketing authorisation, and replace much of the documentation required for the active substance in the marketing authorisation dossier. GMP inspections of active-substance manufacturers can be requested by EDQM in the context of the CEP certification scheme.
2. Does the Agency issue GMP certificates? H+V July 2006
No, the competent authority responsible for carrying out the inspection issues the GMP certificate, or makes an entry of non-compliance into the EudraGMP database.
3. Which EU and EEA authorities conduct mutually recognised inspections and issue GMP certificates? H+V November 2011

All EU and EEA national competent authorities conducting inspections are obliged to enter GMP certificates in the EudraGMP database. Hence, any GMP certificate appearing in the database is mutually recognised and the database authenticates the certificate.
If a certificate cannot be found in the database, the issuing authority should be contacted.

Inspection coordination

1. Does the Agency perform GMP inspections? H+V July 2006

The Agency does not perform inspections. They are carried out on its behalf by the national competent authorities of the member states of the EEA, in connection with products under the centralised marketing-authorisation procedure.

2. If a site in a third country has plans to export products to the EEA, is it possible to apply for a GMP inspection on a voluntary basis? H+V July 2006

Normally, the need for inspection under these circumstances is triggered by an application for a marketing authorisation. It may be possible to request an inspection on a voluntary basis, but as the competent authorities will have other priorities, there is no guarantee that such a request will be met. To explore this possibility, the authorities of the Member State into which the product will be imported into the EEA should be approached. In any case, applicants are encouraged to approach the relevant authority in advance of submission in order to facilitate third-country inspection planning.

3. When a new application is submitted in the EEA and a GMP inspection is deemed necessary, which competent authority carries out the inspection? H+V July 2006

If the site is located in the EEA, the competent authority of the Member State where the site is located carries out the inspection.

For sites located in countries outside the EEA, the responsible authority for inspection (the 'supervisory authority') is the authority in whose territory the importing site is located. If the supervisory authority is not able to carry out the inspection for any reason, it can be delegated to another EEA competent authority.

If there is a mutual recognition agreement (MRA) in place between the countries where the site is located and the European Community, the results of GMP inspections carried out by the MRA partner authority are normally recognised by the EU authorities.

1.1.2 EU GMP Annex 1 Sterile Products

EU GMP guide annexes: Supplementary requirements: Annex 1: Manufacture of sterile medicinal products - UPDATED

1. How should the integrity of sterilising filters be verified? H+V June 2007

Annex 1, paragraph 85 states, 'the integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble-point, diffusive-flow or pressure-hold test.'

The filter sterilisation process may be physically stressful for the filter. For example, high temperatures during the process may cause the filter to distort, potentially leading to fluid pathways that allow the passage of particles greater than 0.2 µm in size. The performance of a filter can improve with use, as particles begin to block individual pathways and remove larger pathways that smaller particles could successfully navigate. For these reasons, filters should be tested both before use but after sterilisation and again after use.

Furthermore, testing should be performed *in situ* in order to verify the integrity of the filter complete with its housing.

2. What are the sampling requirements for sterility testing when a finished product batch of a terminally sterilised medicinal product is made up of more than one steriliser load? H+V October 2008

The sampling plan for sterility testing should take account of the definition of a batch as stated in the glossary of the GMP guideline together with the recommendations of annex 1 section 93 (section 127 in the February 2008 revision). Each steriliser load is considered to be an independent sub-batch. Consequently, one sterility test should be performed per sub-batch. The number of samples per steriliser load should conform to European Pharmacopoeia requirements, section 2.6.1.3.

Can there be any exceptions to this rule?

For large-volume parenterals where the sterilisation cycle has been qualified with an overkill level, an alternative sampling plan in accordance with a specific internal procedure agreed with the supervisory authority can be accepted (unless already specified in the marketing authorisation).

This procedure should state the need to sample from each steriliser load including the coolest location identified during the steriliser qualification. The number of samples per load should be defined based on a risk-based approach and the overall number of samples per batch should conform to European Pharmacopoeia requirements, section 2.6.1.3. An alternative option, which would require a variation to relevant existing marketing authorisations, would be to introduce a system of parametric release, thereby avoiding the need to carry out the sterility test.

3. What are the key changes in the 2008 revision of annex 1 of the EU GMP? H+V January 2010

The revision provides updated guidance on:

- classification of the environmental cleanliness of clean rooms;
- guidance on media simulations;
- guidance on capping of vials;
- bioburden monitoring prior to sterilisation.

4. The new revision to the annex includes a number of revised requirements. What steps are being taken by EU authorities to assure the consistent interpretation of the requirements of the revised annex by EU GMP inspectors during inspections? H+V January 2010

GMP inspectors from the EU have worked together with inspectors from Swissmedic to prepare harmonised guidance on the interpretation of the revised annex to be used during the inspection of manufacturers by their Inspectors. This document has subsequently been proposed and adopted as draft guidance by the Pharmaceutical Inspection Cooperation Scheme (PIC/S): GMP annex 1 revision 2008: Interpretation of most important changes for the manufacture of sterile medicinal products.

5. For an aseptically produced product, where should bioburden monitoring take place? H+V May 2013

According to the EU GMP guideline (annex 1), the bioburden should be monitored before sterilisation and testing should be performed on each batch.

For routine commercial manufacturing, bioburden testing should be performed on the bulk solution, immediately before its sterile filtration. If a presterilising filter is additionally installed, then sampling

for bioburden testing may be performed prior to the prefiltration, provided that no holding time is scheduled for the solution between the two filtration steps.

6. What is the maximum acceptable bioburden level? H+V May 2013

The specification limits for bioburden should be NMT 10 CFU/100 ml, in line with the human and veterinary notes for guidance on manufacture of the finished dosage form (CPMP/QWP/486/95 and EMEA/CVMP/126/95).

When a prefilter is installed, unless otherwise justified, a bioburden limit of 10 CFUs/100 ml before first filtration is achievable in principle and is strongly recommended from a GMP point of view. Higher bioburden limits should not be justified by the high capacity of two consecutive bacteria retaining filters.

However, when appropriate justification is submitted (processes involving fermentation or other biological or herbal components, use of purified water for ophthalmic preparations, etc.), a bioburden limit of higher than 10 CFUs/100 ml before prefiltration may be acceptable. In such cases, it should be demonstrated that the first filter has the capability to achieve a bioburden prior to the last filtration of NMT 10 CFUs/100 ml, in line with the notes for guidance on manufacture of the finished dosage form (CPMP/QWP/486/95 and EMEA/CVMP/126/95).

1.1.3 EU GMP Annex 6: Manufacture of medicinal gases

EU GMP guide annexes: Supplementary requirements: Annex 6: Manufacture of medicinal gases

1. What is traceability? H+V July 2010
Traceability is the ability to retrieve the history of the manufacturing and distribution operations of a batch of a medicinal product.
The data recorded through the traceability system should allow efficient investigation in case an incident occurs and should allow recalls of (potentially) defective products.
In the case of packaged medicinal gases, the packaging components (shells and valves) are reusable. It is therefore necessary to record additional information, in particular in relation to the use and maintenance of these components.

2. Which items should be recorded in the case of medicinal gases filled into cylinders to enable traceability? H+V July 2010
Packaging components (shells and valves)
The cylinder is the combination of the shell and its valve.
Shell
For safety reasons, shells are individually identified (specific reference). Individual traceability is therefore possible. The date of the last hydrostatic pressure test (or equivalent test) should be recorded.
Valve
Shells may be fitted with simple valves (e.g. pin-index valves) or integrated valves. Integrated valves are individually identified (individual identification reference). Individual traceability is therefore possible. This is not the case for simple valves, which mostly have only a serial number corresponding to a group of valves.
The design of integrated valves, which are medical devices, is complex. These valves are also subject to periodic preventive maintenance operations. In terms of risk, more serious incidents have been reported with cylinders having this type of valve.
Therefore:

- in the case of simple valves, the type of valve should be recorded, as well as the name of the manufacturer and the serial number, if one is available;
- in the case of integrated valves, traceability should be ensured for each valve. Records should include in particular the type of integrated valve (including the version), the individual identification reference of the valve, the name of the manufacturer, the date of the last (or next) preventive maintenance and details of any preventive maintenance performed on the valve.

Shell and valve
Each shell-and-valve combination should be traceable.
Finished product
The manufacturing batch records should include the individual identification references of the cylinders of each batch of finished product (see EU GMP guideline annex 6, section 17, (g) and (m)).
Distribution
The distribution records should include the individual identification references of the cylinders delivered to each customer.

3. What means should be implemented to ensure traceability? H+V July 2010
In practice, depending on the scale of operation, it may be difficult to ensure effective traceability without a computerised system. Use of bar codes or electronic chips on the cylinders may facilitate this. Any computerised system used to ensure traceability should conform to the requirements of annex 11 of the EU GMP guideline

4. What should be possible through the system of traceability? H+V July 2010
Should a manufacturer of a medicinal gas receive a serious complaint relating to the quality of the medicinal gas itself or the packaging components, the system in place should allow the identification of the affected cylinders and, where necessary, the recall of any affected cylinders from the market.

A defect relating to packaging components may require identification of specific cylinders within a finished product batch or identification of cylinders present in a number of finished product batches in order to establish the extent of any recall required.
For example, an effective traceability system should allow effective recalls of cylinders fitted with defective valves based on:

- specific type, version or manufacturer's batch for the valves;
- maintenance and calibration operations for the valves during a specific time period.

1.1.4 EU GMP Annex 8: Sampling

EU GMP guide annexes: Supplementary requirements: Annex 8: Sampling of starting and packaging materials: Glycerol

1. What is the background regarding international incidents of glycerol contamination? H+V December 2007

There is a history of sporadic reports from around the world of supplies of glycerol contaminated with diethylene glycol (DEG) resulting in mortality and serious morbidity in patients receiving contaminated products.
In late 2006, DEG-contaminated glycerol in cough syrup was the cause of about 50 deaths in Panama. DEG-contaminated glycerol in paracetamol syrup was also attributed to at least 80 deaths in a similar incident in Haiti in 1995-1996. Other incidents have been reported in Argentina, Bangladesh, India and Nigeria and attributed to the deaths of hundreds of children. DEG was also responsible for a poisoning incident resulting in the death of 107 people in the United States in 1937, following ingestion of contaminated sulphanilamide elixir.
These incidents were related to both accidental cross-contamination of glycerol with industrial grade materials and, in some cases, to intentional substitution.
Recent cases show the following similarities:

- pharmaceutical manufacturers of products containing contaminated glycerol did not perform full identity testing or tests to determine DEG on the glycerol raw material;
- pharmaceutical manufacturers of contaminated products relied on certificates of analysis (COAs) provided by the supplier;
- the origin of glycerine was not apparent from the COA. The COA provided with the glycerol raw material may have been a copy of the original on a distributor letterhead. The supply chain for glycerol was not readily known by the medicinal-product manufacturer because the glycerol may have been sold several times between its manufacture and the medicinal-product manufacturer.

2. How is the EU patient protected from similar contamination occurring in EU products? H+V December 2007

EU GMP requires all manufacturing companies to confirm that all its raw materials are checked on receipt to confirm their identity and quality. Competent authorities expect product manufacturers to routinely ensure that incoming samples of glycerol are tested according to the European Pharmacopoeia monograph.
The European Pharmacopoeia monograph for glycerol includes a specific limit test for diethylene glycol (0.1%).

3. Annex 8 of the GMP provides for derogations from the requirement for identity testing of every container where there is a validated supply chain. Can I use this derogation for the glycerol I purchase? H+V December 2007

It is correct that annex 8 does provide for a relaxation of identity testing of every container, but it also states that this would not normally be possible if brokers or intermediates were involved in the chain of supply.
Glycerol is a commercial article that is widely used in the food and other industries. Generally speaking, the supply chain for glycerol tends to be complex and lengthy. The involvement of brokers is common in the supply chain.

4. What steps are expected of manufacturers based in the EU when purchasing glycerol or of manufacturers based in third countries supplying glycerol-containing medicines? H+V December 2007

When designing supplier-assurance and incoming-goods-control programmes, companies should consider glycerol a higher-risk material.
Companies should be able to exhibit a good knowledge of starting material supply chains and apply this knowledge and principles of quality risk management to their programmes for supply-chain management. Inspectors will look to ensure that the basis for qualification of the supply chain is demonstrably robust for higher-risk materials such as glycerol. It is expected that identity testing and the European Pharmacopoeia limit test for DEG will be performed on each container as a matter of routine.

5. The European Pharmacopoeia limit test for DEG involves a gas chromatographic method, which may be difficult to perform on a large number of containers. H+V December 2007
This point is acknowledged and currently, alternative tests are under consideration with a view to work up a possible change to the identity tests in the monograph. The European Pharmacopoeia DEG limit test remains the official method for confirmation of compliance with the monograph.

6. Are there any considerations applicable to the pharmaceutical assessment of marketing-authorisation applications? H+V July 2008
In application dossiers for new marketing authorisations (MAs), or in case of relevant variations for existing MAs (for example, replacement of an excipient with glycerol) for medicinal products containing glycerol, confirmation of the tests applied on receipt of batches of glycerol to control the risk from potential DEG contamination in relation to the specific intended use of the product should be provided. A test for DEG content should be conducted in addition to identity testing for glycerol. A suitable control for DEG is included in the European Pharmacopoeia monograph for glycerol. Sufficient information regarding satisfactory control of this risk will be required in the dossier before approval of the MA application or variation.
For existing approved medicinal products, no variation application is required, except for those few specific types of variations referred to in the first paragraph. However, as a minimum, the specific European Pharmacopoeia control for DEG should be conducted along with the identity test at receipt of each batch of glycerol. The excipient is required to comply with the current European Pharmacopoeia glycerol monograph, and as the specification approved in the dossier will have been that of the European Pharmacopoeia, the risk of DEG contamination will have been appropriately controlled. Compliance with this requirement will be verified during GMP inspections.

7. My company manufactures products for external use. Does this guidance apply? H+V July 2008
Where a company manufactures products for external use, and when it has justified that the presence of DEG in these products poses a low risk, the omission of the test for DEG on each container may be accepted by the supervisory authority.

EU GMP guide annexes: Supplementary requirements: Annex 8: Sampling of starting and packaging materials: Use of near-infrared (NIR) technology for container-wise identity testing

1. The registered specifications of our starting materials include conventional or pharmacopoeial methods for the confirmation of identity but we wish to use NIR to perform identity testing on each container of starting materials used in the manufacture of parenteral products. Is the use of this alternative method acceptable?
Annex 8 of the GMP guideline states that the identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labeled. However, the annex goes on to say that it is improbable that a procedure could be satisfactorily validated for starting materials for use in parenteral products.
Unless variations are submitted for all affected products, the registered method for confirming identity should be performed. However, there is no restriction on the performance of additional testing and the use of NIR to confirm container-wise confirmation of identity can provide useful information. Under these circumstances, the requirements of the marketing authorisation will be deemed to have been met by carrying out the registered method for confirmation of identity on a statistically representative composite sample when this is supplemented with NIR analysis of every container.
The NIR method should be validated in line with the recommendations of the draft guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations.

1.1.5 EU GMP Annex 11: Computerised systems

EU GMP guide annexes: Supplementary requirements: Annex 11: Computerised systems

1. Appropriate controls for electronic documents such as templates should be implemented. Are there any specific requirements for templates of spreadsheets? H+V February 2011
Templates of spreadsheets help to avoid erroneous calculations from data remaining from previous calculations. They should be suitably checked for accuracy and reliability (annex 11 p7.1). They should be stored in a manner which ensures appropriate version control (chapter 4 p4.1).

2. What type of accuracy checks (annex 11 p 6) are expected for the use of spreadsheets? H+V February 2011
Data integrity should be ensured by suitably implemented and risk-assessed controls. The calculations and the files should be secured in such a way that formulations are not accidentally overwritten. Accidental input of an inappropriate data type should be prevented or result in an error message (e.g. text in a numeric field or a decimal format into an integer field). So-called 'boundary checks' are encouraged.

3. Are there any specific considerations for the validation of spreadsheets? H+V February 2011
Validation according to paragraph 4 of annex 11 is required at least for spreadsheets that contain custom code (e.g. Visual Basic for applications). Formulas or other types of algorithm should be verified for correctness.

4. What measures are required to ensure data security of databases? H+V February 2011
Data security includes integrity, reliability and availability of data. During validation of a database-based or inclusive system, consideration should be given to:

- implementing procedures and mechanisms to ensure data security and keeping the meaning and logical arrangement of data;
- load-testing, taking into account future growth of the database and tools to monitor the saturation of the database;
- precautions for necessary migration of data (annex 11 p17) at the end of the life-cycle of the system.

5. At which phases of the system life-cycle is risk management recommended? H+V February 2011
Risk management should be applied throughout the whole life-cycle. A first risk assessment should be performed to determine the GMP criticality of the system, i.e. does the system have an impact on patient safety, product quality or data integrity? User-requirement specifications are usually developed with consideration of potential risks and form the basis for the first formal risk assessment.
Complex systems should be evaluated in further more detailed risk assessments to determine critical functions. This will help ensure that validation activities cover all critical functions.
Risk management includes the implementation of appropriate controls and their verification.

6. Are user requirements needed as part of the retrospective validation of legacy systems? H+V February 2011
The way to check whether a computerised system is fit for its intended purpose is to define user requirements and perform a gap analysis to determine the validation effort for retrospective validation. These user requirements should be verified.

7. When do I have to revalidate computerised systems? H+V February 2011
Computerised systems should be reviewed periodically to confirm that they remain in a validated state. Periodic evaluation should include, where applicable, the current range of functionality, deviation records, change records, upgrade history, performance, reliability and security. The time period for revaluation and revalidation should be based on the criticality of the system.

8. What are the requirements for storage time of electronic data and documents? H+V February 2011
The requirements for storage of electronically data and documents do not differ from paper documents. It should be ensured that electronic signatures applied to electronic records are valid for the entire storage period for documents.

9. What are the relevant validation efforts for small devices? H+V February 2011
Small devices are usually off-the-shelf pieces of equipment that is widely used. In these cases, the development life-cycle is mainly controlled by the vendor. The pharmaceutical customer should therefore reasonably assess the vendor's capability of developing software according to common standards of quality.
A vendor assessment needs to be performed and the application needs to be verified against the requirements for the intended use. From the perspective of the regulated industry, the implementation of such a device is driven by an implementation life-cycle. At minimum the following items need to be addressed:

- requirement definition for the intended use including process limitations. This should also include a statement indicating whether data are stored or transferred to another system. As per the definition of a small device, data are not stored permanently but temporarily and are not to be modified by a user. Therefore, limited user access handling is acceptable. It needs to be ensured that parameter data influencing the device's behaviour may not be altered without suitable permission;
- risk assessment, taking into consideration the intended use and the risk to patients for associated with the process supported by the small device;
- vendor assessment;
- list of available documentation from the vendor, especially those describing the methodology used and the calculation algorithm, if applicable. A vendor certificate or equivalent detailing the testing performed by the vendor may also be included;
- calibration certificate, if applicable;
- validation plan according to the risk-assessment results;
- verification testing proving that the device fulfills the requirements for the intended use. It may be equivalent to a PQ-phase.

Small manufacturing devices are sometimes only equipped with microprocessors and firmware and are not capable of high-level administration functions. Moreover, data is often transient in nature in these devices. Due to the latter there is no risk of inadvertently modifying data. An audit trail is therefore not necessary and user access may be limited to those functions of parameter control.

10. What alternative controls are accepted in case a system is not capable to generate printouts indicating if any of the data has been changed since the original entry? H+V February 2011
As long as this functionality is not supported by the supplier, it may be acceptable to describe in a procedure the fact that a print-out of the related audit trail report must be generated and linked manually to the record supporting batch release.

The sponsor should ensure that the documents listed in chapter 8, 'essential documents for the conduct of a clinical trial' of the guideline for good clinical practice are maintained and accessible to those parties authorised to review them.

1.1.6 EU GMP Annex 16 QP and Batch Release

EU GMP guide annexes: Supplementary requirements: Annex 16

1. Can a site have more than one QP performing certification of batches?
EU legislation requires a manufacturer to have at least one QP at its disposal but a site may have more than one QP who may certify batches on behalf of the manufacturer.

2. Can there be more than one QP involved in the certification of a given batch?
Annex 16 of the EU GMP guideline gives guidance in relation to situations where different stages of manufacture of a batch take place at different manufacturing sites.
In such cases, the overall responsibility for correct manufacture of the batch lies with the QP performing final certification of the batch before release for sale. It is also possible that, at a single manufacturing site, different QPs could be responsible for certification of different stages of manufacture of the batch. However, as before, the QP performing final certification before release holds overall responsibility for manufacture of the batch in accordance with GMP and the marketing authorisation.

1.1.7 EU GMP Annex 19 Reference Standards

EU GMP guide annexes: Supplementary requirements: Annex 19: Reference and retention samples

1. Is it necessary to retain a sufficient number of samples of each batch of a sterile medicinal product in order to carry out a sterility test on two separate occasions? H+V October 2008

1.1.8 Impurities

Impurities - Calculation of thresholds for impurities

1. What is the basis for the calculation of thresholds to set limits for impurities in the finished product specification? H July 2009

The calculated thresholds should be based on the highest maximum daily dose of the respective active substance in authorised medicinal products. The threshold for impurities should be the same for all strengths.

The same rule applies for combination drugs; the highest possible combined strength should be used for setting the thresholds.

The maximum daily dose used for threshold calculation should be the same for a given active substance irrespective of the medicinal product.

Impurities - Harmonisation of policies on setting specifications for potentially genotoxic impurities, heavy-metal-catalyst residues and class-1 solvent residues

1. What is a reasonable policy for setting specifications for potentially genotoxic impurities which are theoretical or actual impurities in a drug substance manufacturing process? H June 2012

Different possible scenarios can be identified and the applicable policies to be applied for each of them are described below:

Example 1 – A potential genotoxic impurity

The definition for a potential genotoxic impurity is derived from the definition for 'potential impurity': an impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the (new) drug substance (ICH Q3A, glossary).

If a potential genotoxic impurity is just a theoretical impurity i.e. based on theoretical considerations but not found in practice at any key stage in the manufacturing process as demonstrated by studies during development of the manufacture, the impurity does not need to be included in the drug substance specification or a specification of an intermediate.

Example 2 – A (potentially) genotoxic impurity actually formed or introduced prior to the final step of the synthesis

If a (potentially) genotoxic impurity is formed or introduced in a step before the final synthesis step, it is considered possible to not include this impurity in the drug substance specification if it is controlled by a suitable limit in a synthesis intermediate and if it is unambiguously demonstrated by analysis results (use of spiking experiments are encouraged) that presence of this impurity does not exceed 30 % of the limit, derived either from threshold of toxicological concern (TTC) or otherwise defined acceptable limit etc., in the drug substance.

It is considered possible to apply skip testing if the level of the impurity in a synthesis intermediate does not exceed 30% of the limit, derived from either TTC or otherwise defined acceptable limit etc, in the intermediate. Data should be presented for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, a routine test in the intermediate is needed. If the impurity exceeds 30% of the limit, derived either from TTC or otherwise defined acceptable limit etc., in the drug substance the impurity has to be included in the drug substance specification and the test has to be carried out on a routine basis.

Should a genotoxic impurity not be controlled at the intermediate stage, then the scenario of example 3 applies.

Example 3 - A (potentially) genotoxic impurity is formed or introduced in the last synthesis step

If a (potentially) genotoxic impurity is formed or introduced in the final synthesis step, it should be included in the specifications. However, it is considered possible to apply skip testing if the level of the impurity does not exceed 30% of the limit, derived from either TTC or otherwise defined acceptable limit etc., in the drug substance. Data should be presented for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, a routine test in the drug substance specification is needed.

Definitions:

For the purpose of these questions and answers, the following definitions apply:

- *Genotoxic impurity*: an impurity that has been demonstrated to be genotoxic in an appropriate genotoxicity test model, e.g. bacterial gene mutation (Ames) test.
- *Potentially genotoxic impurity*: an impurity that shows (a) structural alert(s) for genotoxicity but that has not been tested in an experimental test model. Here potentially relates to genotoxicity, not to the presence or absence of this impurity.

2. In order to harmonise the policies to be applied for setting specifications for genotoxic impurities and heavy-metal-catalyst residues, what are reasonable policies to be applied when setting specifications for heavy-metal-catalyst residues? H June 2012
In order to harmonise the policy for setting specifications for metal residues with that for setting specifications for genotoxic impurities, some clarifications of the interpretation of sections 4.5 and 4.6 of the heavy-metal-catalyst guideline (EMEA/CHMP/SWP/4446/2000) are given below.
Since it is the class-1 metals that are the most toxic metals with permitted daily exposures (PDEs) that approach the level of the threshold of toxicological concern (TTC) applied for genotoxic impurities, it seems reasonable that class-1 metals are the prime focus for harmonisation with the policy for genotoxic impurities while class-2 and 3 metals could be treated similarly but somewhat less strictly.

Example 1 – A class-1 metal is not used or suspected to be present in a synthesis process
Metals are not expected to be formed in synthesis processes. Only if deliberately introduced or suspected to be present for other reasons, residues of metals can be expected. If not used or suspected to be present, the metal does not need to be included in the drug substance specification or a specification of an intermediate.

Example 2 – A class-1 metal is formed or introduced prior to the final step of the synthesis
If a class-1 metal is introduced in a step before the final synthesis step, it is considered possible to not include this metal in the drug substance specification if it is controlled by a suitable limit in a synthesis intermediate and if it is unambiguously demonstrated by analysis results that the presence of this metal does not exceed 30% of the guideline limit in the drug substance.
It is considered possible to apply skip testing if the level of the class-1 metal in a synthesis intermediate does not exceed 30% of the guideline limit in the intermediate. Data should be presented for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, a routine test in the intermediate is needed. If the class-1 metal exceeds 30% of the guideline limit in the drug substance the impurity has to be included in the drug substance specification and the test has to be carried out on a routine basis.
Should a class-1 metal not be controlled at the intermediate stage, then the scenario of example 3 applies.

Example 3 – A class-1 metal is introduced in the last synthesis step
If a class-1 metal is introduced in the final synthesis step, it should be included in the specifications. However, it is considered possible to apply skip testing if the level of the metal does not exceed 30% of the guideline limit in the drug substance. Data should be presented for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, a routine test in the drug substance specification is needed.

3. In order to harmonise the policies to be applied for setting specifications for genotoxic impurities and class-1 solvent residues, what are reasonable policies to be applied when setting specifications for class-1 solvent residues? H June 2012
In order to harmonise the policy for setting specifications for class-1 solvents with that for setting specifications for genotoxic impurities, some clarifications of the interpretation of annex I to the residual solvents guideline (CPMP/ICH/283/96 / CVMP/VICH/502/99): Specifications for class 1 and class 2 residual solvents in active substances (CPMP/QWP/450/03 / EMEA/CVMP/511/03) are given below.
Since it is the class-1 solvents that are most toxic solvents and have permitted daily exposures (PDEs) that approach the level of the threshold of toxicological concern (TTC) applied for genotoxic impurities, it seems reasonable that clas- 1 solvents are the focus for harmonisation with the policy for genotoxic impurities.

Example 1 – A class-1 solvent is not used or suspected to be present in a synthesis process
If a class-1 solvent is just a potential impurity, not used directly or found in practice as demonstrated by studies during development of the manufacture, the class-1 solvent does not need to be included in the drug substance specification or a specification of an intermediate.

Example 2 – A class-1 solvent is formed or introduced prior to the final step of the synthesis
If a class-1 solvent is formed or introduced in a step before the final synthesis step, it is considered possible to not include this solvent in the drug substance specification if it is controlled by a suitable limit in a starting material or synthesis intermediate and if it is unambiguously demonstrated by analysis results that the presence of this solvent does not exceed 30% of the guideline limit in the drug substance.
It is considered possible to apply skip testing if the level of the solvent in a synthesis intermediate does not exceed 30% of the guideline limit in the intermediate. Data should be presented for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, a routine test in the intermediate is needed. If the solvent exceeds 30% of the guideline limit in the drug substance the solvent has to be included in the drug substance specification and the test has to be carried out on a routine basis.
Should a class-1 solvent not be controlled at the starting material or intermediate stage, then the scenario of example 3 applies.

Example 3 – A class-1 solvent is formed or introduced in the last synthesis step
If a class-1 solvent is formed or introduced in the final synthesis step, it should be included in the specifications. However, it is considered possible to apply skip testing if the level of the solvent does not exceed 30% of the guideline limit in the drug substance. Data should be presented for at least 6 consecutive pilot scale or 3 consecutive production scale batches.

Impurities - Residual solvents
1. Is there a need to take the actual batch results into consideration when specifying class-2 residual solvents for active substances or medicinal products? H+V August 2007

1.2 MHRA (Europe/UK)

1.2.1 Quality Risk Management

1. Do all inspections cover the quality risk management process?
Yes, quality risk management (QRM) is a requirement of Chapter 1 of the EU GMP Guide Part I, II and III. All manufacturing authorisation holders, third country manufacturing sites, blood establishments, blood banks and active pharmaceutical ingredient manufacturers must have a system for QRM. Inspectors will review the QRM system as part of the Quality Systems section of the inspection (along with complaints, recalls, deviations, and product quality reviews etc). Additionally, inspectors may review specific risk assessments when encountered during inspection. Inspectors will allocate time commensurate with their perceived significance of the risk and if necessary request the company to produce a formal summary of the risk assessment, key decisions and conclusions or take copies of risk assessments for further consideration outside the inspection.

2. How will deficiencies be categorised?
As with other areas of inspection, deficiencies will be categorised dependent on the significance of the findings. Typically complete lack of a system should be classed as a major deficiency, while lesser deviations within a system would be classed as other. Critical deficiencies may reference QRM where risk assessments have inappropriately supported release of products that pose a threat to patient safety. QRM deficiencies may be grouped with other quality systems deficiencies under a quality systems heading. As always factual statements of what are seen as deficiencies will be clearly recorded.

3. Should a company have a procedure to describe how it approaches QRM related to manufacture and GMP?
Yes, the procedure should be integrated with the quality system and apply to planned and unplanned risk assessments. It is an expectation of Chapter 1 that companies embody quality risk management. The standard operating procedure (SOP) should define how the management system operates and its general approach to both planned and unplanned risk management. It should include scope, responsibilities, controls, approvals, management systems, applicability, and exclusions.

4. Is it acceptable to link quality risk management with cost saving measures?
The expectation of QRM is to assess risks to the medicinal product and patient and manage these to an acceptable level. It is appropriate for companies to assess their control systems to implement the optimum controls to ensure product quality and patient safety. If this can be achieved in a more cost effective manner while maintaining or reducing risk to the product and patient then this is acceptable. However inappropriate risk assessment and mitigation in order to achieve cost savings is not appropriate.

5. Should sites have a formal risk register and management process?
There is no formal requirement in Annex III for a risk register however MHRA consider that it is helpful to the implementation and ongoing management of QRM that a risk register is established. A risk register (or equivalent title document) should list all key risks identified by the organisation, summarise how these have been mitigated and record the current risk level. They should be considered in the same context as index/lists of complaints received or deviations recorded and as such should have the following attributes:

- Record the source of the risk e.g. complaint, supplier management, change control etc.
- Record a unique identifying number for the risk
- Summarise the risk
- Record the current risk level
- Summarise current status
- Identify if the risk is considered finite (one off) or dynamic (ongoing risk) and thus what ongoing review is required.
- Can be paper based or electronic

A management process should be in place to review QRM and the findings and status from risk assessments – this may be incorporated into the quality management review process. The use of a risk register and management review should enable the owner to view the risks across all areas and ensure that QRM is under control and the cumulative impact of risks are understood.

6. What tools are acceptable to use in quality risk management?
There is no definitive list although a number of examples are given in EU GMP Part III. In some cases combinations of tools or other approaches may be seen. The important criterion is for the tool used to support the key attributes of a good risk assessment (see below).

7. Do formal tools and a full report have to be issued for every risk assessment?
As stated in Chapter 1 of the EU GMP guide '...the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk'. As such expectations of inspectors will be pragmatic regarding the degree of formality that is required, however appropriate evidence should be available of what has been done and as such a written output must be retained. Inspector's pragmatism will be directly related to the nature of the risk with increasingly more formality and detail required for more significant risk (risk being the probability of occurrence of harm and the severity of that harm, often supplemented by the ability to detect the potential harm occurring).

8. What are the key attributes of a good risk assessment?
The following key attributes should be observed (mindful of the risk significance addressed in the previous question):

- clearly identify the process being assessed and what it is attempting to achieve, ie what the harm/risk is and what the impact could be on the patient
- be based on systematic identification of possible risk modes e.g. as per Failure Mode and Effects Analysis (FMEA)
- take full account of current scientific knowledge
- be facilitated by people with experience in the risk assessment process and the process being risk assessed
- use factual evidence supported by expert assessment to reach conclusions
- do not include any unjustified assumptions
- identify all reasonably expected risks – simply and clearly along with a factual assessment and mitigation where required
- be documented to an appropriate level and controlled/approved
- ultimately be linked to the protection of the patient
- should contain objective risk reduction plans.

9. What is the difference between a planned and unplanned risk assessment?
A planned risk assessment is one that is conducted in advance of conducting an activity, either before any activity is conducted or before further activity is conducted. This would often allow quality to be built in to activities and risk reduced (quality by design) eg design of facilities for manufacture of cytotoxic products or organisation/design of a label printing room. An unplanned risk assessment is one that is conducted to assess the impact of a situation that has already occurred, eg impact of a deviation from normal ways of working.

10. Should we expect there to be no risk to patient safety as a conclusion to a risk assessment?
In reality there is always a degree of risk in all situations but risk reduction measures should minimise the probability and severity to an acceptable level of assurance. The degree of risk tolerated very much depends on the circumstances, the proximity to the patient and other controls that may follow the process being assessed before the product is used by the patient. It should be expected that risk mitigation plans are identified and implemented where any risk to patient safety is posed. Companies should take a holistic view and be mindful that critical issues often occur where multiple failures in systems occur together so risk reduction plans should be sufficiently robust to tackle such potential.

Inspectors will be assessing if risk assessments underate either the probability, severity or detection of occurrences in order to make it appear that there is minimal risk to the patient. The factual evidence behind statements may be challenged.

The impact should not consider the financial impact on a site/company to the detriment of the patient.

11. Are any areas out of bounds for risk assessment?
It would be unacceptable for risk assessment to conclude that statutory, regulatory or GMP requirements should not be followed or are not appropriate eg risk assessment could not conclude that it was appropriate for licensed products to be released by someone who was not a qualified person (QP). Otherwise risk assessments can be used within GMP systems as a tool to identify, quantify and minimise and control risk to patient safety.

12. How should risk assessments be controlled?
Risk assessments should be controlled within a defined document management system. If risk assessments are conducted to justify controls for an ongoing process then the assessments should be subject to change control and periodic review, eg line clearance risk assessment. Frequency of review should be appropriate for the nature of the process. Such risk assessments should be seen as living documents that are visible and subject to change as and when required. Risk assessments that were conducted as one off activities to assess a situation that will not recur need not be controlled in a 'live' manner but must be documented, approved and retained eg assessment of a temperature excursion on storage of a batch of starting material. Such 'one off' activities should be controlled as live documents if any conclusions are to be used in any future excursions. Ultimately these may then need to be reviewed in light of experience or developments.

13. Do risk assessments have to be supported by factual evidence or can they just use professional judgment?
There should be factual evidence recorded to support any conclusions drawn eg plant design details in controlling cross contamination - an unsupported assumption that the plant must be suitably designed as we have used it for 10 years or we've had a standard operating procedure (SOP) for five years so it must be suitable is a weak approach that may be unfounded and must be challenged by those conducting risk assessments. Professional judgment should be used in interpretation of factual evidence but must be subject to justification.

14. Scoring in risk assessments is subjective, is there danger that risk assessments may be manipulated to draw desired conclusions?
The scoring system and trigger points for risk reduction are subjective. However as important as the scores in risk assessments is the rationale for the score. If supported by factual evidence it should be more obvious what risk control and reduction measures are required – the control/reduction measure is as important as the score assigned. Companies should not score risks in a blinkered manner without considering the factual causes, probability of detection and severity. Inspectors will be alert to improper use of risk assessments to condone poor practice or exclude patient risk.

15. Is it acceptable to allow external consultants to participate in site risk assessments?
It may be appropriate for consultants to provide support for risk assessments where they can provide specific expertise or knowledge. Their role in the risk assessment should be clear. The reason for delegation and resultant accountability must be understood. Inspectors will expect sites to demonstrate that delegation was effective and that appropriate skill, knowledge, local knowledge and local accountability was appropriate for the life cycle of the risk assessment. A technical agreement may be appropriate with the consultant where GMP responsibility is assumed.

16. Is it acceptable to allow contract staff to participate in site risk assessments?
It would be usual for contract staff, eg contract QPs to lead or participate in risk assessments. The extent of involvement as responsibility/accountability must be documented in the technical agreement between the individual and the organisation.

1.2.2 Out of Specification

1. Has the MHRA produced any guidance?
Out of specification investigations (290Kb)

2. Why is there a need to conduct an investigation of an OOS test result if the decision has been taken to reject the batch?
A phase 1 investigation should always be conducted in order to try and establish an assignable cause and determine whether any other batches may be affected. In determining the assignable and root cause of the problem appropriate corrective and preventative actions can be undertaken.

3. Who should investigate OOS?
Both the manufacturers and the laboratories should be involved in the investigation.

4. How is an out of trend result handled?
Results that are out-of-trend (OOT) should be handled similarly to OOS investigations.

5. Is it acceptable for a contract laboratory (contract acceptor) to use the contract givers' procedure when handling OOS results?
There is an expectation that contract acceptors should follow their own procedures and that these should be flexible enough to accommodate the needs of the contract giver.

It is assumed that the contract giver has assessed the contract acceptor's procedure for handling of out of specification results and has agreed it as being suitable for their intended purpose. Any issues should have been discussed prior to conducting any analysis.|

6. How is a meaningful OOS investigation conducted?
A meaningful OOS investigation should be thorough, timely, unbiased, well-documented, and scientifically defensible.

7. At what point should a manufacturing investigation be initiated?
This should be initiated as part of the phase II investigation and as a result of the phase 1 investigation not revealing a conclusive laboratory error or the error remains unclear with no assignable cause.

8. What should be done if unexpected results are obtained and there is no obvious explanation?
These are also referred to as aberrant/anomalous. Preliminary laboratory investigation should occur and they should be handled similarly to OOS investigations.

9. Under what circumstances could test results become invalid?
If there is clear evidence of a determinant error. Or where the system suitability/method validity checks fail.

10. What should be done in the case where part way through testing the analyst realises there is an error?
If there is clear evidence of the error and it can be corrected without compromising the results or the validity of the method; for example a dilution error 20 ml volumetric flask used instead of a 25 ml volumetric then it should be handled as a deviation and the results are still valid. If there is any doubt as to the impact of the error which could mean the results may not be accurate, for example sample spillage then the testing should be stopped and the issue handled as a deviation to explain what happened.

11. When should the analyst inform the supervisor that they have an OOS results?
In the first instance, the analyst will be responsible for the preliminary laboratory investigation. This will involve them checking their work and confirming that there is no obvious error prior to informing their supervisor and initiating a phase 1 investigation. This should be done within a timely manner, preferably on the day of generating the results.

12. What should be done when the phase 1 investigation does not reveal an assignable cause or evidence of error remains unclear?
A phase II investigation is initiated, which will involve communication between the laboratory and the manufacturer/contract giver. The decision to undertake any further testing should be agreed and approved within a pre defined testing plan.

13. How many repeat tests should be conducted?
The minimum number of retests should be documented within the procedure and be based upon scientifically sound principles. Any statistical review with regards to %RSD and repeatability should relate to the values obtained during method validation, ie accuracy, precision and intermediate precision. The number of retests should be statistically valid.

14. What should be done if after retesting there is a combination of OOS results and pass results?
All results should be reported unless there is clear evidence of a determinant error or an assignable cause that could invalidate any of the results.

15. What should happen if the OOS investigations are inconclusive?
The certifying qualified person should fully consider all of the information prior to making any decisions as to the final disposition of the batch. Any decision to release a batch where OOS results have not been invalidated should come only after a full investigation has shown that the OOS result does not reflect the quality of the batch. In making such a decision quality assurance and the Qualified Person should always err on the side of caution.

16. When is it acceptable to average test results?
Where averaging of separate tests is appropriately specified by the test method, a single averaged result can be reported as the final test result. The validity of averaging depends upon the sample and its purpose. Using averages in the case of microbiological assay can provide more accurate results because of the innate variability of the microbiological test system. For example the kinetic scan of individual wells or endotoxin data from a number of consecutive measurements or with HPLC consecutive replicate injections from the same preparation where the determination is considered one test one result.

17. When is it not acceptable to average test results?
Averaging cannot be used in cases when testing is intended to measure variability within the product, such as powder blend/mixture uniformity or dosage form content uniformity. In the context of additional testing performed during an OOS investigation, averaging the result(s) of the original test that prompted the investigation and additional retest or resample results obtained during the OOS investigation is not appropriate because it hides variability among the individual results.

18. At what stage should retesting occur?
Retesting occurs at phase II of the investigation. The initial hypothesis testing can involve re-measurement of the original preparation or working solutions, however retesting is when the original sample or composite sample is used to perform analysis. Hypothesis testing and retesting are part of the phase II investigation. Only if the original sample is depleted or compromised should a new sample be used.

19. At what stage should re-sampling occur?
Re-sampling at phase II of the investigation should only occur if the original sample is depleted or compromised and the same method should be used. If the investigation determines that there were errors with the initial sampling method only then should a new accurate sampling method be developed, qualified and documented.

20. When is it appropriate to use outlier tests?
Statistical analysis for Outlier test results can be as part of the investigation and analysis. However for validated chemical tests with relatively small variance and that the sample was considered homogeneous it cannot be used to justify the rejection of data.

1.3 ECA Academy (Europe)

1.3.1 EU GMP Annex 11: Computerised System

Chapter 1 – Risk Management
Speakers:
Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)
Dr Jörg Schwamberger, Merck KGaA

> *Annex 11: "Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system."*

What can elements of risk management contribute towards defining the extent of testing of specific elements (such as validation, data integrity)? What does it mean "to determine the extent of validation through risk management"? Does it mean the number of test cases or the depth of the test?
Using elements of risk management, validation measures such as design specifications, extent and depth of testing as well as type and frequency of tests/reviews after putting into operation (periodic evaluation) etc. can be determined precisely.

Chapter 2 – Personnel
Speakers:
Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)
Dr Jörg Schwamberger, Merck KGaA

> *Annex 11: "There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties."*

What should be understood by "close cooperation between all relevant personnel …"? What formal requirements should be observed?
No defined formal requirements exist for close co-operation between all relevant personnel during validation. But efforts must be made to ensure that a corresponding division of roles and tasks between the relevant personnel is clearly defined and implemented, including IT.

What training is expected of the relevant personnel?
Requirements concerning training result from the relevant operational provisions on validation. This means that the relevant personnel should know the main regulations concerning their tasks and be able to demonstrate the internally required qualifications to perform the tasks in question. This already arises from the general GMP requirements over and above Annex 11.

Is a formal qualification required (such as ITIL training or something similar)?
Annex 11 contains no further formal requirements concerning personnel qualification other than that resulting from the operational context (see answer above).

What role has a QP to play in validation?
The QP does not have to play a formal role in validation. But inclusion of a QP is recommended as it is the task of the QP to finally release the manufactured product. This release can only be authorised knowing the quality systems used for the proper validation.

Does the QP substitute QA in validation?
The exact responsibilities need to be laid down in the operation procedures. Annex 11 proposes a division into roles that may, however, be independent of a QP and/or QA. Thus the role of the QA has to be defined internally and independently of the function of a QP.

Chapter 3 – Suppliers and Service Providers
Speakers:
Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)
Dr Jörg Schwamberger, Merck KGaA

Annex 11:
"3.1 When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. IT-departments should be considered analogous.
3.2 The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.
3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.
3.4 Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request."

Why do inspectors want to see the supplier's audit reports? Doesn't this contradict the confidentiality agreements with the suppliers?
Without the opportunity to inspect the activities concerning qualification of suppliers, inspectors may not be able to fully evaluate whether due care was applied. In principle, confidentiality agreements are legally subordinated to the relevant legislative provision. Nevertheless, it is recommended that the confidentiality agreements are adjusted accordingly. Apart from that, inspectors are bound by an obligation of secrecy ex officio.

Which points should be taken into account from the inspectors' point of view when evaluating suppliers?
When evaluating suppliers it has to be ensured in general that the supplier's suitability for the task to which he is to be entrusted, is evaluated as well as his ability to accept responsibility for this task.

Are there requirements concerning the auditing of sub-suppliers?
Sub-suppliers (= external suppliers, sub-contractors) must not be audited separately by the contractor if it can be ensured that the principle supplier has laid down regulations ensuring the quality of his suppliers and that these regulations are demonstrably used. The relevant revisions must be documented. The contractor's evaluation should include the ability of the supplier to evaluate the suppliers on his part.

What demands on user requirements are put on COTS (commercial off the shelf) products?
Insofar as COTS products are used for GMP-regulated tasks, their suitability must be demonstrated accordingly within the context of validation. In doing so, the user requirement should define the intended purpose in the company.

What formal requirements exist concerning the choice of a supplier? Must the choice be documented and justified?
The choice of a supplier must be documented and his suitability demonstrated by means of compliance with the pre-requisites in the user requirements.

Does the external supplier/internal IT have to have his/its own QMS? If so, what requirements does this QMS need to fulfil?
If it is ensured that the external supplier/internal IT works according to the customer's regulations, the external supplier does not need his own QMS. It is recommended that this is possibly laid out in a contract and supported among other things by way of respective training. Otherwise the supplier is obliged to maintain a QMS that is demonstrably suitable for his activities.

Chapter 4 – Validation
Speakers:
Dr Arno Terhechte, Regional Government of Münster (Bezirksregierung von Münster)
Eberhard Kwiatkowski, Bayer HealthCare

Annex 11:
"4.1 The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.
4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.
4.3 An up to date listing of all relevant systems and their GMP functionality (inventory) should be available.
For critical systems an up to date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.
4.4 User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.
4.5 The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.
4.6 For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.
4.7 Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.
4.8 If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process."

What is the definition of "relevant systems"?
Inventory: Relevant / Substantial systems are systems used in order to implement or assist GMP requirements. These systems can be identified within the context of a risk analysis (also supported by a questionnaire).

Is there a definition for "critical"?
No, but Annex 11, chapter 1 gives an indication. Critical systems are systems that directly or indirectly influence patient safety, product quality and data integrity.

How exact must GMP functionalities be described in the inventory?
Only relevant to GMP – yes/no. In the inventory, a description of the general functions is sufficient, i.e. archiving of data, parts list management etc. Detailed information can be found in the system description.

In what way can the URS be created on the basis of a risk analysis if the risk analysis requires an URS as a pre- requisite?
URS and risk analysis are two elements within the context of validation of computerised systems which are closely linked with each other. Requirements can result from a risk analysis but on the other hand it is possible to reach functional solutions on the basis of user requirements on the assessment of risks.

Data flows – does this also mean intersystem interfaces (for example, the interfaces between different modules in ERP- systems)?
Every intersystem interface should be described, including any relevant changes of data format.

Must all user requirements be traceable or only the ones classified as being GMP-relevant?
User requirements, especially those classified as being GxP-critical should be traceable in order to evaluate whether the computerised system is fit for the respective purpose.

What levels of control are expected when using automated test tools?
The level of control results from the criticality of the systems tested and the type of test tools used. A complete validation is not generally expected.

What should test scripts and test results look like in order to be accepted by the inspectors?
Test scripts should contain a specification (expected result) and a description (test performance). The test result should indicate whether the specifications are fulfilled. Failed tests must be evaluated.

Chapter 5 – Data
Speakers:
Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)
Sieghard Wagner, Chemgineering Business Design

> *Annex 11: "Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimize the risks."*

What control mechanisms (such as MD 5) are expected?
The control mechanisms should be suitable for the relevant process or the relevant system. Those mechanisms are to be chosen that minimise the risk adequately.

Should special data formats (such as XML) be preferred?
No, Annex 11 does not specify any directions concerning the data format.

Why are built-in checks required for electronic interfaces if the interface has been validated?
The question cannot be answered as such. The checks of data built in the interface are tested within the context of validation. Changes in a system can be problematic if they concern data that is transferred via that interface.

Chapter 6 – Accuracy Checks
Speakers:
Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)
Sieghard Wagner, Chemgineering Business Design

> *Annex 11: "For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management. "*

To what extent must the erroneous entering of data be checked during validation?
It depends on the criticality of the entry. If the entry of critical data is to be checked not by a second operator but by a validated electronic means, it should be checked during validation whether erroneous entries really are detected.

How do inspectors deal with the risk assessment if a residual risk remains in the review?
ICH Q9 clearly points out that there will always be resi-dual risks. What residual risks are acceptable always depends on their potential influences on patients. Principally the residual risk is not the problem but possibly its level.

Chapter 7 – Data Storage
Speakers:
Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)
Sieghard Wagner, Chemgineering Business Design

> *Annex 11: "7.1 Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.*
> *7.2 Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically."*

How often should the readability and accessibility of data be checked?
The period should be defined depending on the risk. Readability should be checked immediately after copying and then depending on the medium used.

What requirements are made concerning physical protection?
Physical protection must be adequate to the risk. Physical protection comprises the protection of data storage devices from unauthorised parties as well as the environmental impacts influencing the respective data storage devices. A DVD should not be put in the sun; but this will be less problematic with a hard disk.

Chapter 8 – Printouts
Speakers:
Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)
Sieghard Wagner, Chemgineering Business Design

> *Annex 11: "8.1 It should be possible to obtain clear printed copies of electronically stored data.*
> *8.2 For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry."*

Are dedicated printouts demanded or are electronic documents sufficient?
Dedicated printouts.

What is the difference between a clear printed printout and a normal printout?
"Clear printed" means that apart from the values themselves, the units and the respective context can also be seen in the printout.

Chapter 9 – Audit Trails
Speakers:
Dr Christa Färber, Staatliches Gewerbeaufsichtsamt Hannover (State Labour Inspectorate, Hannover)
Frank Behnisch, CSL Behring

> *Annex 11: "Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed."*

What are the essential parts of an audit trail?
An audit trail has to at least record the critical variables/values, indicate the initial value and the changed one, indicate who has changed what and when.
This includes a unique identification of the user, a date and time stamp as well as possibly a comment. What's new pursuant to Annex 11 is the comment on the reason for change. Here it would be possible to restrict the number of parameters to be commented by using risk assessment.

What are the requirements on a regular evaluation of the audit trail?
Regularly would also be every ten years. The period of time must be substantiated by means of the process risk and documented. Example: Part of the periodic review or in the case of a batch release, part of the system's event log, and therefore at every release.

What shall be done in the case of legacy systems without audit trail?

First of all, it must be clarified whether the data can be changed at all (e.g.: electronic recorders or SPS). If not, this should be the reasoning within the risk assessment for the audit trail not being necessary. Define in an SOP that each change has to be documented e.g. in a logbook and verified by a second person.

Is a "paper-based" audit trail also possible?
Not with a new system. If a system is introduced today, it must comply with the requirements of Annex 11. An exemption are legacy systems, though. In the case of legacy systems this can be regulated by an SOP if it has been checked beforehand that there is no other possibility.

What does GMP-relevant data mean?
21 CFR Part 11 describes this very well, stating that this means all data required in preceding regulations (in this case this would be, e.g. the GMP Guide, AMG, AMWHV,…). Here, it means at least that data concerning or possibly influencing the product's reproducibility, identity, purity, labelling, efficiency or security.

Chapter 10 – Change and Configuration Management
Speakers:
Dr Christa Färber, Staatliches Gewerbeaufsichtsamt Hannover (State Labour Inspectorate, Hannover)
Frank Behnisch, CSL Behring

> *Annex 11: "Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure."*

What controls are required in the case of a change of configuration?
This has to be defined system-specifically. Measures need to be defined according to a risk assessment. Here, a distinction can be drawn between configurations that are for intended use and are only documented by means of a logbook (such as infrastructure, virus scanner, …) and configurations which have to be formally authorised and documented by means of a change control (such as release work flow with electronic signature).

Must changes which are not GMP-relevant also be carried out in a controlled manner?
If the whole system is not GMP-relevant = NO. If the system is GMP-relevant = YES, because in an integrated system it must also be evaluated that there is no negative influence. It can also only be ascertained by means of a "risk assessment" that a standard update or standard patch poses no risk and that it therefore can be registered and performed.

Chapter 11 – Periodic Evaluation
Speakers:
Dr Christa Färber, Staatliches Gewerbeaufsichtsamt Hannover (State Labour Inspectorate, Hannover)
Frank Behnisch, CSL Behring

> *Annex 11: "Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports."*

What does periodic mean? What period of times is expected as a minimum, for example?
Periodic in this case means regularly and recurrently. No minimum period of time is defined. It must be substantiated that the period of time is adequate in order to control the process risk.

Can such periodical evaluations be incorporated in the annual report or PQR? Must they be incorporated there?
They can be incorporated in the Annual Product Review, but they need not be. Annotation Behnisch: I would not recommend to generally incorporate them in the Annual Product Review as the periods of time in the Periodic Review can usually be longer than the Annual Product Review since the systems are subject to strict change control and possible deviations in the company are controlled by means of the CAPA process.

Since 30 June 2011 the industry has to implement all requirements of Annex 11 "Computerised Systems" of the EU GMP Guideline. Within the context of the Conference on Computer Validation in Mannheim, Germany, in June 2011, authority representatives and industry experts have answered questions concerning the 17 chapters of Annex 11. Here you will find the questions and answers on some of these chapters. Further Q&As were published in the GMP Journal October/November 2011 and April/May 2012 issues.

Chapter 12 – Security
Speakers:
Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)
Sieghard Wagner, Chemgineering Business Design

> *Annex 11: "12.1 Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.*
> *12.2 The extent of security controls depends on the criticality of the computerised system.*
> *12.3 Creation, change, and cancellation of access authorisations should be recorded.*
> *12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.*"

Does "Operators" mean the users of the system? If so, what is the difference to the audit trail requirement?
The audit trail targets documents of the record/report type. In the case of instruction-type documents, documentation is expected, for example, on who has entered when what version of an SOP in the electronic document system as valid document or suspended it and when.

The identity of operators of management systems for data and for documents should be recorded. Is this requirement valid for control systems?
It refers primarily to DMS; this requirement is not applicable to control systems.

How often do users have to change their passwords? How often must user profiles be checked?
The frequency of change as well as the frequency of control of user profiles depends on the risk. Annex 11 does not pose any requirements on the frequency of password changes.

Chapter 13 – Incident Management
Speakers:
Dr. Christa Färber, Staatliches Gewerbeaufsichtsamt Hannover (State Labour Inspectorate, Hannover)
Frank Behnisch, CSL Behring

> *Annex 11: "All incidents, not only system failures and data errors, should be reported and assessed.*
> *The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions.*"

What exactly does "all incidents" mean? Does it also mean service requests (such as resetting a password)?
It means per definition all incidents. But the company can define what an incident is and what the intended use is. Resetting a password, for instance, can be a regular task of the administration and therefore it is no incident since the system documents resetting via log files. Here, you can limit the incidents.

Are workarounds accepted for preventive actions?
Yes, provided they are described and regulated – for instance, in SOPs.

Chapter 14 – Electronic Signature
Speakers:
Klaus Eichmüller, Regierung von Oberbayern (Government of Upper Bavaria)
Yves Samson, Kereon

> *Annex 11: "Electronic records may be signed electronically. Electronic signatures are expected to:*
> *a. have the same impact as hand-written signatures within the boundaries of the company,*
> *b. be permanently linked to their respective record,*
> *c. include the time and date that they were applied."*

Is it intentional that the "meaning" (as in Part 11) is not required in Annex 11?
Eichmüller/Samson: In GxP processes, the meaning of a signature is always part of a signature. For the GMP sector, this is regulated in Chapters 1 and 4 of the EU GMP Guideline. This is the reason why this requirement was not repeated in Annex 11. A repetition of this requirement would have ensured improved clarity – without causing unnecessary redundancy. But principally, the actual wording is not confusing.

How long must data concerning electronic signatures be kept?
Eichmüller/Samson: What data? The signed data may no longer be separated from the signature. Signature and signed data must be kept for an equal period of time. The retention period to be specified must be defined according to the underlying requirements, such as GxP requirements (other requirements may also be relevant: commercial law, liability law etc.). Data concerning the undersigned has to be kept at least as long as the signed data (data concerning the undersigned is in fact metadata of the signed data). In any case, the user data should be kept as long as the system is operated and as long as the signed data must be kept.

How significant is the requirement of the binding legal force in the internal relationship of the company?
Samson: The legal context differs between the USA and the European Union. The USA is one state and does not have a general law on electronic signatures. The EU is a Union consisting of 27 states, subordinated to European law. But these states are obliged to transpose this subordinated law into specific national legislation. This means that the national provisions on electronic signatures may differ slightly from state to state. Where electronic signatures are concerned, there are two directives valid in the EU: Directive 1999/93/EC on a Community framework for electronic signatures and Directive 2000/31/EC on electronic commerce. In Germany, the signature law is also valid. The sentence: "Electronic signatures are expected to have the same meaning as hand-written signatures in the internal relationship of a company …" means that external regulations such as the Signature Law are not applicable for GxP-relevant electronic signatures within a regulated pharmaceutical organisation.
Eichmüller: Because of the different possibilities of the Member States with regard to regulations on the binding legal force of electronic signatures in external relationships, Annex 11 only describes the binding legal force in the internal relationship.

What does "same impact within the boundaries of the company" mean?
Eichmüller/Samson: As a logical consequence of the information above, GxP-relevant electronic signatures can be recognised as equivalent to hand-written signatures within the regulated pharmaceutical organisation.

Chapter 15 – Batch Release
Speakers:
Klaus Eichmüller, Regierung von Oberbayern (Government of Upper Bavaria)
Yves Samson, Kereon

> *Annex 11: "When a computerised system is used for recording certification and batch release, the system should allow only Qualified Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature."*

Is this approach also valid for hybrid systems where the release is paper-based, but the release is recorded in an electronic system?
Eichmüller: The requirement that the relationships of the single documents need to be stated in an unambiguous way in a hybrid system is decisive. If documentation of the release decision is paper-based, Annex 11 is to be applied only with regard to the supporting documents. A mere reproduction of a paper-based release decision in an electronic system implies the application of the requirements of Annex 11 but not the requirement of a further electronic signature.

Is there an electronic release?
Eichmüller: A release is carried out by a human being, in the case of a release according to §16 AMWHV or Annex 16 by the Qualified Person (QP).

Is an automatic release possible in the case of real-time release?
Samson: In order to make that absolutely clear, it has to be noted that the so-called Real Time Release has to be understood as Real Time Release Testing (RTRT). There has never been an intention to carry out batch releases automatically. Rather, and in the sense of ICH Q8, it is possible to replace release-relevant quality controls in the laboratory with real-time testing as long as the process and validation permit such testing.
Eichmüller: It is true that automated aggregations of data are possible by means of validated processes but the release is carried out by people. In terms of RTRT, further possibilities of application can be anticipated for the future (compare EMA's relevant Concept Paper) but I don't see the possibility of an automated release yet. (Annotation: At the end, there also is the question about responsibility and the related liability).

Chapter 16 – Business Continuity
Speakers:
Klaus Eichmüller, Regierung von Oberbayern (Government of Upper Bavaria)
Yves Samson, Kereon

> *Annex 11: "For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested."*

Is a high availability of critical processes required independently of the question as to whether such availability is necessary?
Samson: The availability of a process should be proportionate to the needs. This means that a process which is applied only seldom needs not to have a high availability even if it is a critical process from the GxP point of view. The process should only be available if needed. It has to be noted however that a process which is applied often or continuously might be assessed as being more critical from a business perspective than it is according to GxP.
Eichmüller: Chapter 16 focuses on the criticality of restoring process support. This leaves room for manoeuvre for GxP-critical processes. But the relevant decisions must be substantiated rationally on the basis of risk assessments.

Must the system availability of each single system be tested or is a general test sufficient?
Eichmüller/Samson: First of all the systems requiring higher availability must be identified. The availability of a group of systems can not only be tested "generally". To be efficient and in conformity with the requirements, contingency plans need to be designed system-specifically and sufficiently in

detail. Contingency plans can either be defined as SOP or be accompanied by SOPs. In any case, the contingency plans should be trained and practiced regularly. They must invariably be directed so that plans and measures are reviewed and possibly adapted in the case of hardware or software changes or organisational changes. Furthermore, the co-operation by the emergency measures of the individual systems should be reviewed and trained in the case of complex processes with embedded or interconnected systems.

Chapter 17 – Archiving
Speakers:
Klaus Eichmüller, Regierung von Oberbayern (Government of Upper Bavaria)
Yves Samson, Kereon

> *Annex 11: "Data may be archived. This data should be checked for accessibility, readability and integrity.*
> *If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested."*

How often should the readability of archived data be checked?
Eichmüller: This is to be defined by the company and depends on a set of further factors (see below) – apart from the type of system or data.
Samson: There is no simple and general answer to this question since the readability of a data storage device depends on various factors; including the technology used, the storage conditions of the data storage devices and the reliability of the requisite disk drives. That is the reason why the period of review should be defined based on the identified risks, the criticality of the data and, if applicable, experience. This point should in any case be a subject of the periodical evaluation.

Is a single test enough to demonstrate the readability of archived data?
Eichmüller: A single test does not at all fulfil the requirement of ensuring readability. The frequency of testing depends on different factors such as the archived process and the software and hardware used (see above and below) and should, for logical reasons, be defined individually. Samson: A single readability test is definitely not enough, since the aging process of the data storage devices and the disk drives used cannot be taken into account in that case. Furthermore, the availability of the requisite hardware and system software can play an important role as regards very old systems. This is the reason why periodic control of readability is indispensible.

1.4 FDA (USA)

1.4.1 General GMP

1. Are USP general chapters above <999> considered equivalent to FDA guidance? What are their purpose and how should manufacturers use these informational chapters?

No, FDA is the only source of policy on pharmaceutical CGMPs and quality. CGMP requirements are found in statutes and regulations, and FDA's current thinking on these requirements is explained in the Agency's guidance documents.

The USP is a private, non-governmental organization. While products labeled as USP are required to meet the criteria in product monographs when tested by the methods of analysis outlined in the tests and assays section, the suggestions found in General Chapters above <999> are only informational. The views expressed in these chapters are solely USP's. As with all information sources, these chapters might include some recommendations that may help a firm meet CGMPs.

References:

- Food Drug & Cosmetic Act[1]
- United States Pharmacopeia[2]

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Date: 6/14/2007

2. How does one comment on FDA's proposed guidance documents? How about USP proposals?
Both USP and FDA have mechanisms in place for interested parties to make comments on proposed documents.

1. Guidance Documents
FDA's proposed guidance documents are written using good guidance practices and published for comment per 21 Code of Federal Regulations 10.115. They are easily accessible to the public via our Web site and through the *Federal Register* Web site (http://www.gpoaccess.gov/fr/index.html[3]). FDA's Division of Dockets Management (DM) is the office responsible for receiving all comments on proposed guidance. Interested parties can read and submit comments via FDA's Dockets Management Web site (http://www.fda.gov/ohrms/dockets/default.htm[4]). FDA reviews all received public comments, makes appropriate modifications, and publishes a final document.

2. USP Monographs
USP publishes proposed chapters or monographs in the Pharmacopeial Forum, a publication that is issued bimonthly. USP subscribers have access to these publications, and can send comments (within a 90-day post publication comment period) for consideration by the USP. Finalized proposals (official revisions, new chapters or monographs) are published in subsequent supplements to, or editions of the Pharmacopeia.

References:
United States Pharmacopeia[5]

Contact for further information:
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Date: 4/30/2009

1. What is Penicillin?

Penicillin is defined as a group of natural or semi-synthetic antibiotics derived from fungi strains of the genus Penicillium. Generally, all penicillin share a three-carbon, one-nitrogen, and four-member cyclic amide structure, known as the beta-lactam ring.
Date: 6/29/2009

2. What are the Penicillin drugs?

The Manual of Clinical Microbiology, 9th edition, identifies penicillin drugs as follows:
Natural Penicillins:
• Benzylpenicillin* (commonly known as penicillin G)
• Benzylpenicilloyl-polylysine (BPP)
• Phenoxymethyl penicillin* (commonly known as penicillin V)
Semi-synthetic Penicillins:
• Methicillin
• Nafcillin
• Cloxacillin*
• Dicloxacillin*
• Ampicillin*
• Amoxicillin*
• Bacampicillin
• Pivampicillin
• Carbenicillin
• Ticarcillin*
• Azlocillin
• Mezlocillin
• Piperacillin
• Hetacillin*
*Penicillins approved for veterinary use

Please be aware that penicillin trade names may vary by region and country. Manufacturers, including repackers, are responsible for knowing whether their drug is penicillin. FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) or Drugs@FDA, both of which are located at FDA's website[1], enable searching by trade name (i.e., proprietary name) and by active ingredient name (i.e., generic or non-proprietary name).
Date: 6/29/2009

3. Is cross-contamination a concern with Penicillin drugs?

Yes, penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Differences in the chemically substituted 6-aminopenicillanic acid side chain can generate allergic reactions ranging from skin rashes to life-threatening anaphylaxis.
Date: 6/29/2009

4. Are there special manufacturing requirements for Penicillin drugs?

Yes, all penicillin finished pharmaceutical manufacturers, including repackers, are required by the CGMP regulations to establish a comprehensive control strategy designed to prevent cross-contamination of other drugs with penicillin. These requirements include:
• 21 CFR 211.42(d): Separation of facility and equipment
• 21 CFR 211.46(d): Separate air handling systems (HVAC)
• 21 CFR 211.176: Test for traces of penicillin where possible exposure exits.

Penicillin Active Pharmaceutical Ingredients (APIs) are also required to be manufactured under CGMPs in accordance with Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. FDA has published internationally harmonized guidance on the manufacture of APIs; see International Conference on Harmonization (ICH) Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Chapter 4, section 4.4 of this guidance describes actions API manufacturers, including those who manufacture or package APIs or penicillin intermediates, are to follow to ensure such material is contained and does not contaminate other drugs.

References-See below

Contact for further information:
Division of Manufacturing and Product Quality (HFD-320): CGMP Subject Contacts
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm[2]
Date: 6/29/2009

5. Why is FDA concerned about drug contamination with halogenated anisole compounds, such as 2,4,6-tribromoanisole (TBA)?

Reports, including some dating back several decades, describe a moldy or musty odor in food (and wine) products due to contamination with trace amounts of halogenated anisole compounds such as 2,4,6-tribromoanisole (TBA). An odor attributable to the presence of a halogenated anisole compound can be detected by consumers even when the offending compound is present at parts per billion or lesser levels. Recently, an upward trend in consumer complaints about musty or moldy odor led a drug firm to identify TBA as the odor-causing compound. The firm's investigation of this incident led to the detection of TBA in several oral products. The firm traced all of the contamination back to the use of certain wooden pallets used to transport drug packaging materials. TBA is prone to volatilize and adsorb onto articles stored near the TBA source. Because of their volatility, it appears that even minute levels of halogenated anisole compounds can adversely affect a large quantity of product in a single contamination incident.
Date: 3/12/2010

6. Are there any health effects associated with ingestion of halogenated anisole compounds?

Although there is no meaningful toxicological data on TBA at these levels, the health risks appear to be minimal. Currently available data indicate that serious adverse health effects have not resulted from ingestion of drugs or foods contaminated with halogenated anisole compounds at the levels of contamination that have been reported. However, there are some reports of gastrointestinal events by consumers who also report sensing a foul odor, or taste, in drug products contaminated with the typical trace levels of TBA. Even if the health effects are minimal, FDA is concerned that patients sensing an unusual odor that is not intrinsic to the product will stop taking their medication.
Date: 3/12/2010

7. Has FDA identified the source of the halogenated anisole compounds that have recently contaminated drug products?

The source of TBA-contaminated drug products appears to have been 2,4,6-tribromophenol (TBP), a chemical used as a wood preservative. Certain fungi are able to survive in TBP-treated wood by converting TBP to its anisole analog, TBA[1]. In the recent contamination incident, an investigation found that TBP-treated wood was used to manufacture pallets that were then used to ship and store drug packaging material. Currently, the use of halogenated phenolic compounds to preserve wood appears to be very rare as this practice is either discouraged or prohibited in many regions of the world, including the US. However, TBP treatment of wood continues in some regions that supply wood to the US and other countries.
Date: 3/12/2010

8. What is FDA's expectation for preventing contamination of drug products with halogenated anisole compounds?

FDA recommends that manufacturers and distributors take precautions to prevent the use of wood products treated with or exposed to a halogenated phenolic preservative anywhere in supply chain. This includes all facilities that manufacture, hold, or distribute drug products, components, or packaging materials. We recommend that manufacturers not store drug products, components, or packaging materials near wood or wood-derived storage materials unless there is assurance that the wood material has not been treated with a halogenated phenolic preservative.

FDA further recommends that manufacturers establish agreements and request certification from suppliers to provide assurance that halogenated phenolic preservatives are not present. Manufacturers should also be vigilant to the characteristic odor of the offending compounds so they can intervene before product is contaminated or further distributed.
Date: 3/12/2010

9. Are there any standards applicable to preventing contamination of drug products with halogenated anisole compounds?

U.S. (ASTM) and international standards (International Standard for Phytosanitary Measures (ISPM)) recommend heat treatment, or fumigation with methyl bromide, for the preservation of wood-derived packaging storage materials, including wood pallets. For more information, including certification to these standards, refer to Standard Practice for Treatment and/or Marking of Wood Packaging Materials (ASTM D 6253-05a) and Guidelines for Regulating Wood Packaging Material in International Trade (ISPM 15).
Date: 3/12/2010

10. Can contamination of drug products with halogenated anisole compounds be detected?

Although methods for detection exist and might be practical for periodic screening, FDA expects that manufacturers prevent such contamination through adherence to Current Good Manufacturing Practices (CGMPs). A CGMP-compliant quality system will ensure that assurances are obtained from suppliers and that measures are taken to prevent exposure to problematic compounds. Manufacturers of finished pharmaceuticals are reminded that the CGMP regulations at 21 CFR 211.56(c) require written procedures for sanitation designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, and drug products. Analogous recommendations for manufacturers of active pharmaceutical ingredients are included in internationally harmonized (European Union, Japan, United States) guidance for industry ICH Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients (section 4.72).

[1] Trichlorophenol (TCP) is another example of a compound that can be converted to a halogenated anisole compound

References:

1. Yao, Joseph D. C., and Robert C. Moellering, Jr. "Antibacterial Agents." Manual of Clinical Microbiology. 9th ed. Washington D.C., ASM, 2007
2. FDA CGMP regulations (21 C.F.R. Parts 210-211)
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm095412.htm[3]
3. The Federal Food, Drug, & Cosmetic Act 501(a)(2)(B)
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm[4]
4. Code of Federal Regulations – 21 CFR Part 211.56
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.56[5]
5. ICH Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients (section 4.72)[6]
6. Standard Practice for Treatment and/or Marking of Wood Packaging Materials (ASTM D 6253-05a) - ASTM International (http://www.astm.org/[7])
7. Guidelines for Regulating Wood Packaging Material in International Trade (ISPM 15) - Secretariat of

the International Plant Protection Convention of the Food and Agriculture Organization of the United Nations (https://www.ippc.int/[8])

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Division of Manufacturing and Product Quality (HFD-320): CGMP Subject Contacts
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm[9]
Date: 3/12/2010

1. Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?
The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified--a common frequency is once a year--using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries.

References:

- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.160(b)(4): General requirements (Lab Controls)
- USP Chapter <41> Weights and Balances
- See also: ASTM standard E 617: Standard Specification for Laboratory Weights and Precision Mass Standards (this standard is incorporated into the USP by reference; other widely recognized standards may be acceptable)

Contact for further information:
CDER/OC Office of Manufacturing and Product Quality: CGMP Subject Matter Contacts
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[1]
Date: 8/4/2004

2. Is there a list of approved drug manufacturing equipment?
No. The CGMP regulations neither approve nor prohibit specific equipment for use in manufacturing of pharmaceutical products (with the exception of asbestos and fiber-releasing filters, see 211.72). We do not maintain a list of approved equipment. Firms are afforded the flexibility to select equipment that best satisfies their particular needs and that is capable of meeting the relevant CGMP requirements. Each firm is responsible for selecting all equipment used in their manufacturing process to produce quality product in accordance with CGMP. They are also responsible for selecting the appropriate intended use for the equipment's operation, and are free to modify standard equipment designs to best suit their process and that are compatible with the product under process.
The CGMPs require that equipment be of appropriate design to facilitate operations for its intended use and for cleaning and maintenance (see 211.63 and 211.67) and, that any equipment surface in contact with components, in-process materials, or drug products not be reactive, additive, or absorptive so as to "alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 211.65).

References:

- 21 CFR 211.63: Equipment design, size, and location
- 21 CFR 211.65: Equipment construction
- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.72: Filters

Contact for further information:

CDER/OC Office of Manufacturing and Product Quality: CGMP Subject Matter Contacts
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[2]
Date: 5/18/2005

3. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?

Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues.
TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. In order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is an important exercise because some organic compounds cannot be reliably detected using TOC.
TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit 'background' carbon (i.e., carbon from sources other than the contaminant being removed) as much as possible. If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantitation.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance.
- 21 CFR 211.160(b): General requirements (Laboratory Controls)
- USP 643 Total Organic Carbon
- Guide to Inspections of Cleaning Validation, 1993

Contact for further information:

Brian Hasselbalch, CDER
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Date: 5/18/2005

4. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm recently had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (non-sterile bulk powder) from a commercial source, and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.
Acholeplasma laidlawii belongs to an order of mycoplasma. Mycoplasma contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram

stain. Individual organisms are pleomorphic (assume various shape from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, et al.). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of mycoplasma requires selective media (PPLO broth or agar).

Resolution:
For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for mycoplasma and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:
- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S., Eisenhuth, J., Howard, G., Brandwein, H. Application of membrane filtration for removal of diminutive bioburden organisms in pharmaceutical products and processes. PDA J. Pharm. Sci. Technol. 1999 Jul-Aug; 53(4): 186-201.
- Kong, F., James, G., Gordon, S., Zekynski, A., Gilbert, G.L. Species-specific PCR for identification of common contaminant mollicutes in cell culture. Appl. Environ. Microbiol. 2001 Jul; 67(7): 3195-200.
- Murray, P., Baron, E., Pfaller, M., Tenover, F., Yolken, R. Manual of Clinical Microbiology ASM Press, Sixth Edition.

Contact for further information:
CDER/OC Office of Manufacturing and Product Quality: CGMP Subject Matter Contacts
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[3]
Date: 5/18/2005

1. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?
The CGMP regulations (21 CFR 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question were from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified.
However, any documentation of corrective action as a result of such an audit would have to be retained (see 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see 211.192).
In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (211.198), vendor qualification (211.84), periodic review of records and data (211.180(e)), and a failure investigation (211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see 211.180).

References:
- Preamble to the *Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding* regulations; Federal Register, September 29, 1978 (vol. 43, no. 190), page 45015, paragraph 4:

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM206779.pdf[1]

- 21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
- 21 CFR 211.180: General requirements
- 21 CFR 211.192: Production record review
- 21 CFR 211.198: Complaint files
- Compliance Policy Guide Sec. 130-300, (7151.02) http://www.fda.gov/ora/compliance_ref/cpg/cpggenl/cpg130-300.html[2]

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2. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?
Yes. Generally, we believe that sampling in a typical drug manufacturing facility warehouse would not represent a risk to the container/closure or affect the integrity of the sample results. But whether the act of collecting a sample in the warehouse violates the CGMPs requirement that containers "be opened, sampled, and sealed in a manner designed to prevent contamination of their contents..." will depend on the purported quality characteristics of the material under sample and the warehouse environment. For container/closures purporting to be sterile or depyrogenated, sampling should be under conditions equivalent to the purported quality of the material: a warehouse environment would not suffice (see 211.94 and 211.113(b)). This is to preserve the fitness for use of the remaining container/closures as well as ensure sample integrity, if they are to be examined for microbial contamination. At a minimum, any sampling should be performed in a manner to limit exposure to the environment during and after the time samples are removed (i.e., wiping outside surfaces, limiting time that the original package is open, and properly resealing original package). Well-written and followed procedures are the critical elements.
Note that the CGMPs at 211.84 permit a manufacturer to release for use a shipment of containers/closures based on the supplier's certificate of analysis and a visual identification of the containers/closures. Once a supplier's reliability has been established by validation of their test results, a manufacturer could perform the visual examination entirely in the warehouse.

References:

- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.113(b): Control of microbiological contamination
- 21 CFR 211.122: Materials examination and usage criteria

Contact for further information:
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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[3]

3. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?
A firm recently had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (non-sterile bulk powder) from a commercial source, and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii*

in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.
Acholeplasma laidlawii belongs to an order of mycoplasma. Mycoplasma contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shape from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, et al.). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of mycoplasma requires selective media (PPLO broth or agar).

Resolution:
For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for mycoplasma and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S., Eisenhuth, J., Howard, G., Brandwein, H. Application of membrane filtration for removal of diminutive bioburden organisms in pharmaceutical products and processes. PDA J. Pharm. Sci. Technol. 1999 Jul-Aug; 53(4): 186-201.
- Kong, F., James, G., Gordon, S., Zekynski, A., Gilbert, G.L. Species-specific PCR for identification of common contaminant mollicutes in cell culture. Appl. Environ. Microbiol. 2001 Jul; 67(7): 3195-200.
- Murray, P., Baron, E., Pfaller, M., Tenover, F., Yolken, R. Manual of Clinical Microbiology ASM Press, Sixth Edition.

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4. How many containers of each component from each shipment must a firm sample and test to comply with the CGMP requirements for identity testing? Do the CGMPs permit the identity test on a pooled, or composite, sample of multiple containers?
The Current Good Manufacturing Practice (CGMP) regulations address component sampling and testing primarily at 21 CFR 211.84. These regulations require representative samples of each shipment of each lot of active and inactive component (or raw materials) to be tested to confirm the identity of the component as labeled prior to release for use in drug product manufacturing. The regulations acknowledge that more than one test may be needed to ascertain a component's identity. For the purpose of this answer, a component's identity is its chemical structure and its physical form (e.g., polymorph, solvate, and appearance) including, if appropriate, its stereochemistry or immunochemistry. (See also ICH Q6A[5] and Q6B[6])
The CGMP regulations do not specify the number of containers to be sampled from each received shipment. However, 21 CFR 211.84(b) establishes the principles to be followed in designing a sampling program for components. The requirements of this section can be summarized as follows:
- samples are to be representative of the shipment received;
- the number of containers sampled as well as the amount of material sampled from each container is to be based on statistical criteria for component variability, confidence levels, and the degree of precision required;
- the sample program takes into account the past quality history of the supplier; and,
- the sample amount is to be sufficient for the necessary analysis and reserve samples.

The first three are most relevant to the question of how many containers to sample for identity testing, i.e., representative sampling, tolerance for variability and confidence required, and past history. (The amount needed for analysis and reserve can be readily met by sampling even one container, so the number of containers is not an important issue once the shipment's identity is verified.)
Unlike most component attributes, a component's identity is generally a discrete variable, i.e., the material in the container either is or is not what the label purports it to be. The component container's content might differ from what the container label states due to mistakes in filling and labeling by the supplier or repacker, or as a result of the substitution of a container's contents during distribution and warehousing before receipt by the drug product manufacturer. Using a wrong component in processing could result in a serious public health hazard. For these reasons, manufacturers need to develop an approach that provides a high degree of confidence that each container in each shipment contains the material purported by the label. (See also 21 CFR 211.160(b), which requires all sampling to be representative and scientifically sound.) The approach must account for the fact that the material's identity must not vary from what is specified. The past quality history of a supplier and the scope of their operations is relevant to the chance for mistakes to occur under a supplier's control, but does not necessarily bear on what happens to a drug once it is outside the supplier's control.

How many containers of each component from each shipment must a firm sample and test to comply with the CGMP requirements for identity testing?
The regulation at 21 CFR 211.84 requires that representative samples of each shipment of each lot shall be collected for testing. Some manufacturers have interpreted the CGMPs to require that each container in a shipment be sampled and tested for the attribute of identity. Testing samples from every container to determine identity may be valuable particularly for components purchased from distributors. (Analytical equipment and methods are readily available that permit rapid, non-destructive identification of material directly in containers in a warehouse area.) The CGMPs permit each drug product manufacturer to make its own decision as to the number of containers to sample, as long as the sampling plan is scientifically sound, leads to representative samples, and complies with the principles established at 21 CFR 211.84(b). An important caveat applies with respect to 21 CFR 211.84: samples are to be taken by the drug product manufacturer from containers after receipt (i.e., pre-shipment samples or so-called "piggyback" samples are generally not acceptable).

Do the CGMPs permit the identity test on a pooled, or composite, sample of multiple containers?
The CGMPs address the issue of sample compositing directly but only in the context of individual container sampling. Section 21 CFR 211.84(c)(4) explicitly prohibits compositing samples taken from the top, middle, and bottom of a single container when such stratified sampling is considered necessary (as might be the case when moisture content needs to be controlled, particularly when only a portion of a container may be used in a drug product batch). The preamble for 21 CFR 211.84(c)(4) explains further that there "is no general prohibition... on compositing samples [from single containers] where such compositing would not mask subdivisions of the sample that do not meet specifications" (see 1978 preamble[7], par. 231).
Testing individual samples from multiple containers provides a high level of assurance and is consistent with CGMP. Testing a composite sample for identity could satisfy the CGMP regulations (21 CFR 211.84 and 21 CFR 211.160) but only if a manufacturer demonstrates either that the detection of a single non-conforming container is not masked by compositing or that an additional test(s) routinely performed on the composite sample assures that all containers sampled contain the same material. Thus, a purity assay on a composite sample prepared by mixing equal aliquots from each container may be acceptable provided such a test is sufficiently sensitive to reveal the presence of a single non-conforming container.

References:

- Preamble to the *Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding* regulations; Federal Register, September 29, 1978 (vol. 43, no. 190) http://www.fda.gov/cder/dmpq/preamble.txt[8]
- 21 CFR 211.82[9]: Receipt and storage of untested components, drug product containers, and closures
- 21 CFR 211.84[10]: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.160[11]: General requirements (Subpart I, Laboratory Controls)

- International Conference on Harmonization, Q6A: *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* [Text[12]] or [PDF[13]] (12/29/2000)
- International Conference on Harmonization, Q6B: *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* [PDF[14]] (Issued 8/1999, Posted 12/14/2001)

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5. What methods of analysis are suitable for testing for melamine contamination in pharmaceutical components?
FDA recommends using a method demonstrated to be suitable for detecting melamine adulteration based on the manufacturer's risk assessment and prevention strategy. The manufacturer's selection of a sampling approach and test method sensitivity should address the possibility that 1) melamine might not be uniformly distributed in an at-risk component, or 2) that the source of intentional melamine contamination might be the starting material used to produce the at-risk component. The guidance provides a web-link to assay methods capable of detecting melamine at levels as low as 2.5ppm. These methods can detect melamine and cyanuric acid in complex matrices (protein materials) and, therefore, may be useful in developing test methods for other at-risk drug components. FDA also recognizes that a less sensitive method might also be appropriate for screening in certain cases.

References:
- 21 CFR Subpart E: Control of Components and Drug Product Containers and Closures
- Guidance for Industry: *Pharmaceutical Components at Risk for Melamine Contamination*[15] (August 2009)

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Date: 12/17/2009

6. Does FDA require or recommend any special precautions or controls over the manufacturing of animal-derived drug ingredients to prevent contamination?

Yes, FDA requires that animal-derived ingredients be controlled in a manner to assure that contamination does not occur, beginning with initial collection and handling of the animal-derived material through its processing and subsequent use in a finished pharmaceutical. See, for example, the Federal Food, Drug, and Cosmetic Act sections 501(a)(2)(A) and 501(a)(2)(B).

FDA has special concerns regarding the vulnerability of animal-derived ingredients to contamination by pathogenic agents (i.e., agents that can cause disease or illness in humans or other animals). As background, ingredients are also called "components," and there are two categories of components used in finished pharmaceutical production: inactive ingredient (often called excipients) and active ingredient (often called Active Pharmaceutical Ingredient). For the purpose of this guidance, an animal-derived ingredient is a substance of animal origin used to manufacture a drug product. They are primarily derived from by-products of food production and include extractions from certain animal material, and include milked animal fluids (e.g., venoms) and may even be human-derived. Products of animal cell cultures, including monoclonal antibodies and therapeutic proteins, are not considered animal-derived APIs for the purpose of this guidance. For additional information concerning biotechnology, products refer to Guidance for Industry, Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.

Ingredient manufacturers are responsible for the quality and safety of the material they produce for use in finished pharmaceuticals. Ingredients are drugs and drugs are required to conform with current good manufacturing practice (FD&C Act section 501(a)(2)(B)). Finished pharmaceutical manufacturers are also responsible for their selection, qualification, and use of ingredients in finished pharmaceuticals (e.g., the CGMP regulations at 21 CFR Part 211, subpart E, Control of Components and Drug Product Containers and Closures). Ingredient and finished pharmaceutical manufacturers should fully understand the potential for pathogenic agent contamination beginning with the livestock processing establishment (LPE) and continuing through subsequent handling and processing, and establish stringent controls to prevent contamination. It is also essential that appropriate tests or examinations are developed and applied to detect contamination as part of any meaningful control program.
Date: 1/27/2011

7. What are FDA's primary concerns about pathogenic agent contamination of animal-derived drug ingredients?

The FDA is concerned about contamination of animal-derived ingredients by pathogenic agents during processing at the LPE, at a subsequent consolidator of animal material or raw material processing plant, or during the manufacturing process to create the final ingredient. One should assume that animal-derived materials will not only harbor but often support growth of pathogens, and accordingly should assure appropriate control over the handling and processing of these materials. Current good manufacturing practice (CGMP) is to be followed in handling such material to assure that contamination does not occur that would affect the material's quality and purity, or that would be harmful when the product is administered to patients. Pathogenic agent contamination includes bacteria, molds, viruses, protozoa, parasites, and prions. Pathogenic agents can enter the manufacturing facility within the animal material, and contaminate excipients, water, processing equipment, personnel, environment, or packaging. Contaminated drug ingredients present potential health risks that may affect various patient populations, including immune-compromised patients, as well as otherwise healthy people of all ages.

An agent may be considered pathogenic if its presence represents a significant risk to patient safety. Factors affecting the pathogenic agent's ability to cause harm include:

- the nature of the agent (pathogenicity, virulence)
- the amount of pathogenic agent,
- the type of manufacturing process and whether it affects the pathogenic agent's ability to survive
- the ability of the pathogenic agent to grow within the ingredient
- the type of drug product, and its route and length of administration, and
- the patient population (including the most vulnerable patients that may take the drug) for the drug product.

Date: 1/27/2011

8. What manufacturing contamination risks are presented by the different pathogenic agents?

Manufacturing contamination risks presented by the different pathogenic agents can include the following:

<u>Vegetative Bacteria</u>
Vegetative bacteria are actively growing and reproducing bacteria. If there are no steps in the manufacturing process to kill vegetative bacteria, they can proliferate and accumulate during drug ingredient processing.

<u>Toxin-Producing Microorganisms</u>
Several genera and species of microorganisms are capable of producing toxins. Microbial toxins can be divided into two general groups: exotoxins and endotoxins. An exotoxin is a soluble protein excreted by a microorganism, including bacteria, fungi, algae, and protozoa. Exotoxins can include heat-stable toxins that remain active at temperatures as high as 100°C or heat-labile toxins that are readily inactivated by heat treatment. Exotoxins, especially heat-stable exotoxins, can remain in the

ingredient throughout the manufacturing process and adversely affect patient health. An endotoxin is a component of the outer membrane of a Gram-negative bacterium. Unlike exotoxins, endotoxins are only released when the organisms are disrupted or destroyed. Endotoxins are heat- and chemical-resistant and, if injected, may induce reactions including febrile effect, hypotension, and shock.

Spore-Forming Bacteria
Spore-forming bacteria can be difficult to eliminate from the manufacturing environment because the spores may be extremely resistant to heat, freezing, extreme pH, desiccation, and chemicals. Spore-forming bacteria can produce exotoxins and can remain dormant without nutrients for extended periods. Spores can be resistant to harsh manufacturing processes that will kill vegetative bacteria. When dormant spores are re-introduced into an acceptable germination environment they can become active reproductive vegetative cells. Once spores germinate and begin reproducing as vegetative cells, production of exotoxins can occur in a short period of time.

Fungi/Molds
Molds are a subset of fungi that reproduce by releasing spores into the air which, if they land on a moist nutrient source or animal tissue, can germinate. Some species of molds produce toxic byproducts called mycotoxins. Mycotoxins can accumulate in animal tissues, rendering the affected organs/tissues unfit for use as a source of starting material for the production of animal-derived drug ingredients. It is important to prevent molds from growing in drug ingredients and when feasible and valuable remove all molds that may contaminate such ingredients.

Yeasts, another type of fungi, can also be pathogenic or cause spoilage of an ingredient.

Viruses
Although a virus can only multiply within its host, the inadvertent use of material from virus-infected animals or contact of the drug ingredient with virus-contaminated surfaces can transmit viral particles to patients. Virus survival rates differ based on virus type and variables associated with surface materials that become contaminated. On hard, nonporous surfaces, some virus species can survive and remain transmissible for days or weeks. The probability of an animal virus contaminating an animal-derived ingredient will depend on the viral load of the raw material (e.g., tissue, glands, blood) and the viral clearance capability of the drug ingredient manufacturing process. Both of these factors should be considered when assessing the risk of viral contamination of the ingredient.

Internal Animal Parasites
Transmission of internal parasites occurs from host to host through consumption of contaminated food or water. Parasites live and reproduce within the tissues and organs of infected hosts, and are often excreted in feces. Government inspectors are trained to look for internal parasites and prevent unhealthy animals from entering the food supply. Animals deemed fit for food consumption are inspected and certified as healthy.

Prions
Protection from prion contamination includes obtaining bovine meat and meat byproducts from animals not infected with Bovine Spongiform Encephalopathy and protecting against contamination of product with high-risk tissues, especially brain and spinal cord tissue. Drug manufacturers importing bovine material into the United States should be familiar with and adhere to all import eligibility requirements and government regulations pertaining to food and drugs. It is important that farms, slaughterhouses and renderers observe government regulations prohibiting the use of unhealthy animals in the food supply. Animals deemed fit for food consumption are normally inspected and certified as healthy in many countries.
Date: 1/27/2011

9. What are some ways to minimize pathogenic agent contamination in incoming animal-derived raw material?

The drug component and finished product CGMP guidances and regulations emphasize prevention of problems and avoidance of contamination rather than final testing or examination alone. In other words, control strategies that prevent contamination are central to CGMP, while control strategies based on testing alone do not comply with CGMPs. Raw materials from animals can have microbial pathogen health risks based on country of origin, LPE processing, transportation, and manufacturing

processing. Under the right circumstances, raw material from animals can provide a suitable (e.g., nutrient-rich) environment for bacteria and mold to proliferate, or for viruses and other pathogenic agents to remain infective. If undetected contaminated raw material enters the manufacturing process, it can remain pathogenic in the product and a hazard to the consumer. The manufacturing conditions used in most ingredient manufacturing processes are often insufficient to eliminate all pathogenic agents from the ingredient. Methods of minimizing contamination of raw material with pathogenic agents may include the following:

Animal Source:
When animal-derived material is used, it is important that it be derived from healthy, disease-free animals. The occurrence of pathogens can vary greatly among different animal species. Ingredient manufacturers should understand the pathogenic risks associated with different animal species and with different organs, glands, or tissues within species. Drug ingredient manufacturers should be aware that even healthy animals can be reservoirs for pathogenic agents and improper handling can spread contamination. If improperly handled, microbial contamination can transfer to uncontaminated tissues and cause contamination.

Ensuring the health of U.S. livestock is the responsibility of many federal agencies, most of which are part of the U.S. Department of Agriculture (USDA). Animal-health and food-safety regulations are detailed in Titles 9 and 21 of the Code of Federal Regulations (9 CFR, 21 CFR). Animal health authorities in each state develop regulations that are consistent with the federal agencies, and are responsible for monitoring and controlling diseases in its domestic livestock and poultry. State inspectors ensure compliance by companies with individual state standards as well as with federal meat and poultry inspection statutes. States assist in controlling diseases through inspections, testing, vaccinations, treatments, quarantines, and other activities.

Awareness of the conditions of control and monitoring of source animals will aid in determining what animals and animal parts are appropriate for drug product manufacturing.

LPE:
Ingredient manufacturers should consider auditing the LPEs supplying raw materials to them and ensure their compliance with all federal and state government regulations. It is recommended that manufacturers develop Standard Operating Procedures and define sanitation requirements of raw materials immediately after butchering, including, for example, the following:

- chilling requirements, if indicated, including temperature ranges and how soon after butchering chilling should begin;
- chemical preservation methods, if indicated, including types and concentrations of chemical preservatives used;
- storage processes, including sanitization of containers, container type/material (stainless steel vs. food grade plastics, etc.);
- transportation criteria, including sanitization of containers, if different from storage and temperature ranges

The overall contamination of carcasses with pathogens depends on not only the prevalence and numbers of the pathogens on the hair, skin, and in the intestinal tract of the animal, but is significantly affected by the degree of cross-contamination occurring from these sources during slaughter and processing (see USDA references, below, for additional information). The FDA expects that manufacturers will establish appropriate specifications for bioburden in their in-coming raw materials.
Date: 1/27/2011

10. Are there control measures for minimizing pathogenic agent contamination in animal-derived drug ingredient manufacturing facilities?

Yes, control measures may include the following:

Process Control:
Holding and processing times for animal-derived material should be minimized to reduce the likelihood of microbial proliferation. The process qualification studies should includes microbial sampling at multiple time points to evaluate the effects of time, temperature and processing conditions on microbial growth. Routine microbial identification will provide valuable information regarding the types

of organisms present in incoming material and throughout the manufacturing process. Processing conditions can then be adjusted to help control the number and types of organisms present during the manufacturing process. Spores and many bacteria can be removed by filtration when filtration or filtration cascade systems are possible. Usually filters with a pore size rating of 0.45 micron or smaller will remove spores and many bacteria from a preparation. Viruses and many toxins are heat labile so a heat treatment should be considered early in process development. Many purification and concentration systems may have antimicrobial effects. The timing and sequence location in the process along with appropriate holding and processing times may serve to optimize the antimicrobial effects of the processes.

Development of process monitoring tests and acceptance criteria should be established during process development stage.

Facility and Equipment Controls:
Facilities can also be reservoirs for pathogenic agents. Maintaining a facility within CGMP should include but not be limited to:

- having adequately trained staff,
- using suitable quality water during manufacturing,
- having a facility design that minimizes the risk of cross-contamination,
- providing for proper storage of the ingredient

Cleaning procedures should include cleaning of facilities and equipment that ensures the removal of all raw materials between batches. Designing an effective cleaning program involves setting specific standards, understanding the facility's microbial environmental isolates, and selecting the right disinfecting agents to inactivate isolates that may be in the product or in the environment. Ingredient manufacturers should use sporicidal agents at appropriate intervals in the cleaning schedule to destroy bacterial and fungal spores.

References:

1. Guidance for Industry, (ICH Q7), *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073497.pdf[17]

1. United States Pharmacopeia General Information Chapter <1072> *Disinfectants and Antiseptics* (USP33/NF 28 Reissue, 2010)

2. Prescott, Harley and Kleins Microbiology, McGraw Hill Higher Education, Boston, 2008.

3. USDA Animal and Plant Health Inspection Service - http://www.aphis.usda.gov/[18]
   - Import and Export http://www.aphis.usda.gov/import_export/index.shtml[19]

4. USDA Food Safety and Inspection Service – Parasites and Foodborne Illness Fact Sheet (http://www.fsis.usda.gov/Fact_Sheets/Parasites_and_Foodborne_Illness/index.asp[20])

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Date: 1/27/2011

11. What should drug manufacturers do to prevent formation of glass lamellae (glass fragments) in injectable drugs filled in small-volume glass vials?

Under certain conditions, glass vials can shed thin, flexible fragments called "glass lamellae" (1, 2). These lamellae are shed from the interior surface of the glass container directly into the drug and are difficult to detect by visual inspection. Several drugs have recently been recalled due to this problem (3).

No adverse events to date have been reported nor can be directly attributed to this phenomenon. However, there is the potential for drugs administered intravenously that contain these fragments to cause embolic, thrombotic and other vascular events (e.g., phlebitis); and, when administered subcutaneously, to lead to development of foreign body granuloma, local injection site reactions, and increased immunogenicity (4).

The following conditions have been associated with a higher incidence of the formation of glass lamellae:

- Glass vials manufactured by a tubing process (and thus manufactured under higher heat). These vials are less resistant than molded glass vials and may shed lamellae more easily (5). The processing conditions used to manufacture glass vials can be designed to mitigate the potential for later delamination.
- Drug solutions formulated at high pH (alkaline) and with certain buffers. Common buffers associated with lamellae formation include citrate and tartrate (6).
- Length of time the drug product is exposed to the inner surface of the container. The time duration has a direct correlation to the potential for glass lamellae formation to occur during the product shelf life (1).
- Drug products with room temperature storage requirements. Drugs stored at room temperature have a greater chance of glass lamellae formation than do products stored at colder temperatures (7).
- Terminal sterilization has a significant effect on glass stability (2).

The referenced literature, below, includes recommended actions to help prevent the formation of glass lamellae. For example, for products "at risk," the vial surface alkalinity can be minimized by proper selection of glass composition (e.g., highly resistant, non-alkaline earth borosilicate glass), appropriate selection and qualification of vendors, and proper quality control of the incoming vials. Accordingly, FDA advises drug manufacturers of products to re-examine their supplier quality management program with the glass vial manufacturers to assure that this phenomenon is not occurring. Further, the Agency reminds finished drug product manufacturers that the current good manufacturing practice regulations require that drug containers not be reactive or additive so as to alter the safety or quality of the drug (8, 9,10).

References:

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4. Singh SK, Afonina N, et al. (2010). An industry perspective on the monitoring of subvisible particles as a quality attribute for protein therapeutics. J. Pharm. Sci. 99(8): 3302-3321.
5. Ennis RD, Pritchard R, et al. (2001). Glass vials for small volume parenterals: influence of drug and manufacturing process on glass delamination. Pharm. Dev. and Tech.; 6(3):393-405.
6. Sacha, G., et al. (2010). Practical fundamentals of glass, rubber, and plastic sterile packaging systems. Pharm. Dev. and Tech.; 15(1):6-34.
7. Iacocca, R.G. and Allgeier, M. (2007). Corrosive attack of glass by a pharmaceutical compound. J. Mater. Sci. 42: 801-811.
8. 21 CFR 211.94, Drug Product Containers and Closures. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm[23]

9. *Rx-360, An International Pharmaceutical Supply Chain Consortium*, has recently commented on the issue of delamination. http://www.rx-360.org[24]
10. See deviation reporting regulations for Field Alert Reports (21 CFR 314.81) and Biological Product Deviation Reports (21 CFR 600.14)

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[25]
Date: 3/25/2011

12. Are there any special processing or handling concerns for flexible intravenous (IV) solution bags?

Yes, due to their soft and flexible design, IV solution bags can be easily damaged if not handled properly during processing and labeling. A damaged IV solution bag may not protect the contents from exposure to microbiological contamination as intended. Detection of a damaged IV solution bag by leaks or by examination of the bag may not be possible. In fact, a microscopic defect may not be evident until microbiological contamination becomes visible, which is too late. Prevention of this potentially serious problem is important.

FDA is aware of recent product recalls where IV products in flexible plastic bags were exposed to rough surfaces or sharp objects during labeling, creating microscopic punctures, or weakening the bag surfaces. When a compromised IV solution bag is filled with liquid and expands as intended, holes may form at the weak points, leading to a loss of sterility or assurance of sterility.

Manufacturers are reminded that drug product containers and closures must be handled and stored in a manner to prevent contamination (see 21 CFR 211.80(b) and also 211.94).
Date: 7/5/2011

13. What can IV drug manufactures do to help prevent the loss of sterility due to compromised IV solution bag integrity during labeling?

The risk of loss of sterility during labeling can be reduced through the use of non-impression printing devices for labeling. If a manufacturer uses labeling equipment to apply a label on an IV solution bag and that labeling equipment makes an impression on the IV bag, procedures should be in place to inspect the labeling equipment regularly, particularly after any maintenance is performed. Manufacturing equipment must not have any rough or sharp surfaces that will create punctures or areas of weakness in the IV solution bags. Prevention is important: damaged IV bags may elude detection by standard examinations and tests, including checks for leaks.

Manufacturers are reminded that equipment maintenance and cleaning must be appropriate to prevent malfunctions or contamination that would alter the quality or purity of a drug product (see 21 CFR 211.67).

Additional information: FDA Guidances

- Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070342.pdf[26]

- Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf[27]

References:

- 21 CFR Part 211: CGMP regulations for finished pharmaceuticals http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm[28]
  - 21 CFR 211.22: Responsibilities of quality control unit
  - 21 CFR 211.80: General requirements (for the control of components and containers)
  - 21 CFR 211.94: Drug product containers and closures
  - 21 CFR 211.67: Equipment cleaning and maintenance
  - 21 CFR 211.100: Written procedures; deviations

Recall announcements:
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm214034.htm[29]

FDA Warning Letters:
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm233010.htm[30]

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[31]

Date: 7/5/2011

1. Do the CGMPs require a firm to retain the equipment status identification labels with the batch record or other file? Assuming each major piece of equipment has a unique "Cleaning and Use Log" that is adequately retained, is it acceptable to discard these 'quick reference' equipment labels?

The CGMP regulations for finished pharmaceuticals require the retention of cleaning and use logs for non-dedicated equipment, but no similar requirement exists for retaining what are intended to be "quick reference" or temporary status labels. Examples of these kinds of status labels include "mixing lot ###"; "clean, ready for use as of d/M/y"; "not clean." We see no value in the retention of such labels in addition to the required equipment log or batch record documentation. The labels serve a valuable, temporary purpose of positively identifying the current status of equipment and the material under process. Any status label should be correct, legible, readily visible, and associated with the correct piece of equipment. The information on the temporary status label should correspond with the information recorded in the equipment cleaning and use log, or the previous batch record for non-dedicated equipment.

Labels are merely one way to display temporary status information about a piece of equipment. It is considered acceptable practice to display temporary equipment status information on dry-erase boards or chalkboards. And it would be appropriate for an FDA investigator to verify that the information on a temporary status label is consistent with the log.

References:

- 21 CFR 211.182: Equipment cleaning and use log
- 21 CFR 211.105: Equipment identification

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2. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?

Yes. Generally, we believe that sampling in a typical drug manufacturing facility warehouse would not represent a risk to the container/closure or affect the integrity of the sample results. But whether the act of collecting a sample in the warehouse violates the CGMPs requirement that containers "be opened, sampled, and sealed in a manner designed to prevent contamination of their contents..." will depend on the purported quality characteristics of the material under sample and the warehouse environment. For container/closures purporting to be sterile or depyrogenated, sampling should be under conditions equivalent to the purported quality of the material: a warehouse environment would not suffice (see 211.94 and 211.113(b)). This is to preserve the fitness for use of the remaining container/closures as well as ensure sample integrity, if they are to be examined for microbial contamination. At a minimum, any sampling should be performed in a manner to limit exposure to the environment during and after the time samples are removed (i.e., wiping outside surfaces, limiting time that the original package is open, and properly resealing original package). Well-written and followed procedures are the critical elements.

Note that the CGMPs at 211.84 permit a manufacturer to release for use a shipment of containers/closures based on the supplier's certificate of analysis and a visual identification of the containers/closures. Once a supplier's reliability has been established by validation of their test results, a manufacturer could perform the visual examination entirely in the warehouse.

References:

- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.113(b): Control of microbiological contamination
- 21 CFR 211.122: Materials examination and usage criteria

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3. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm recently had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (non-sterile bulk powder) from a commercial source, and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

Acholeplasma laidlawii belongs to an order of mycoplasma. Mycoplasma contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shape from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, et al.). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of mycoplasma requires selective media (PPLO broth or agar).

Resolution:
For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for mycoplasma and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:
- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S., Eisenhuth, J., Howard, G., Brandwein, H. Application of membrane filtration for removal of diminutive bioburden organisms in pharmaceutical products and processes. PDA J. Pharm. Sci. Technol. 1999 Jul-Aug; 53(4): 186-201.
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- Murray, P., Baron, E., Pfaller, M., Tenover, F., Yolken, R. Manual of Clinical Microbiology ASM Press, Sixth Edition.

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[2]

4. Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?
Maybe. It depends on the cause and consistency of the reject rate. Many transdermal patch manufacturing processes produce more waste (i.e., lower yield from theoretical) than other pharmaceutical processes. This should not of itself be a concern. The waste is usually due to the cumulative effect of roll splicing, line start-ups and stoppages, roll-stock changes, and perhaps higher rates of in-process sampling. This is most pronounced for processes involving lamination of rolls of various component layers. Roll-stock defects detected during adhesive coating of the roll, for example, can often only be rejected from the roll after final fabrication/lamination of the entire patch, which contributes to the final process waste stream.
We expect that validated and well-controlled processes will achieve fairly consistent waste amounts batch-to-batch. Waste in excess of the normal operating rates may need (see 211.192) to be evaluated to determine cause (e.g., due to increase in sampling or higher than normal component defects... or both) and the consequences on product quality assessed. We've seen a small number of cases where unusually high intra-batch rejects/losses were due to excessive component quality variability and poorly developed processes.
References:
- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.103: Calculation of yield
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.192: Production record review

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5. **Do CGMPs require three successful process validation batches before a new active pharmaceutical ingredient (API) or a finished drug product is released for distribution?**
No. Neither the CGMP regulations nor FDA policy specifies a minimum number of batches to validate a manufacturing process. The current industry guidance on APIs (see ICH Q7A[3] for APIs) also does not specify a specific number of batches for process validation.

FDA recognizes that validating a manufacturing process, or a change to a process, cannot be reduced to so simplistic a formula as the completion of three successful full scale batches. The agency acknowledges that the idea of three validation batches has become prevalent, in part due to language in its own guidance documents. However, FDA is now clarifying current expectations on process validation. The 1987 *Guideline of General Principles of Process Validation* is currently being revised to address this issue. The emphasis for demonstrating validated processes is placed on the manufacturer's process design and development studies in addition to its demonstration of reproducibility at scale, a goal that has always been expected.

However, a minimum number of conformance (a.k.a. validation) batches necessary to validate the manufacturing processes is not specified. The manufacturer is expected to have a sound rationale for its choices in this regard. The agency encourages the use of science based approaches to process validation.

In March 2004, FDA revised the Compliance Policy Guide (CPG) (Sec. 490.100) on *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*[4]. The CPG describes the concept that, after having identified and establishing control of all critical sources of variability, conformance batches are prepared to demonstrate that under normal conditions and operating parameters, the process results in the production of acceptable product. Successful completion of the initial conformance batches would normally be expected before commercial distribution begins, but some possible exceptions are described in the CPG. For example, although the CPG does not specifically mention concurrent validation for an API in short supply, the agency would consider the use of concurrent validation when it is necessary to address a true short-supply situation, and if the concurrent validation study conforms to the conditions identified in the CPG (See paragraph 4. a-c).

The conditions outlined in the CPG include expanded testing for each batch intended to address a short-supply situation. Expanded testing, conducted according to an established validation protocol could provide added assurance that the batch meets all established and appropriate criteria before the API is used in the finished drug product. Additionally, confidence in the API manufacturing process may be gained by enhanced sampling (larger sample size representative of batch) and perhaps the testing of additional attributes. Validated analytical methods are needed for testing every batch, including validation batches. The agency would also expect the manufacturer to use a validation protocol which includes a review and final report after multiple batches are completed, even though the earlier batches may have been distributed or used in the finished drug product.

References:

- 21 CFR 211.100[5]: Written procedures; deviations
- 21 CFR 211.110[6]: Sampling and testing of in-process materials and drug products
- CPG 490.100[7] Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval.
- ICH Q7A[8] Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

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6. Is it generally acceptable from a cGMP perspective for a manufacturer of sterile drug products produced by aseptic processing to rely solely on ISO 14644-1 and ISO 14644-2 when qualifying their facility?

No. It is generally not acceptable from a current good manufacturing practice ("cGMP") perspective for a manufacturer of sterile drug products produced by aseptic processing to rely solely on *ISO 14644-1 Part 1: Classification of Air Cleanliness* ("14644-1") and *ISO 14644-2 Part 2: Specifications for Testing and Monitoring to Prove Compliance with ISO 14644-1* ("14644-2") when qualifying their facility. Rather, a manufacturer of sterile drug products produced by aseptic processing should use these ISO standards in combination with applicable FDA regulations, guidance and other relevant references to ensure a pharmaceutical facility is under an appropriate state of control. Consequently, appropriate measures augmenting ISO's recommendations (e.g., with microbiological data) would likely be expected for a firm to meet or exceed CGMP in a pharmaceutical facility.

Please understand that 14644-1 and 14644-2 have superseded *Federal Standard 209E, Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones* ("Federal Standard 209E"). In November 2001, the U.S. General Services Administration canceled Federal Standard 209E.

While not FDA regulations or FDA guidance, the Agency believes 14644-1 and 14644-2 are useful in facilitating the international harmonization of industrial air classification for non-viable particle cleanliness in multiple industries (e.g., computer, aerospace, pharmaceutical). As such, FDA adopted these particle cleanliness ratings in the 2004 guidance for industry *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*. However, due to the unique aspects of producing sterile drug products by aseptic processing (e.g., microbiological issues) an aseptic processing manufacturer should not rely solely on 14644-1 and 14644-2 when qualifying their facility.

References:

- U.S. Food and Drug Administration website[9].
- International Organization for Standardization website[10].
- ISO 14644-1 Part 1*: Classification of Air Cleanliness*.
- ISO 14644-2 Part 2: *Specifications for Testing and Monitoring to Prove Compliance with ISO 14644-1*.
- Guidance for Industry: *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*[11] (2004).
- Current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals[12] (Title 21, Code of Federal Regulations, Part 211).

Contact Information:
CDER/OC Office of Manufacturing and Product Quality: CGMP Subject Matter Contacts
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[13]

7. In 2004, FDA issued a guidance entitled "PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" that encouraged industry to modernize manufacturing through enhancements in process control. How can I implement PAT (Process Analytical Technology)?
The objective of FDA's PAT program is to facilitate adoption of PAT. In our 2004 guidance, we discuss FDA's collaborative approach to promote industry uptake of new and beneficial technologies that modernize manufacturing operations and enhance process control. FDA recognizes that firms should be encouraged to promptly implement new systems that improve assurance of quality and process efficiency. Accordingly, our approach to PAT implementation is risk based, and includes multiple options:

1. PAT can be implemented under the facility's own quality system. CGMP inspections by a PAT certified Investigator can precede or follow PAT implementation.

2. As another quality system implementation option, FDA invites manufacturers to request a preoperational review of their PAT manufacturing facility and process (see ORA Field Management Directive No.135, available at:
http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm096042.htm[14]).

3. A supplement (CBE, CBE-30 or PAS) can be submitted to the Agency prior to implementation, and, if necessary, an inspection can be performed by a PAT certified Investigator before implementation. This option should be used, for example, when an end product testing specification established in the application will be changed.

4. A comparability protocol can be submitted to the Agency outlining PAT research, validation and implementation strategies, and time lines. Following collaborative review of the general strategy outlined in the comparability protocol, the regulatory pathway can include implementation under the facility's own quality system, a pre-operational review, CGMP inspections (either before or after PAT implementation), a combination of these, or another flexible approach.
Manufacturers should evaluate and discuss with the Agency the most appropriate option for PAT implementation (see Questions 8 and 9, below).
Date Revised: 9/16/2013

8. How do I contact CDER with questions about Process Analytical Technology?
Manufacturers should contact the CGMP Subject Matter Contact listed for PAT (see below) and/or the appropriate review division in CDER to discuss applicability of PAT to CDER-regulated products.

Contact for Further information:
CDER/OC Office of Manufacturing and Product Quality: CGMP Subject Contacts:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[15]
Date Revised: 9/16/2013

9 . How do I contact CBER with questions about Process Analytical Technology?
Manufacturers should contact the appropriate review division in CBER to discuss applicability of PAT to CBER-regulated products.
Date Revised: 9/16/2013

10. What is the acceptable media fill frequency in relation to the number of shifts? Normally, media fills should be repeated twice per shift per line per year. Is the same frequency expected of a process conducted in an isolator?
A firm's justification for the frequency of media fills in relation to shifts should be risk-based, depending on the type of operations and the media fill study design. For *closed*, highly automated systems run on multiple shifts, a firm with a rigorous media fill design may be justified to conduct a lower number of total media fill runs. Such a program can be appropriate provided that it still assures performance of media fills for each aseptic processing line at least semi-annually. The 2004 guidance for industry on *Sterile Drug Products Produced by Aseptic Processing* states that "[A]ctivities and interventions representative of each shift, and shift changeover, should be incorporated into the design of the semi-annual qualification program." In addition, the EU Annex 1, *Manufacture of Sterile Medicinal Products,* states that "Normally, process simulation tests should be repeated twice a year per shift and process."
Certain modern manufacturing designs (isolators and "closed vial" filling) afford isolation of the aseptic process from microbiological contamination risks (e.g., operators and surrounding room environment) throughout processing. For such *closed* systemsï¼ , if the design of the processing equipment is robust and the extent of manual manipulation in the manufacturing process is minimized, a firm can consider this information in determining its media fill validation approach. For example, it is expected that a conventional aseptic processing line that operates on two shifts be evaluated twice per year per shift, and culminate in four media fills. However, for aseptic filling conducted in an isolator over two shifts, it may be justified to perform fewer than four media fill runs per year, while still evaluating the line semi-annually to assure a continued state of aseptic process control. This lower total number of media fill runs would be based on sound risk rationale and would be subject to re-evaluation if contamination issues (e.g., product non-sterility, media fill failure, any problematic environmental trends) occur.
ï¼ This does not apply to RABS (Restricted Access Barrier Systems)

References:
1. 21 CFR 211.63, 211.65, and 211.67 address, respectively, "Equipment design, size, and location," "Equipment construction," and "Equipment cleaning and maintenance."
2. 21 CFR 211.84(c)(3) states that "Sterile equipment and aseptic sampling techniques shall be used when necessary."
3. 21 CFR 211.113(b) states that "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and any sterilization process."
4. FDA Guidance for Industry *Sterile Drug Products Produced by Aseptic Processing* (2004)
5. EU Annex 1, *Manufacture of Sterile Medicinal Products* (2003)

Contact for further information:
CDER/OC Office of Manufacturing and Product Quality: CGMP Subject Matter Contacts
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[16]
Date: 12/3/2009

11. Why is the FDA concerned about human topical antiseptic drug products?
FDA has identified several incidents of objectionable microbial contamination of topical antiseptic drug products (e.g., alcohol pads or swabs used to prepare the skin prior to an injection). Microbial contamination may be caused by substandard manufacturing practices and the agency is concerned about safety risks, such as from infection, associated with this contamination.
Date: 12/21/2011

12. What specific current good manufacturing practice (CGMP) regulations might be useful to manufacturers of topical antiseptic drug products?

Section 501(a) (2) (B) of the Federal Food, Drug, and Cosmetic Act requires all drugs to be manufactured in conformance with CGMP. The CGMP regulations in 21 CFR Parts 210 and 211 for finished pharmaceuticals apply equally to over-the-counter (OTC) and prescription (Rx) drug products.[1]

The CGMP regulations provide the minimum legal requirements for conducting reliable operations.[2]

Some relevant CGMP regulations, with a brief description, are given below:

Manufacturing Design and Control – CGMP Requirements and Recommended Guidance for Manufacturers

- **Design manufacturing facilities (21 CFR 211.42) and processes (see below) to prevent microbial contamination** :
    - **For non-sterile drug products –** establish control procedures to monitor output and validate processes to include bioburden testing (21 CFR 211.110 (a) (6)), 211.111) and establish and follow written procedures designed to prevent the introduction of objectionable microorganisms (211.113(a)).
    - **For sterile drug products**[3] **-** establish and follow written procedures designed to prevent microbial contamination (211.113(b)).
- **Conduct process validation studies**[4] to ensure acceptable output (e.g., with topical antiseptics, particularly product microbiological quality) (211.110(a). Implement and validate needed changes when deficient manufacturing steps, equipment, or raw materials may be adversely affecting process control.
- **Ensure that operating procedures** will consistently produce a quality product (211.100). Review and evaluate any deviations or discrepancies documented during manufacturing and testing to determine if a product lacks assurance of sterility (for sterile antiseptics) or may be contaminated with objectionable microorganisms (for non-sterile antiseptics). Document and implement any corrective actions deriving from the evaluation (211.192).
- **Ensure that all equipment,** including water systems, is clean, sanitary, operates consistently, and is suitable for its intended use (211.63, 211.65, 211.67, and 211.68).
- **Establish and follow in-process bioburden testing** procedures to help monitor in-process control, including understanding the bioburden challenge to a final sterilization process (211.110(a)(6)).

Components, In-process Materials, Container/Closure and Finished Product Testing - CGMP Requirements for Manufacturers

- **Establish appropriate written testing standards/specifications and sampling plans** for components, in-process materials, containers/closures, and finished products (211.160).
- **Establish procedures for testing** and approval or rejection of components, drug product containers, and closures (211.80). Test each lot of a drug product component and container/closure, including those that may be vulnerable to microbiological contamination (211.84)(d)(4-5), including applicator material (e.g., cotton pads) and water used as an ingredient in the product.
- **Conduct appropriate microbiological tests** before a batch disposition decision is made. Test each batch of a sterile product for sterility (211.167). Test each batch of a non-sterile product to ensure absence of objectionable microorganisms (211.165(b)).

Management[5,6]

The CGMPs require that the management of a manufacturing facility maintains a well-functioning quality system, which includes an effective quality unit vested with the responsibilities and authorities required under CGMP (211.22).

Date: 12/21/2011

13. How can manufacturers assess and address the risk of microbiological contamination of topical antiseptics?

Since there are potentially many different root causes of product contamination by microorganisms, it is imperative that manufacturers perform a manufacturing risk assessment to understand manufacturing failure modes and implement prevention measures.

In addition, any risk assessment approach should be informed by an understanding of the microbial contamination vulnerabilities of the concerned product. For example, some product considerations for manufacturers include, but are not limited to:

- Determine the types of microbes that might survive or thrive in your products. Provide additional controls and testing based on the output of the risk assessment to ensure product quality.
- Ensure that your microbial recovery methods are capable of detecting the types of microbes that may affect product quality.
- Evaluate risk of contamination from components, including during component production, storage, or due to the intrinsic risk from source materials. Consider all possible sources of microbial contamination, including the following:
    - Components or products stored in open bins can be at risk for contamination by spore-forming microbes, such as *Bacillus cereus,*[7,8] as well as by *Serratia* species and other worrisome airborne microbes. Manufacturing areas exposed to windy or poor HVAC conditions may increase the potential for this environmental contamination risk.
    - Some materials, especially from natural sources, may have high or objectionable intrinsic bioburden.
    - Water quality can pose a significant risk, as most antiseptics include water as a key ingredient. Contaminated purified water has been the root cause of multiple recalls of antiseptics, including instances of antiseptics contaminated with *Burkholderia* (previously *Pseudomonas*) *cepacia*, an opportunistic pathogen.
    - Unsanitary practices or sources
    - When manufacturing in areas with high humidity, molds can be of special concern.

References:

1. Compliance Policy Guide Sec. 450.100 *CGMP Enforcement Policy - OTC vs. Rx Drugs* (http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074387.htm[17])
2. Code of Federal Regulations (CFR), Title 21, Part 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS[18] (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=211)[19]
3. FDA Guidance for Industry on *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf[20])
4. FDA Guidance for Industry on *Process Validation* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf[21]
5. FDA Guidance for Industry on *ICH Q9 – Quality Risk Management* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf[22])
6. FDA Guidance for Industry on *ICH Q10 – Pharmaceutical Quality System* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf[23]
7. FDA News Release - *FDA reminds health care professionals about safe use of non-sterile alcohol prep pads* (2/1/2011) (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm241750.htm[24])
8. CDC Morbidity and Mortality Weekly Report (MMWR) - *Contamination of Alcohol Prep Pads with* Bacillus cereus *Group and* Bacillus *Species* (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6011a5.htm[25])

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Date: 12/21/2011

14. Can Leptospira species penetrate sterilizing-grade filters? If so, what should manufacturers keep in mind in their ongoing lifecycle risk management efforts to assure microbial control?

FDA is aware of a recent report [ref. 2, below] of *Leptospira licerasiae* contamination in cell cultures. There is no indication that this bacterium ultimately contaminated either the finished drug substance or drug product. This bacterium has been found to pass through 0.1 µm pore size rated sterilizing-grade membrane filters. While this specific species was the identified contaminant in this case, other *Leptospira* species also are capable of passing through 0.1 µm pore size rated filters [ref. 3, below]. Compendial microbiological test methods typically used in association with upstream biotechnology and pharmaceutical production are not capable of detecting this type of bacteria. Whether this apparently rare contamination risk may be more widespread is unknown, and we are sharing this information so that manufacturers can consider whether this hazard may be relevant to their operations.

Leptospira are Gram-negative aerobic spirochetes that are flexible, highly motile, and spiral-shaped with internal flagella. The bacteria measure 1µm in diameter and 10-20 µm in length. *Leptospira* are obligate aerobes that use oxygen as the electron receptor and long-chain fatty acids as a major source of energy. While some of the *Leptospira* are harmless fresh-water saprophytes, other species are pathogenic and can cause leptosporosis, a significant disease in humans and animals [ref. 4-6, below).

Based on current information, *Leptospira* contamination does not appear to occur frequently, and purification steps that follow cell culture in a typical biotechnology operation would be expected to prevent carryover to the finished drug substance. Testing of bulk drug substances produced in the reported cases did not detect *Leptospira* spp., and no evidence of deleterious effects on in-process product were observed in the known case study. However, we are providing this communication to alert manufacturers that these types of bacteria can potentially:

- penetrate sterilizing-grade membrane filters
- be present in the manufacturing site environment
- impact in-process production (e.g., production yields, impurity levels, process performance)
- go undetected due to the limitations of current compendial bioburden tests in detecting this microbial genus

As a general principle, manufacturers should use sound risk management and be aware of unusual microbiota reported in the literature that may impact their manufacturing processes (e.g., cell culture biotechnology, conventional sterile drug manufacturing).
Manufacturers should assess their operations, be aware of potential risks, and apply appropriate risk management based on an understanding of possible or emerging contamination risks [ref. 1 (see Section 18.3)]. As appropriate, preventive measures should be implemented during the product and process lifecycle.

To illustrate, if leptospiral contamination is considered possible, or has occurred, risk mitigation procedures and practices for this microorganism should include at least the following:

1. Review of available published articles from the scientific literature and technical reports by related industry organizations that may provide further understanding on how to mitigate this contamination hazard.

2. Use of molecular or nonconventional microbial monitoring methods at appropriate intervals to detect microbial flora that may exist in processing steps or in the immediate environment, but are not readily detected by current routine methods. Such expanded testing should be used to modify the strategy (e.g., timing, frequency, types of tests) of detection and control in the event of newly-identified risk posed by the viable, but not easily cultured, microorganism.

Examples include:

a) Use of specialized media such as EMJH [ref. 7, below] or other suitable media [ref. 8, below]. It should be noted that these bacteria typically grow very slowly.

b) Use of validated PCR methods (e.g., as an investigative tool) for rapid screening and detection of spirochete bacteria.
c) Consideration of special stain techniques or other means to identify the presence of *Leptospira* [ref. 9, below].

3. Use of conventional approaches. Firms should continue to properly employ basic, standard microbiology laboratory practices to detect contamination. For example, the laboratory should ensure that microscopic examination is part of its routine cell culture process control program, as it provides an important means of detecting microbial contaminants that may not readily grow on conventional media.

4. Implementing such quality risk-management measures into the initial design (i.e., preventive actions), and promptly implementing an appropriate corrective action plan in response to newly-identified contamination sources, throughout the lifecycle of the product.

References:

1. Guidance for Industry ICH Q7 – Good Manufacturing Practices for Active Pharmaceutical Ingredients. 2001
2. Chen, J.; Bergenvin, J.; Kiss, R.; Walker, G.; Battistoni, T.; Lufburrow, P.; Lam, H.; Vinther, A. Case study – A novel bacterial contamination in cell culture production – *Leptospira licerasiae*. PDA J. Pharm. Sci. Technol. November-December 2012.

3. WHO – Leptospira. Faine, S. (Ed.). Guidelines for the Control of Leptospirosis. World Health Organization, Geneva. 1982.

4. Ricaldi, JN; Fouts, DE; Selengut, JD; Harkins, DM; Patra, KP; et al. Whole Genome Analysis of *Leptospira licerasiae* Provides Insight into Leptospiral Evolution and Pathogenicity. PLoS Negl Trop Dis 2012 October, 6(10): e1853.

5. Matthias, MA; Ricaldi, JN; Cespedes, M; Diaz, MM; Galloway, RL; et al., Human Leptospirosis Caused by a New Antigenically Unique Leptopspira Associated with a *Rattus* Species Reservoir in the Peruvian Amazon. PLoS Negl Trop Dis 2008 (2(4): e213.

6. Bharti, AR; Nally, JE; Ricaldi, JN; Matthias, MA; Diaz, MM; et al. Leptospirosis: A zoonotic disease of global importance. Lancet Infect Dis. 2003:3:757-771.

7. Ellinghausen, H. C. and McCullough W. G. Nutrition of Leptospira Pomona and growth of 13 other serotypes: fractionation of oleic albumin complex (OAC) and a medium of bovine albumin and polysorbate 80. Am. J. Vet. 1965, 26: pp 45-51.

8. Rule Pl, Alexander AD. J. Clin Microbiol, 1986, 23(3):500-504.

9. Frank S. Kohn. J. Amer. Med Technology, July-Aug, 1973.

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Date: 12/20/2012

15. FDA recently announced the withdrawal of its draft guidance for industry on *Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment.* What were the Agency's major concerns with this guidance?

FDA's major concern was that Sections V and VII of the withdrawn draft guidance no longer represented the Agency's current thinking, as explained below.

Section V (Exhibit/Validation Batch Powder Mix Homogeneity) recommended that at least three replicate samples be taken from at least ten locations in the powder blender, but that only one of the three replicates be evaluated to assess powder blend uniformity. The Agency currently recommends that *all* replicate samples taken from various locations in the blender be evaluated to perform a statistically valid analysis. This analysis can demonstrate that variability attributable to sample location is not significant and that the powder blend is homogenous. Statistical tools are available to ascertain both the number of replicates and the number of sampling locations across the blender that should be analyzed to conduct a valid analysis.

Section VII (Routine Manufacturing Batch Testing Methods) acceptance criteria designated to the Standard Criteria Method and the Marginal Criteria Method were based upon the limits published in the United States Pharmacopeia (USP) General Chapter <905> *Uniformity of Dosage Units*. However, the procedures and acceptance criteria in USP <905> are not a statistical sampling plan and so the results of the procedures should not be extrapolated to larger populations. Therefore, because the procedure and acceptance criteria prescribed in section VII provided only limited statistical assurance that batches of drug products met appropriate specifications and statistical quality control criteria, FDA no longer supports their use for batch release. Currently, there are several standard statistical practices (see references) that, if used correctly, can help to ensure compliance with the current good manufacturing practice (CGMP) regulations, including 21 CFR 211.110 *Sampling and testing of in-process materials and drug products*, 21 CFR 211.160 *General Requirements* [Subpart I, Laboratory Controls],and 21 CFR 211.165 *Testing and release* [of the finished drug product] *for distribution*.[1]

References:

1. FDA CGMP regulations: 21 CFR 211.110; 211.160; 211.165. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=211[28]

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Date: 8/6/2013

16. Why is FDA concerned about proper sampling of powder blends?

The CGMPs require that all sampling plans be scientifically sound and representative of the batch under test (see 211.160(b)). Further, in-process testing of powder blends to demonstrate adequacy of mixing is a CGMP requirement (21 CFR 211.110). Between- and within-location variability in the powder blend is a critical component of finished product quality and therefore should be evaluated. Drug product manufacturers need to use a science- and risk-based sampling approach to assure (a) adequacy of blend mixing and (b) that sampling of the blend is done at a suitable juncture in the manufacturing process. The sampling and analysis needs to ensure that no differences exist between locations in a blend that could adversely affect finished product quality. Traditional sampling using a powder-thief may have drawbacks and limitations, such as causing disturbance to the powder bed, powder segregation, or other sampling errors. However, powder-thief sampling remains widely used and provides reliable results in many cases. The Agency encourages firms to adopt more innovative approaches to ensuring adequacy of mixing (see, e.g., the PAT guidance). If a manufacturer proposes to use a thief sampling method, the reliability of the method should be evaluated as part of analytical methods development.

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Date: 8/6/2013

17. What are some recommended innovative approaches to ensuring adequacy of mixing of powder blends?

Innovative approaches to consider include, but are not limited to: (a) Process Analytical Technology (PAT) real-time monitoring and feedforward controlling of the powder blending process[1] and (b) use of Statistical Process Control (SPC) tools to monitor the powder blending process and to maintain a state of control.

When a manufacturer decides to implement PAT or other process-monitoring and control techniques for powder blend homogeneity assessment, its decision should be supported with appropriate data and rationale using a science- and risk-based approach. For example, the effective sample size of powder examined by PAT probes has to be estimated, such that the scale of scrutiny of the PAT powder blending monitoring can be justified.[2] The number of PAT probes and their locations also have to be justified. If a scientifically sound PAT monitoring and control strategy is established, it can facilitate the assessment of: (a) variability across locations within the powder bed,[3] (b) the variability over time of one location, and (c) the potential correlation between the powder sample and the unit dosage form.

References:

1. FDA Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. September 2004. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070305.pdf[31]
2. Wu, H.; Tawakkul, M.; White, M.; Khan, M. Quality-by-Design (QbD): An Integrated Multivariate Approach for the Component Quantification in Powder Blends. International Journal of Pharmaceutics, vol. 372 issue 1-2 May 8, 2009. p. 39-48.
3. El-Hagrasy, A.; Morris, H.; D'Amico, F; et al. Near-infrared Spectroscopy and Imaging for the Monitoring of Powder Blend Homogeneity.Journal of Pharmaceutical Sciences, vol. 90 issue 9, September 2001. p. 1298 – 1307.

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Date: 8/6/2013

18. What are the Agency's recommendations regarding in-process stratified sampling of finished dosage units?

Stratified sampling is recommended to be used when the population is known to have several subdivisions (i.e., locations) which may give different results for the quality characteristics measured. The Agency expects that no significant differences should exist between in-process locations that could affect finished product quality. Between- and within- location variability is a critical component of finished product quality and therefore should be evaluated. Please refer to ASTM E2709[6] and ASTM E2810[7] for further guidance on establishing acceptance criteria for a stratified sampling plan.

References

1. ASTM E2709: Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure.
2. ASTM E2810: Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units.

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Date: 8/6/2013

1. What is a recall?

Recalls are actions taken by a firm to remove from the market any product that is in violation of laws administered by the FDA. Recalls of a drug may be conducted on a firm's own initiative or by FDA request.

A recall is an alternative to a Food and Drug Administration-initiated court action for removing or correcting violative, distributed products [see 21 CFR 7.40(a)]. Under the FDA's Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals, manufacturers must establish and follow written procedures to facilitate the recall of defective products from the market [see 21 CFR 211.150(b)].
Date:8/9/2010

2. Can FDA mandate a recall of human drugs?

FDA does not have authority to mandate a recall of a human drug, but it can take more authoritative legal actions against manufacturers that persist in marketing a defective product, such as seizure and injunction.

A recall is a firm's removal or correction of marketed product that FDA considers to be in violation of the laws it administers, and against which FDA would otherwise initiate more powerful legal action [see 21 CFR 7.40(c); also see FDA Investigations Operations Manual, Chapter 7- *Recalls*, section 7.1.1.1, available at: http://www.fda.gov/ICECI/Inspections/IOM/ucm122545.htm[1]]. Thus, manufacturers typically initiate voluntary recalls when a defect is found within a marketed batch to avoid a potentially more significant enforcement action by FDA.
Date: 8/9/2010

3. Are OTC drugs subject to the same recall provisions as prescription drugs?

Yes, FDA's recall expectations for drugs apply equally to OTC and prescription. The CGMP regulations also apply to all drug products, whether OTC or prescription (see Compliance Policy Guide 450.100, CGMP Enforcement Policy - OTC vs. Rx Drugs, available at: http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074387.htm[2]. Date:8/9/2010

4. Do manufacturers of OTC products have to report quality defects?

Manufacturers of OTC drugs approved in a new drug application are required to report quality defects (see 21 CFR 314.81). Manufacturers or distributors of OTC monograph drugs (these are drugs that are not approved in a product-specific application), are not required to submit quality defect reports. However, the manufacturer, packer, or distributor whose name appears on the label of an OTC drug without an approved application (i.e., OTC monograph drugs) must submit to FDA any report received of a serious adverse event associated with such drug when used in the United States (see section 760 of the Act). Thus, if a serious adverse event is caused by a quality defect, FDA will receive a report about the event (see also Guidance for Industry, "Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed without an Approved Application[3]" Date: 8/9/2010

5. Does FDA expect firms to investigate both released and rejected lots for potential recalls?

Yes. Under 21 CFR 211.180(e), manufacturers must establish and follow written procedures for periodically reviewing complaints, recalls, returned or salvaged drug products, and investigations of product discrepancies. Firms must also review an appropriate number of batches, whether approved or rejected, and, where applicable, records associated with the batches, to ensure that all potentially affected product is thoroughly investigated and appropriate follow-up action is taken [21 CFR 211.192].
Date: 8/9/2010

6. What happens if a firm does not voluntarily recall a defective product?

FDA expects that a firm will voluntarily recall a drug that is defective or flawed if it could be hazardous to health. Seizure, multiple seizure, or other court action is indicated when a firm refuses to undertake a recall requested by the FDA, or where the agency has reason to believe that a recall would not be effective, determines that a recall is ineffective, or discovers that a violation is continuing [21 CFR 7.40(c)].

References:

- Code of Federal Regulations (CFR) Title 21 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm[4]

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Date: 8/9/2010

1. Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?
The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of a product manufactured between two successive verifications would be affected should the check of the

auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified--a common frequency is once a year--using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries.

References:

- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.160(b)(4): General requirements (Lab Controls)
- USP Chapter <41> Weights and Balances
- See also: ASTM standard E 617: Standard Specification for Laboratory Weights and Precision Mass Standards (this standard is incorporated into the USP by reference; other widely recognized standards may be acceptable)

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2. Do CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability-indicating?

No. Drug product stress testing (forced degradation) may not be necessary when the routes of degradation and the suitability of the analytical procedures can be determined through use of the following:

- data from stress testing of drug substance
- reference materials for process impurities and degradants
- data from accelerated and long-term studies on drug substance
- data from accelerated and long-term studies on drug product

Additional supportive information on the specificity of the analytical methods and on degradation pathways of the drug substance may be available from literature sources.

Section 211.165(e) of the CGMP regulations states that the accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented. Further, section 211.166(a)(3) requires that stability test methods be reliable, meaningful, and specific, which means that the content of active ingredient, degradation products, and other components of interest in a drug product can be accurately measured without interference, often called "stability-indicating."

The CGMP regulations do not specify what techniques or tests are to be used to ensure that one's test methods are stability-indicating. However, evaluating the specificity of the test methods during forced degradation studies (i.e., exposing drug to extremes of pH, temperature, oxygen, etc.) of drug substance and drug product often is necessary to ensure that stability test methods are stability-indicating. But in certain circumstances conducting a forced degradation study of just the drug substance may be sufficient to evaluate the stability-indicating properties of a test method.

Generally, in determining whether it is necessary to conduct forced degradation studies of the drug product, the specificity of the test method should be evaluated for its ability to assay drug substance, degradants, and impurities, in the presence of each other, without interference. The evaluation also should provide assurance that there is not a potential for interaction between drug substance, degradants, impurities, excipients, and container-closure system during the course of the shelf-life of the finished drug product.

Last, the rationale for any decision made concerning the extent of the forced degradation studies conducted as well as the rationale for concluding that a test method is stability-indicating should be fully documented.

References:

- 21 CFR 211.137: Expiration dating
- 21 CFR 211.165(e): Testing and release for distribution
- 21 CFR 211.166(a)(3): Stability testing
- Compliance Policy Guide, Section 480.100 (7132a.04), *Requirements for Expiration Dating and Stability Testing*

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3. When performing the USP <788> Particulate Matter in Injections test for a Large Volume Parenteral (LVP), is it acceptable to take the average among the units tested to determine if the batch meets its specification for this attribute?

No. It is not acceptable to take the average among the LVP units tested in each batch/lot when following this method because the purpose of this method is to measure and limit intra-batch variability.

"Particulate matter" refers to small, sub-visible particles. USP <788> provides two tests for detecting such particulates--light obscuration and microscopic assay. Both are generally accepted for use in testing LVPs and small volume parenterals (SVP) for the determination of sub-visible particulate matter. Normally, samples are first tested by the light obscuration method; if the sample fails the specified limits, the microscopic assay method can then be used. However, the microscopic method can be the sole test if there is a documented technical reason or interference from the product under test that would make the light obscuration method unsuitable or the results invalid.

Confusion about when averaging data is and is not acceptable is probably due to the sample preparation method for the light obscuration test (USP <788>). At least 2, 5-mL aliquots from each sampled unit or the pooled sample (see below) are to be used in the particulate count determination, and the results from these aliquots are to be averaged for comparison with the specification. Note that the average is of the results from examining each aliquot and not between units. (The results of the first aliquot examined by light obscuration are to be discarded, and the subsequent aliquots--2 or more--are retained.) Pooling units prior to analysis is permitted only if the volume in each unit is less than 25 mL, in which case 10 or more units may be pooled. If the volume in the SVP or LVP is 25 mL or more per unit, single units are to be examined by this method (USP <788>).

Results **among** the test units cannot be averaged because particulate matter is assumed to be non-uniformly dispersed throughout the lot. The intent of assessing results from each individual unit is to ensure adequate representation of the lot and to detect potential variation within a lot.

As to the number of individual units to be tested for LVP and SVP units having a volume of 25mL or more, the USP states that the number of units tested depends on "statistically sound sampling plans," and "sampling plans should be based on consideration of product volume, numbers of particles historically found to be present in comparison to limits, particle size distribution of particles present, and variability of particle counts between units." The USP also suggests that the total number of units tested for any given batch may be less than 10 units (for LVP and pooled SVPs) with proper justification. This is consistent with the CGMP requirement for statistical sampling plans (see 211.165).

Reference:

- 21 CFR 211.160: General requirements (laboratory controls)
- 21 CFR 211.165(c),(d): Testing and release for distribution
- USP <788> Particulate Matter in Injections
- For information only: Draft Guidance: Guidance for Industry: Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[2]

4. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?

Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues.

We think TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. But in order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is not a trivial exercise because we know that some organic compounds cannot be reliably detected using TOC.

TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit 'background' carbon (i.e., carbon from

sources other than the contaminant being removed) as much as possible. The established limit, or the amount of residue detected for comparison to the specification, should correct for the target material's composition of carbon. As for any cleaning method, recovery studies are necessary (211.160(b)). If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantitation.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance.
- 21 CFR 211.160(b): General requirements (Laboratory Controls)
- USP <643> Total Organic Carbon
- *Guide to Inspections of Cleaning Validation, 1993*

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5. Would a paramagnetic or laser oxygen analyzer be able to detect all possible contaminants or impurities in a medical gas?

No. Although, paramagnetic and laser oxygen analyzers are very accurate and reliable when calibrated correctly, these types of analyzers can only detect the identification and strength of oxygen. They are unable to detect contaminants or impurities that may be present, such as hydrocarbons or arsenic compounds. According to the USP General Notices, Foreign Substances and Impurities section, "it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present." The USP monograph test for oxygen does not include an impurity screen and other analyzers may need to be used. For example, assays for hydrocarbon impurities are routinely conducted during the oxygen manufacturing process even though the USP does not list hydrocarbons as an impurity. Also, alternative methods may be needed to test high-pressure cylinders for cleaning solution residues.

References:

- 21 CFR 211.160: General requirements (Laboratory Controls)
- 21 CFR 211.165: Testing and release for distribution
- United States Pharmacopoeia

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[3]

6. Can up to twelve month expiration-dating be assigned to oral solid and liquid dosage forms repackaged into unit-dose containers based on guidance in the May 2005 draft revision of Compliance Policy Guide, Section 480.200 (7132b.11), "Expiration Dating of Unit Dose Repackaged Drugs"?

No. In May 2005, a Notice of Availability of the draft revision of FDA's Compliance Policy Guide Section 480.200 (CPG 7132b.11), "Expiration Dating of Unit-Dose Repackaged Drugs," was announced in the Federal Register. The draft CPG specifies certain conditions when it may be possible to assign up to twelve month expiration-dating to non-sterile solid and liquid oral drug products repackaged into unit-dose containers without conducting new stability studies to support the length of expiration-dating on the repackaged products. The draft CPG was prompted by United States Pharmacopeia (USP) standards for assigning up to a twelve month "beyond-use date" to non-sterile solid and liquid oral dosage forms dispensed in unit-dose containers. ("Beyond-use date" is USP's pharmacy dispensing term for specifying a date on a prescription container beyond which a patient should not use the product.) If finalized, FDA's draft CPG would replace the current version of CPG Section 480.200. The current version of CPG Section 480.200 was finalized in March 1995 and provides conditions under which FDA will not initiate action for assigning up to six month expiration dating for drug products repackaged into unit-dose containers without conducting new stability studies.

FDA is conducting a stability study of certain commercially repackaged drugs to determine the suitability of the draft revision of CPG Section 480.200. Until the stability study is complete and FDA

evaluates all comments submitted to the public docket in response to the May 2005 Federal Register Notice of Availability, the agency does not intend to make a final decision on the draft revision of CPG Section 480.200. Consequently, at this time and until FDA announces a final decision on the draft CPG, the current CPG Section.480.200, which was finalized in March 1995, is in effect.

References:

- Compliance Policy Guide section 480.200 (CPG 7132b.11)
- Federal Register: May 31, 2005 (Volume 70, Number 103) pages 30953-30954
- CFR 211.137 and 211.166

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7. Is it ever appropriate to use an unvalidated method to test a drug component or product?

The CGMP regulations require the use of validated methods when performing routine testing of raw material, in process material, and finished product (21 CFR 211.160, 211.165(e), and 211.194) for manufacturing finished drug products. Method validation studies establish proof that a method is suitable for its intended purpose. The purpose is generally to measure a particular material's conformance to an established specification (see FDA Guidance for Industry, ICH Q2 (R1)).

FDA recognizes, however, that test methods developed based on scientifically sound principles (e.g., sufficient accuracy and precision) but which are not fully validated may be suitable for use in certain instances during an investigation of a potential quality problem or defect. For example, investigation of an atypical impurity or possible contaminant of a drug product or any of its components (e.g., OSCS in heparin) may indicate the need for additional methods beyond routine quality control tests. Such testing may be critical to promptly and adequately evaluate the problem and protect public health. Full evaluation of a method's robustness and reproducibility may not initially be feasible or appropriate when conducting tests in certain investigations.

When a company, for whatever reason, tests drug components or products using an unvalidated method, it is important to recognize the possibility of greater uncertainty in the test results derived from these unvalidated test methods, as compared to validated test methods. Nevertheless, the resulting data may yield important information indicating the need for prompt corrective action. Accordingly, we expect all such test results on drug components or products to be reviewed to assess the need for follow-up action (211.192 and 211.180(e)).

References:

- 21 CFR Part 210 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210&showFR=1[4]
- 21 CFR Part 211 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211[5]
- ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129098.pdf[6]
- Guidance for Industry, ICH Q2 (R1), *Validation of Analytical Procedures: Text and Methodology* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm[7]

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Date: 1/6/2011

8. Did the FDA withdraw the 1987 Guideline on *Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human Parenteral Drugs, Biological Products, and Medical Devices*?
Yes, the FDA withdrew the 1987 Guideline. The 1987 Guideline is considered obsolete and does not reflect the Agency's current thinking on the topic.
Date: 7/12/2011

9. Where can drug manufacturers find information regarding endotoxin testing?
The United States Pharmacopeia (USP) publishes endotoxin testing recommendations and acceptance criteria in General Chapter <85> *Bacterial Endotoxins Test*. USP <85> provides methods and calculation of limits for drugs. FDA may, as needed, provide additional guidance to clarify the Agency's current thinking on use of LAL, recombinant LAL, and other endotoxin testing methods.

References:

- United States Pharmacopeia, General Chapter <85> *Bacterial Endotoxins Test*. United States Pharmacopeial Convention: Rockville, MD.

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[8]
Date 7/12/2011

1. Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?
Maybe. It depends on the cause and consistency of the reject rate. Many transdermal patch manufacturing processes produce more waste (i.e., lower yield from theoretical) than other pharmaceutical processes. This should not of itself be a concern. The waste is usually due to the cumulative effect of roll splicing, line start-ups and stoppages, roll-stock changes, and perhaps higher rates of in-process sampling. This is most pronounced for processes involving lamination of rolls of various component layers. Roll-stock defects detected during adhesive coating of the roll, for example, can often only be rejected from the roll after final fabrication/lamination of the entire patch, which contributes to the final process waste stream.
We expect that validated and well-controlled processes will achieve fairly consistent waste amounts batch-to-batch. Waste in excess of the normal operating rates may need (see 211.192) to be evaluated to determine cause (e.g., due to increase in sampling or higher than normal component defects... or both) and the consequences on product quality assessed. We've seen a small number of cases where unusually high intra-batch rejects/losses were due to excessive component quality variability and poorly developed processes.

References:
- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.103: Calculation of yield
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.192: Production record review

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2. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?

The CGMP regulations (21 CFR 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question were from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified.

However, any documentation of corrective action as a result of such an audit would have to be retained (see 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see 211.192).

In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (211.198), vendor qualification (211.84), periodic review of records and data (211.180(e)), and a failure investigation (211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see 211.180).

References:

- Preamble to the *Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding* regulations; Federal Register, September 29, 1978 (vol. 43, no. 190), page 45015, paragraph 4: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM206779.pdf[1]
- 21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
- 21 CFR 211.180: General requirements
- 21 CFR 211.192: Production record review
- 21 CFR 211.198: Complaint files
- Compliance Policy Guide Sec. 130-300, (7151.02) http://www.fda.gov/ora/compliance_ref/cpg/cpggenl/cpg130-300.html[2]

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3. How do the Part 11 regulations and "predicate rule requirements" (in 21 CFR Part 211) apply to the electronic records created by computerized laboratory systems and the associated printed chromatograms that are used in drug manufacturing and testing?

Some in industry misinterpret the following text from "The Guidance for Industry – Part 11, Electronic Records; Electronic Signatures – Scope and Application" (Part 11 Guidance; lines 164 to 171) to mean that in all cases paper printouts of electronic records satisfy predicate rule requirements in 21 CFR Part 211.

"Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be 'using electronic records in lieu of paper records' under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11."

The Part 11 Guidance also states (in lines 150-152), that:

"…persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules."

For High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) systems (and other computerized systems involving user inputs, outputs, audit trials, etc.), the predicate rules, such as 21 CFR 211.68 and 21 CFR 211.180(d), require the electronic records themselves to be retained and maintained in accordance with those regulations. 21 CFR 211.180(d) requires records to be

retained "either as original records or true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records." 21 CFR 211.68 further states that: "[H]ard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained" (emphasis added). The printed paper copy of the chromatogram would not be considered a "true copy" of the entire electronic raw data used to create that chromatogram, as required by 21 CFR 211.180(d). The printed chromatogram would also not be considered an "exact and complete" copy of the electronic raw data used to create the chromatogram, as required by 21 CFR 211.68. The chromatogram does not generally include, for example, the injection sequence, instrument method, integration method, or the audit trail, of which all were used to create the chromatogram or are associated with its validity. Therefore, the printed chromatograms used in drug manufacturing and testing do not satisfy the predicate rule requirements in 21 CFR Part 211. The electronic records created by the computerized laboratory systems must be maintained under these requirements.
We recognize that there are cases where it could be appropriate for the printed chromatogram to be used within laboratories for the review of test results. Similarly, it also may be acceptable to provide the printed chromatogram during a regulatory inspection or for application review purposes. However, the electronic record must be maintained and readily available for review by, for example, QC/QA personnel or the FDA investigator.

In summary, decisions on how to maintain records for computerized systems should be based on predicate rule requirements. We recommend that these decisions be supported by a sound risk assessment.

References:
• Guidance for Industry – Part 11, Electronic Records; Electronic Signatures – Scope and Application (http://www.fda.gov/cder/guidance/5667fnl.pdf)
• 21 CFR 211.180(d): General Requirements
• 21 CFR 211.68: Automatic, Mechanical, and Electronic Equipment

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[3]
Date: 8/3/2010

4. How does the FDA interpret the regulations (21 CFR Part 211) regarding the establishment of expiry dating for chemicals, reagents, solutions, and solvents?

Laboratory "reagents, and standard solutions," as referenced in the CGMP regulations at 211.194, includes laboratory chemicals such as solvents (including mobile phases), dry chemicals (salts, primary standards, etc.), and solutions (buffers, acids/bases, quantitative analytical preparations, etc.), whether purchased or prepared in-house. Laboratory reagents and solutions are used in analytical tests of components, in-process materials, and finished products.

If the purchased laboratory reagent or solution includes a manufacturer's suggested "use by" or expiry date, that date should be followed. For purchased laboratory reagents and solutions without a "use by" or expiry date, FDA would expect that an assessment be conducted (literature review may be acceptable) of that specific chemical's or chemical family's stability and that an appropriate "use by" or expiry date be determined.

For in-house prepared solutions, such as mobile phases or other non-quantitative solutions, FDA would expect that an assessment be conducted (again, literature review may be acceptable) to determine an appropriate expiry period. However, for in-house prepared solutions used for quantitative analysis, such as sample or standard solutions used in assay or impurity testing or titration solutions, FDA requires that formal stability studies be conducted to determine an appropriate expiry. As mentioned in *Guidance for Industry: Q2B Validation of Analytical Procedures: Methodology,* the stability of analytical solutions is a typical method variation that should be evaluated during robustness testing during method validation. Method validation is a CGMP requirement at 211.160(b).

The determined "use by" or expiry dates should be documented within a procedure and followed. Procedures for any in-house prepared laboratory solution should include the determined stability timeframe, and should instruct that these solutions be labeled with the appropriately determined "use by" or expiration date upon preparation and discarded upon expiration.

These principles would also apply to API manufacturing and testing sites. The use of "reagents and solutions" and "use by" dates are found throughout *Guidance for Industry: Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

References:

- FDA Current Good Manufacturing Practice for Finished Pharmaceuticals regulations at 21 CFR 211.160 and 211.194
  - 211.160 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.160[4]
  - 211.194 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.194[5]
- FDA Guidance for Industry
  - ICH Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Section 11, Laboratory Controls http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf[6]
  - ICH Q2B, Validation of Analytical Procedures: Methodology http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073384.pdf[7]

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[8]
Date: 7/19/2011

1. What should a firm do if its drug products or components have been subjected to improper storage conditions such as those caused by a natural disaster?

Drug products that have been subjected to improper storage conditions (including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation) due, for example, to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Such exposure can pose a serious risk to a drug's identity, strength, quality, purity or safety (see 21 CFR Part 211.208, Drug Product Salvaging). This fundamental CGMP principle applies to any component, in-process material, or finished drug product subjected to such conditions.

In some cases, there may be substantial and reasonable uncertainty whether a drug was subjected to these conditions. In such a circumstance, it is essential that a firm nonetheless err on the side of caution in its risk assessment to assure an appropriate lot disposition decision and conduct a rigorous evaluation in accord with the standards described under 21 CFR Part 211.208.

When there is reasonable uncertainty whether a drug was subjected to such conditions, salvaging operations may be conducted only if there is evidence from laboratory testing that the drugs meet all applicable standards of identity, strength, quality, and purity, and from inspection that the drugs and their associated packaging were not subject to improper storage conditions as a result of the disaster or accident.

When determining whether drugs have been subjected to such improper conditions, a firm's actions should include but not be limited to:

- Obtaining supply chain information, including knowing the names and addresses of all suppliers and distributors of a drug (including components and packaging) to determine if there is a reasonable possibility that such materials were stored under improper conditions.

- Determining details such as the timeframe, duration, nature, scope, and location of exposure as well as identity of all lots potentially subjected to the improper conditions (e.g., ramifications of a natural disaster such as power disruptions should be considered to assure a complete risk assessment).

- Obtaining certification (either on the certificate of analysis or as a separate statement) declaring that drug lots, including components and packaging, were not subjected to improper storage conditions.

For more information, see references below.

Date: 4/22/2011

2. What if the improper storage conditions include exposure to toxic fumes or radiation?

Exposure to potentially harmful levels of toxic fumes or radiation is considered to be an improper storage condition (see above). It is essential that firms exercise due diligence to ensure that their drugs were manufactured, processed, packaged, and held under conditions consistent with current good manufacturing practice. This includes assuring acceptability of both raw materials and drug products.

FDA routinely monitors the quality of marketed drug products, including those imported into the U.S. In response to natural disasters, FDA may increase its monitoring and detection capabilities and apply appropriate regulatory action to help ensure the quality and safety of the drug supply.

References:

1. 21 CFR Part 211.208, Drug Product Salvaging http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.208[1]
2. FDA Import Alert 99-33 - *Detention Without Physical Examination of Products from Japan Due to Radionuclide Contamination http://www.accessdata.fda.gov/cms_ia/importalert_621.html*[2]
3. FDA Public Health Focus - Radiation Safety http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm247403.htm[3]
4. Food Safety: The EU Reinforces Controls on Imports from Japan http://europa.eu/rapid/pressReleasesAction.do?reference=IP/11/362[4]

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Date: 4/22/2011

3. What should be considered in performing an assessment of whether a firm's drug product, or its components or packaging materials may have been contaminated with radioactive material?

Radioactive materials (radionuclides) release radiation, also called "ionizing radiation," as high-energy particles or electromagnetic energy (e.g., gamma rays) as their unstable atoms transition to a more stable state. Low levels of radiation occur naturally in the environment (as "background radiation"), but elevated levels may occur, for example, during or following a nuclear reactor accident. Radioactive materials released into the environment by such an accident may contaminate drug products, components, or packaging materials. In these circumstances, firms should determine if any of these articles has become contaminated with radionuclides. If a drug product has been subjected to improper storage, including contamination with radioactive material, the product must not be salvaged and returned to the marketplace (21 CFR 211.208). Similarly, contaminated drug components and packaging materials should not be used or salvaged to manufacture drug products. It is important for manufacturers to know the origin and complete supply chain of a drug product, component, or packaging to better enable an assessment for possible contamination arising from, e.g., the accidental release of radioactivity

Some general concerns about radionuclide contamination from nuclear accidents include, but are not limited to, the following:

- Drug products and/or components may become contaminated with radionuclides from various sources, including contaminated atmospheric fallout, ground water, soil, or naturally-derived raw materials.
- A contaminated water supply used in drug manufacture may result in poor-quality products that fail to meet specifications.
- Certain dosage forms, such as injectable and inhalable drugs, may present greater risk to patients if contaminated with radionuclides, because these drugs more directly enter into the bloodstream.
- Drug products and/or drug components contaminated with radionuclides may result in poor-quality products that fail to meet stability specifications (e.g., reduced efficacy).

Manufacturers of finished drugs must assure that their products comply with FDA regulations, which includes assurance that the components are of appropriate quality (see, e.g., 21 CFR 211). In addition, manufacturers of drug components and primary containers must also assure the quality of their material. FDA expects drug manufacturers and distributors to be extra vigilant and to take enhanced measures to assure the quality and safety of their drugs that may have been exposed to radioactive contaminants. It may be appropriate for a firm to undertake measures to prevent purchase of at-risk materials as well as to increase testing of incoming components and finished products before final release. See Title 21 Code of Federal Regulations (CFR), Part 211, including:

- CFR Part 211.65, *Testing and Release for Distribution*
- CFR Part 211.84, *Testing and Approval or Rejection of Components, Drug Product Containers, and Closures*
- CFR Part 211.94, *Drug Product Containers and Closures*
- CFR Part 211.208, *Drug Product Salvaging*

References:

1. 21 CFR Part 211[6]
2. FDA Import Alert 99-33 - *Detention Without Physical Examination of Products from Japan Due to Radionuclide Contamination*[7]
3. FDA Public Health Focus - Radiation Safety[8]

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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm096102.htm[9]
Date: 6/24/2011

1.5 Health Canada

1.5.1 General Issues

Q.1 Are firms required to use high-efficiency particulate air (HEPA) filters for air supply in areas used for the manufacture of non-sterile dosage forms?

A.1 Division 2, Good Manufacturing Practices (GMP), of the *Food and Drug Regulations* does not specifically require manufacturing facilities for non-sterile drugs to maintain HEPA filtered air.

The Regulations do require the use of equipment for adequate control over air pressure, microorganisms, dust, humidity and temperature, when appropriate. In addition, this section calls for use of air filtration systems, including prefilters and particulate matter air filters on air supplies to production areas, as appropriate. These provisions speak to measures to prevent cross contamination, and the key phrase is "when appropriate".

Despite the lack of an explicit GMP requirement, some firms may elect to use HEPA filtered air systems as part of their dust control procedures. For example, firms may perform dust containment assessments and decide that such filters are warranted to prevent cross contamination of highly potent drugs that, even in small quantities, could pose a significant health hazard when carried over into other products.

Q.2 Is there an acceptable substitute for dioctyl phtalate (DOP) to integrity testing of high-efficiency particulate air (HEPA) filters?

A.2 Yes. Dioctyl phthalate aerosols also called Di (2-ethylhexyl) phthalate, di-sec octyl phthalate, DOP, or DEHP, have long been used to test the integrity of HEPA filters but concern about the potential health effects to people working with DOP test aerosols has led to a search for a safer equivalent replacement.

The product of choice from US Army testing with assistance from various private companies was a Henkel Corporation (Emery Group) product called Emery 3004 PAO. This product is a polyalphaolefin (POA) in the 4 centistoke (4 cSt) viscosity grade, used primarily as a lubricant base stock for oils, lubricants, and electrical/hydraulic fluids.

Emery 3004 (POA) can replace DOP in HEPA integrity testing.

Q.3 What is the acceptable limit for dew point of the compressed air used in pneumatic equipment and to dry the manufacturing tanks after cleaning?

A.3 Under the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)", there is no limit for the relative humidity % of the air used for pneumatic equipment and to dry manufacturing tanks. From a general perspective, based on Interpretation 4 under Section C.02.004 Premises, the humidity must be controlled where required to safeguard sensitive materials. Consequently, it is the fabricator, packager/labeller's responsibility to establish the pertinence of such control. If the humidity % of the compressed air used at the last step of drying of a reservoir is too high, micro-droplets of water could be generated on the internal surfaces by condensation, hence contributing to the possibility of microbial growth following storage. Similarly, it is important to make sure that residual water has been completely eliminated from hard to reach surfaces of the equipment after cleaning operations.

Q.4 What are the requirements applicable to Quality Control (QC) and engineering personnel who travel many times daily between self-contained facilities and the regular facilities?

A.4 Movement of personnel between self-contained and other facilities must be subject to procedures that will prevent cross-contamination. This may include but is not limited to decontamination procedures such as showering and change of clothes.

Q.5 What should be the standard of compressed air used in the manufacture of a drug?

A.5 Air that comes into direct contact with primary contact surfaces and/or the product should be monitored to control the level of particulates, microbial contamination, and the absence of hydrocarbons. Limits used should take into consideration the stage of manufacture, product, etc. Additional tests might be required due to the nature of the product. Gas used in aseptic processes must be sterile and filters checked for integrity.

Q.6 Does the concept of self-contained facilities apply equally to research and development laboratories (susceptible to contain highly sensitizing, highly potent or potentially pathogenic material in the analytical scale) that may be in the same building as the manufacturing facilities, or is this concept limited to actual manufacturing operations?

A.6 It is the responsibility of the manufacturer to ensure that their premises and operations have been designed in such a manner that the risk of contamination between products is minimized. This would include research and development areas within facilities where marketed drug products are fabricated and packaged. Further guidance can be found under Interpretation 11, Section C.02.004 Premises of the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)".

Equipment - C.02.005

Q. 1 Should equipment be labelled with calibration dates?

A.1 Major equipment should be identified with a distinctive number or code that is recorded in batch records. This identification requirement is intended to help document which pieces of equipment were used to make which batches of drug product.

Division 2, Good Manufacturing Practices (GMP), of the *Food and Drug Regulations* does not require that each piece of equipment bear status labelling as to its state of calibration or maintenance. However, equipment must be calibrated and/or maintained according to an established schedule, and records must be kept documenting such activities.

The regulations do not distinguish critical from non-critical equipment for calibration and maintenance purposes. However, the need for calibrating a given piece of equipment depends on its function. In general, equipment that measure materials warrant calibration. Equipment not requiring calibration/maintenance need not be tracked or included in the firm's calibration/maintenance program, but the firm must be able to support its decision to exclude a particular piece of equipment from the calibration/maintenance program.

During an inspection a firm should be able to document when a specific piece of equipment was last calibrated/maintained, the results or action, and when its next calibration/maintenance is scheduled. The absence of such documentation is considered a GMP deviation. While the absence of a calibration/maintenance tag is not objectionable, the presence of a calibration/maintenance tag alone should not be assumed to satisfy regulatory demands, and the supporting documentation should be audited. The firm should also be able to support its decision to not include a particular piece of equipment in the calibration/maintenance program.

Personnel - C.02.006

Q.1 Is a company required to notify the Inspectorate of a change in key personnel, such as the person in charge of Quality Control (QC) or manufacturing department?

A.1 No. However, it is the company's responsibility to make sure that the new person meets the requirements of Interpretation 1, 2, 3, or 4 under C.02.006 Personnel, depending on the activities performed.

Sanitation - C.02.007 & C.02.008

Q.1 Is fumigation a requirement under sanitation?

A.1 The written sanitation program should include procedures for pest control as well as precautions required to prevent contamination of a drug when fumigating agents are used.

Fumigation is not a requirement per se. Infestation should be monitored and controlled. Where fumigation is used, appropriate precautions should be taken.

Methods of sanitary control that satisfy the requirements of Sections 8 and 11 of the *Food and Drugs Act* would be considered to be acceptable.

Q.2 What limits are acceptable on product residues regarding sanitation?

A.2 Guidance for the establishment of limits can be obtained from the "Cleaning Validation Guidelines (GUI-0028)".

Q.3 Are gowning rooms required even in pilot plant operations?

A.3 Even in a pilot plant consisting of a small laminar flow area where the apparatus for filter sterilization of solutions are set up, it is an unacceptable practice to gown in there. A change room should be available besides their sterile pilot plant production area.

Based on the assumption that the pilot plant will produce drugs for sale - including clinical studies - then the same principles and considerations that apply to full scale production operations must also be utilized in pilot plant facilities.

Q.4 What are considered as being acceptable limits for cross-contamination when performing cleaning validation?

A.4 Guidance for the establishment of limits can be obtained from the "Cleaning Validation Guidelines (GUI-0028)".

Q.5 In terms of cleaning, what would be the frequency and type of cleaning for equipment and premises for successive manufacturing of batches of the same product? And for different strengths of the same product?

A.5 Interpretation 3.5 under Section C.02.007 Sanitation specifies that "a cleaning procedure requiring complete product removal may not be necessary between batches of the same drug". The frequency and type of cleaning for equipment and premises must address the length of time between consecutive lots with the ultimate goal that a particular lot won't be contaminated by the previous lot or the environment. It must also ensure that residual quantities of the previous lot won't impact on the quality of the following lot. Thus, a partial cleaning would be required between two lots of the same product, especially for forms such as liquids or suspensions, in order to prevent a few units at the beginning of a new lot from being filled with residual quantities from the previous lot that may be located in equipment such as hoses or pumps. A procedure should be established to ensure adequate removal of residual quantities from the previous lot and validation available for the maximum period

of time between two successive lots in order to avoid problems such as microbial contamination, accumulation of residue, or degradation of product. The number of lots of the same product which could be manufactured before a complete/full cleaning should be determined.

Q.6 Clothing: Is it acceptable to have two levels of clothing in the non-sterile manufacturing areas, i.e., one level for operators with full gowning and coveralls and another level for QA auditors and visitors? What environmental monitoring data is required?

A.6 Yes. There are basic clothing requirements for any person entering the manufacturing areas, such as hair, mustache and beard covering, as well as protective garments. However, a firm may decide to apply more stringent requirements for operators, such as dedicated shoes and garments providing a higher level of protection. There are no specific environmental monitoring requirements for clothing worn in the non- sterile manufacturing areas.

Q.7 Can the sampling for the microbial monitoring of air in non-sterile areas where susceptible products are produced be conducted when there are no manufacturing packaging activities?

A.7 The sampling should occur during actual manufacturing or packaging in order to reflect the conditions to which the products being produced are really exposed. Monitoring between production runs is also advisable in order to detect potential problems before they arise.

Q.8 Must written procedures be available to prevent objectionable microorganisms in drug products not required to be sterile?

A.8 Yes. Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, should be established and followed. This means that even though a drug product is not sterile, a firm must follow written procedures that pro-actively prevent contamination and proliferation of microorganisms that are objectionable.

Q.9 Should individuals who are known carriers of communicable disease be allowed to work in production areas?

A.9 Under Section C.02.008 of the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)", a person who is a carrier of a disease in a communicable form should not have access to any area where a drug is exposed. The likelihood of disease transmission by means of a drug product would depend on the nature of the disease and the type of work the employee carries out. It may be advisable to consult with a physician. Certain diseases could be transmitted through a drug product if proper hygiene procedures are not followed by an infected employee handling the product. However, an employee may also be a carrier of a communicable disease and not be aware of it. Therefore, in addition to strict personal hygiene procedures, systems should be in place to provide an effective barrier that would preclude contamination of the product. These procedures must be followed at all times by all employees. In the event that an employee is found to be a carrier of a communicable disease, the company is to contact Health Canada and perform a risk analysis to determine if there is any affected drug products.

Raw Material Testing - C.02.009 & C.02.010

Q.1 What are requirements of maintaining an impurity profile?

A.1 The United States Pharmacopoeia (USP) defines an impurity profile as "a description of the impurities present in a typical lot of drug substance produced by a given manufacturing process. " (ref. USP <1086>). Each commercial lot should be comparable in purity to this standard release profile which is developed early on and maintained for each pharmaceutical chemical. We can also call this profile a "Reference Profile" because the quality control unit refers to it (1) when assessing the purity of each batch of active pharmaceutical ingredient (API), and (2) when evaluating the viability of proposed process changes.

For further information regarding the control of impurities, please consult Impurities in New Drug Substances - ICH Q3A (R) & Impurities in New Drug Products - ICH Q3B (R).

Q.2 Does every individual container of a raw material need to be sampled for identification (ID) purposes regardless of the number of containers of the same lot available or are composite samples acceptable provided they are obtained from a maximum of 10 containers?

A.2 For human drugs, according to Interpretation 6.1 under C.02.009 Raw Material Testing, each container of a lot of a raw material must be tested for the identity of its contents. Therefore, each container of all raw materials, including excipients and active pharmaceutical ingredients (API), must be opened and sampled. Then, 2 options are available:

1. To test every sample for ID using a discriminating method (it is not mandatory to perform all ID tests in the specifications, for example United States Pharmacopoeia (USP), but the test must be specific).
2. If the raw material can be tested for potency, the other option is to mix and pool individual samples taken from each containers in a composite sample but without exceeding 10 individual samples in a composite. A specific ID test is then performed on each composite **and**, in addition, a potency test is performed to assure the mass balance of the composite. (In such cases, an equal quantity of each individual sample in the composite must be weighed to ensure that the mass balance is representative.)

As an example, say 72 containers of the same lot of a raw material are received. Each and all containers must be opened and a sample taken from each container. After that, the first option is to test each sample for ID (which implies 72 ID tests). The second option is to combine equal quantities of those individual samples in a way that the number of samples in any composite does not exceed 10 and test those composites for ID and potency. In this case, the easiest way to combine those samples would be 8 composites of 9 individual samples. For a given composite, a potency result of 88.8 % or so would indicate that one of the containers does not contain the right material as each individual sample contributes 1/9 or 11.11% of the total mass of the composite (similarly a result of 77,7 % would indicate 2 containers with the wrong material). In such case, each container selected for this particular composite would have to be tested for ID to pinpoint the one (or more) containers with the wrong material.

However, the use of a composite sample to establish the ID of a raw material cannot be used when the potency limits are too wide or, similarly, when the precision of the assay method is not sufficient to properly establish the mass balance.

Q.3a An active pharmaceutical ingredient (API) can be used after the retest date assigned by the API fabricator if a re-analysis done immediately before use shows that it still meets its specifications. Can the new data generated be used by the drug fabricator to assign a longer retest date to future lots of this API obtained from the same fabricator?

A.3a No. The extension of the retest date originally assigned to the API should be supported by data generated through a formal stability protocol. This may require the filing of a notifiable change submission. Please refer to the appropriate review Directorate.

Q.3b What about inactive ingredients?

A.3b Normally, any inactive raw material should bear an expiry date. When an inactive raw material is received without an expiry date, the fabricator should assign either an expiry date or a re-test date based on stability data or other documented evidence that this raw material is not subject to chemical / physical modifications or is not susceptible to microbial contamination.

Q.4 With respect to the re-test date of the drug substances, we have the stability data of a drug substance for up to 24 months at real time stability condition. The re-test period is assigned up to 24 months. According to the "Evaluation of Stability Data - ICH Q1E" , 2.4.1.1(the proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data), the retest period can be assigned up to 36 months. Can we assign the retest period up 36 months? If yes, does it require retesting of the active pharmaceutical ingredient (API) at 24 months?

A.4 Retest period and expiry date for APIs should be based on stability data. If an expiry date has been assigned to an API then its batches cannot be used after the expiry period. However, if a retest period has been assigned to the API, then after the retest period is over the API batch can be tested and used immediately (e.g., within one month of the testing). In the scenario presented above extrapolation of expiry date beyond 24 months should be based on stability data both at long-term and accelerated storage conditions. If the test results are satisfactory the retest period can be extended to a period not exceeding 36 months. Once the retest period of the API has been extended to 36 months, testing batches at the 24 months time point would be part of the ongoing stability protocol (it will not be considered *retest*). For further guidance on retest period and expiry period please consult Stability Testing of New Drug Substances - ICH Q1 A (R2) & Evaluation of Stability Data - ICH Q1E.

Q.5 We are a subsidiary of a United States (US) corporation. This US corporation supplies us with active pharmaceutical ingredients (APIs) that are fully tested after receipt on its premises. Can the US site be certified for the purpose of testing exemptions for the Canadian site?

A.5 The US parent company cannot be considered the vendor. To be certified, the vendor must be the original source of the API. In this instance, the US company would be acting as a contract laboratory and should meet the requirements under Interpretation 6.10, Section C.02.015 Quality Control Department. When received by the Canadian site, a specific identity test must be performed and if for an API, the testing must be as per Interpretation 6.1, Section C.02.009 Raw Material Testing (i.e., each container sampled and tested). The above mentioned would be acceptable based on the fact that no repackaging is done by the US site (i.e., the materials must be supplied in their original containers with the original labels and Certificate of Analysis (C of A) as received from the vendor).

Q.6 What documentation does a laboratory have to have in place to be considered qualified to run a test method for raw materials (drug substances and excipients) in order to satisfy Health Canada Regulations?

A.6 Documentation should include a summary of the analytical method validation, an assessment of the results and comparison to the acceptance criteria, and a conclusion as to the acceptability of the data as they relate to the ability of the laboratory analysts to successfully perform the procedure in the particular laboratory.

Q.7 Is the sampling plan based on the (√n+1) acceptable for identifying the number of containers of raw material to be sampled?

A.7 Sampling plans and procedures must be statistically valid and should be based on scientifically sound sampling practices taking into account the risk associated with the acceptance of the defective product based on predetermined classification of defects, criticality of the material, and past quality history of the vendor. In some circumstances, such as for large number of containers, a sampling plan based on (√n+1) may be acceptable. However, a sampling plan based on (√n+1) may present a significant risk of accepting defective goods in certain circumstances, such as the sampling of a small number of containers. As with all sampling plans, documented justification must be available.

Q8. If we already test each batch of our finished product for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, is it required to test it also for the purified water?

A8. Yes, you are required to test the purified water for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It is the general expectation that raw material testing support finished product testing.

Q.9 Interpretation 6.1 under Section C.02.009 specifies that "...each container of a lot of a raw material is tested for the identity of its contents using a specifically discriminating identity test." Does this requirement apply to raw materials used to fabricate finished products imported from non-Mutual Recognition Agreement (non-MRA) countries?

A.9 Any drug that is imported into Canada must meet the requirements in Division 2, Part C of the *Food and Drug Regulations*. The sampling and testing requirements for raw materials used in finished products imported from non-MRA countries should be equivalent to the requirements in Division 2, Part C of the *Food and Drug Regulations* as described in the " Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)". Importers should have evidence (e.g. technical agreements) that their suppliers in the non-MRA countries have equivalent requirements for sampling and testing of raw materials used in finished products imported from non-MRA countries.

Manufacturing Control - C.02.011 & C.02.012

Q.1 Can a single lot number be assigned to two or more co-mingled lots of bulk finished drug products packaged during the same run?

A.1 The "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)" require that each batch must be identified by an individually numbered manufacturing batch document, each lot or batch of the finished product shall be fully tested against the specification and retained samples for each lot or batch shall be kept. Packaging of multiple lots of bulk finished drug product in a single packaging run with one lot number should be done only in exceptional circumstances and should be well documented with appropriate justification. The shortest expiry date of all the lots packaged must be indicated on the label. In case of a product recall, the company must recall the entire lot comprising all the sub-lots.

Q.2 What is the acceptable deviation in physical counts of finished product stock?

A.2 The allowable deviation between physical counts versus counts as per records (including computer records) should be zero. All finished product stock must be fully accounted for and records of distribution and disposition must be maintained. Any deviations from physical counts versus expected counts as per the records, should be investigated and the results of such investigations should be documented.

Q.3 When are independent checks by another operator necessary?

A.3 The "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)" indicate that a number of measures be taken to maintain the integrity of a drug product from the moment the

various relevant raw materials enter the plant to the time the finished dosage form is released for sale. These measures seek to eliminate as many sources of error as possible so that only those drugs which have met established specifications are distributed.

One of the approaches proposed to achieve this goal is to have written procedures that ensure that each ingredient added to a batch is subjected to one or more checks for identity and quantity by qualified personnel.

If by its design, construction, operations and security features the procedure is such that the company assures that it is impossible to make an error, an independent check by another operator may not be considered necessary.

Checks for identity and quantity of dispensed materials also require independent checks by a second individual.

However, independent checks that materials have been added to the batch have traditionally been assumed to take place at the time of actual addition of the materials.

Other means of verifying the addition of materials may be considered. One alternative involves checking staged materials in the immediate compounding area prior to starting processing and then afterwards, verifying the empty containers before clearing the compounding area. This would be in conjunction with the use of individual processing rooms, otherwise we would need to be satisfied that there was very good separation of compounding operations.

Q.4 What are the expectations on label accountability?

A.4 It is expected that sufficient controls are in place to ensure that correct labels are applied during a labelling operation and that printed packaging materials are accounted for.

One acceptable means of meeting this requirement is to issue an accurately counted number of labels. That number should be reconciled with the number of labels used, damaged and returned to stock.

In theory, the target set in your procedure should be "0" deviation for labels and other printed packaging materials. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units packaged is investigated and satisfactorily accounted for before release.

Q.5 Is verification of empty containers an acceptable check for addition of ingredients?

A.5 Yes. It is acceptable to check staged materials prior to and after processing as a method of checks for addition through verification of empty containers.

The preferred method for conducting addition checks is by direct observation by the verifier. The verification of empty containers is an acceptable alternative, but only where stringent controls exist regarding the handling of dispensed raw materials.

Such controls include:

- assurance that a dispensed raw material does not end up in the wrong batch; locked portable cages are being used by some firms and only pertinent cages are permitted in the room at the same time.
- adequate operator awareness, training and motivation; the operator has to assure that additions are performed in the proper sequence; any spillage of raw materials must be promptly reported.
- pre and post checking should be performed by qualified personnel and whenever possible should be the same person.
- the post processing check must be performed prior to removal of any material from the area.

Q.6 Are quarantine and release stickers required on all containers of raw materials and packaging materials?

A.6 Quarantine and release stickers are required on all containers of raw materials and packaging components to identify status when a physical quarantine/release system is used.

However, such stickers are not required when a validated electronic quarantine system which effectively prevents the possibility of inadvertent use of unreleased material is in place.

When fully computerized storage systems are used, backup systems should be available in case of system failure.

Q.7 Is an answering machine acceptable for recall activation outside normal working hours?

A.7 A telephone answering machine may be used as part of the provisions for off-hours product recall activation. It should provide information on who to contact, their phone numbers, etc. Its use, functions and monitoring requirements should be included in the written procedures.

Q.8 Is it necessary to document quantities by lot numbers of finished stock destroyed?

A.8 For products returned to the distributor's facility for destruction due to reasons such as damaged or expired product, it may not be mandatory to document the quantities destroyed by lot number.

For products returned following a recall, it is mandatory to document the returns by lot number as it is a requirement to perform a final reconciliation.

If an establishment recall procedures depend on dates of first and last sale of a given lot, records of destruction by lot numbers may provide necessary information pertaining to accountability per lot.

Q.9 Is there a standard on what should be stated in a recall procedure?

A.9 Section C.02.012(1)(a) of the *Food and Drug Regulations* requires that every fabricator, packager/labeller, distributor, importer, and wholesaler of a drug maintains a system of control that permits complete and rapid recall of any lot of batch of the drug that is on the market. Such a system must be tailored to an individual organization and operation.

A written recall system should be in place to ensure compliance with Section C.01.051 of the *Food and Drug Regulations* and should include the requirements outlined in Interpretations 1.1 to 1.11 under Section C.02.012 Manufacturing Control of the "Good Manufacturing Practices Guidelines, 2009 Edition (GUI-0001)". Additional information is available in the "Recall Policy (POL-0016)" and the document entitled "Product Recall Procedures".

Q.10 Under what circumstances must one initiate a recall?

A.10 Please refer to the "Recall Policy (POL-0016)" and the document entitled "Product Recall Procedures".

Q.11 May firms omit second person component weight check if scales are connected to a computer system?

A.11 No, for an automated system that do not include checks on component quality control release status and proper identification of containers.

Yes, for a validated automated system with bar code reader that registers the raw materials identification, lot number and expiry date and that is integrated with the recorded accurate weight data.

Q.12 For a contract fabricator, is it a requirement to test the raw materials offered by customers?

A.12 Testing of raw materials (RM) is a responsibility of the fabricator. Therefore, an observation will be made to a fabricator for not testing a particular RM (even when this RM is provided by the client) if he is not excluded by his client according to a contract. Interpretation 3.2 under Section C.02.012 Manufacturing Control covers the written agreements with regard to the fabrication, and packaging/labelling among the parties involved, and Interpretation 6.10 under Section C.02.015 Quality Control Department covers the written agreements with regard to the testing among the parties involved. If no such agreement is in place, the observation will be made against the party responsible according to the Good Manufacturing Practices.

Q.13 If the customer asks a contract fabricator not to test a finished product, is it necessary for the contract fabricator to test the product?

A.13 Interpretation 3.2 under Section C.02.012 Manufacturing Control covers the written agreements with regard to the fabrication, and packaging/labelling among the parties involved, and Interpretation 6.10 under Section C.02.015 Quality Control Department covers the written agreements with regard to the testing among the parties involved. If no such agreement is in place, the observation will be made against the party responsible according to the Good Manufacturing Practices.

Q.14 Is a contract fabricator or packager responsible for qualification of utilities and systems and cleaning validation or is it the responsibility of the distributor? And what about the validation of the manufacturing/packaging process and test methods?

A.14 The contract fabricator is responsible for the qualification of utilities and systems and cleaning validation as those requirements are not product specific.

For process validation and test method validation, the main responsibility rests with the distributor, according to Section C.02.003 of the *Food and Drug Regulations*. The contract fabricator, packager or tester retains responsibility in terms of process or test methods validation unless a written agreement is signed by both parties that excludes the responsibility of the contract fabricator, packager or tester to perform validation activities.

Q.15 How long in advance can the raw materials be weighed?

A.15 It is acceptable to weigh the raw material (RM) in advance of the scheduled date of production. However, the firm should be able to demonstrate that the materials and design of the containers in which the RM are weighed and kept will not alter their quality, the characteristics of the RM must also be taken into consideration. Interpretation 2 of Section C.02.026 Samples may provide guidance to this effect. Pre-weighed material should be appropriately labelled to ensure traceability. A system should be in place to ensure that the material is still suitable for use on the date of manufacturing.

Q.16 If a licensed packager/labeller is packaging a drug for a foreign establishment which is not intended to be sold in Canada as described under Section 1.0 of "Conditions for Provision of Packaging/Labelling Services for Drugs under Foreign Ownership (GUI-0067)", should this foreign site be listed on the licence of the packager/labeller?

A.16 No. Since this drug would not be sold by the packager/labeller, this establishment would not be considered as an importer under Division 1A of the *Food and Drug Regulations* and thus, this site would not have to be listed on the licence of the packager/labeller. However, the packager/labeller would still need to fulfil all the requirements outlined under Section 4.0 of GUI-0067 that is: obtaining evidence of GMP compliance of the foreign site and supplying the proper information to Health Canada within the prescribed time frame.

Q.17 A Canadian firm does business with a foreign company, and that foreign company contracts out the fabrication, packaging and testing of a product. Is it acceptable to only

have a written agreement between the Canadian firm and the foreign company, and not with the contract company?

A 17 In this case, no subcontracting of any work should occur without written authorization from the Canadian firm. In the event of subcontracting, there should be a written agreement between the contracting and subcontracting parties (e.g., contract between Canadian firm and foreign company, foreign company and subcontractor). Copies of the relevant agreements should be available to the Canadian firm.

All establishments conducting licensable activities must hold an Establishment Licence (EL) or be listed on an importer's EL. As per Interpretation 3 under C.02.012 Manufacturing Control and Interpretation 6.10 under C.02.015 Quality Control Department of the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)", all arrangements for external fabrication, packaging/labelling, and testing are in accordance with the marketing authorization for the drug product concerned, and there is a written agreement covering all activities between the parties involved.

Q.18 What are the expectations surrounding a firm's management review of the Annual Product Quality Review (APQR)?

A.18 Senior management should be aware of significant outcomes from the APQR process and dedicate the resources to address the identified concerns. Evidence to demonstrate that senior management has been made aware could include such things as meeting agendas and/or minutes, quarterly reports, management sign-off of APQR reports, etc.

Q.19 Do all products as described in Interpretation 51 (Regular periodic or rolling quality reviews of all drugs) include low risk Category IV products?

A.19 Yes, we do expect to see Annual Product Quality Reviews completed for Category IV products.

Q.20 For biologics, for which annual reports are already being prepared by fabricators, is a separate APQR required?

A.20 There are some gaps between the information required by the Yearly Biologic Product Reports (YBPR) as described in section 5.1 of Health Canada's Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs, and the Annual Product Quality Review. For example: review of the adequacy of any equipment corrective actions, qualification status of relevant equipment and systems (For example, HVAC, water, compressed gases), contractual agreements, roles/responsibilities of the Quality Control department in APQR, etc. The YBPR would be acceptable providing that an Addendum is available addressing those aspects not covered by the YBPR.

Q.21 Is an importer only responsible for reporting on batches which are physically received/ imported for sale in Canada?

A.21 No. The scope of the APQR should extend to all batches made using the same process, facilities and formulation as the imported product.

Q.22 In C.02.011 Manufacturing Control, Interpretation 51.9 states: "A review of agreements to ensure that they are up to date" and Interpretation 54 states: "Where required, there should be an agreement in place between the various parties involved (For example, importer and fabricator) that defines their respective responsibilities in producing and assessing the quality review and taking any subsequent corrective and preventative actions."

Do these statements mean that an importer should have a quality agreement with the fabricator and this agreement should be reviewed yearly?

A.22 Yes. The importer should have a quality agreement with the fabricator (outlining responsibilities referencing APQR, etc) and that agreement should be reviewed at least once a year, and updated as necessary.

Quality Control Department - C.02.013, C.02.014 & C.02.015

Q.1 If a product fails its particulate matter specifications, can it be released for sale?

A.1 No. The particulate matter requirement is treated in the same way as any other specification: failure would constitute non-compliance with the labelled standard.

Q.2 Are the United States Pharmacopoeia (USP) general notices enforceable?

A.2 Yes. The USP General Notices provide in summary form the basic guidelines for interpreting and applying the standards, tests, assays, and other specifications of the USP so that these general statements do not need to be repeated in the various monographs and chapters throughout the book. Where exceptions to the General Notices exist, the wording in an individual monograph or general test chapter takes precedence.

This concept is further emphasized in the introduction to the General Information chapters which states, "The official requirements for Pharmacopeial articles are set forth in the General Notices, the individual monographs, and the General Tests and Assays chapters of this Pharmacopeia." The General Tests and Assays chapters are those numbered lower than 1000.

Q.3 If a lot meets United States Pharmacopoeia (USP) specifications but fails the firm's internal specifications, can it be released?

A.3 If a lot does not meet its declared release specifications, then the lot should not be released. Where more stringent internal specifications act as an alert limit and not as the basis for release, then the lot may be released after investigation and justification provided it meets its release specifications.

Q.4 Is it acceptable for firms to export expired drugs for charity?

A.4 No. While it is recognized the dire need for drugs in distressed parts of the world, once the expiration date has passed there is no assurance that the drugs have the safety, identity, strength, quality and purity characteristics they purport or represent to possess. As such, expired drugs are considered adulterated and their introduction or delivery for introduction into commerce is prohibited.

Q.5 Explain the United States Pharmacopoeia (USP) measurement uncertainty (MU) requirement for balances.

A.5 USP General Chapter <41> Weights and Balance states a weighing device providing accurate weighing for assay and test is to have MU of less than 0.1% of the reading and gives an example of 50 mg ± 50 µg as acceptable. To qualify MU of a balance, an appropriate National Institute of Standards & Technology (NIST) traceable weight within the weighing range of the balance is weighed 10 times or more. The resulting weights are calculated so that three times the calculated standard deviation divided by the amount weighed should be less than 0.001.

For different balance class designations and detailed information on weights and balance, the USP General Chapter <41> is to be consulted.

Q.6 Can an older version of an official method be used or must the most updated version always be used?

A.6 In resolving issues of conformance to an "official standard", the most up to date version of the analytical method is the method that must be used to determine compliance.

Q.7 What is the Inspectorate's position on the use of secondary reference standards (RS) and what are the conditions for the use of secondary reference standards?

A.7 While the Inspectorate recommends the use of the official standards for the analysis of compendia articles, the use of a secondary RS is acceptable if each lot's suitability is determined prior to use by comparison against the current official reference standard and each lot is requalified periodically in accordance with a written protocol. The protocol should clearly address the receipt, storage, handling and use of primary reference standards, the purification of secondary standards, and their qualification against official reference standards.

Q.8 Is it acceptable to use a third party lab's available pharmacopeial reference standard to qualify an establishment's secondary standard?

A.8 This practice is acceptable providing the contract testing lab has an Establishment Licence (EL) and has been audited by the client to demonstrate its capability to qualify the secondary standard (i.e., the official standard and the proper equipment is available on the tester's premises, the method used has been validated, etc.). Transfer of the standard between the sites should be under controlled conditions.

Q.9 What is the Inspectorate's position on the use of loose work sheets as opposed to bound notebooks for the purpose of recording laboratory data?

A.9 The recommended method of recording laboratory data is a bound book but the use of loose work sheets would be acceptable as long as it is controlled by a system or a procedure to ensure that all raw data are true and accurate, properly recorded and captured, adequately maintained and easily retrievable. The system should also provide accountability and traceability of work sheets.

Q.10 It is generally accepted in the industry to perform process validation on three consecutive lots. How does the Inspectorate view validation when reworking is required (i.e., three consecutive incidents will never happen)?

A.10 Reworking of a batch should be a very rare occurrence. As such, validation of reworking is not considered mandatory as it is not generally feasible. The reworking should be carried out in accordance with a defined procedure approved by Quality Control (QC) and with the conditions described in Interpretation 6 of Section C.02.014 Quality Control Department. This procedure should include supplementary measures and testing during the reworking operations to ensure that the quality of the final product is not compromised.

It is mandatory that rework proposals and reworked product also be fully investigated with respect to impact on release characteristics and potential impact on bio-availability. Changes in formulation due to reworks including the incorporation of additional lubricant or dissolution aid or additional critical processes may require comparative bio-availability studies. Furthermore concomitant stability studies must be undertaken on reworked batches to ensure that critical characteristics are not compromised with time due to the rework.

Q.11 Is it mandatory for the approval of a procedure to sign each page or is it acceptable to only sign the first page?

A.11 It is not mandatory for the approvers to sign each page of the procedure. It would also be acceptable to only sign the last page.

Q.12 If we perform a Total Aerobic Count (TAC) of purified water and that we identify each species found (if any) during the TAC, showing the absence of the two pathogens, is it required to perform a specific test to show the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*?

A 12 Yes, specific tests are required to show the absence of the two pathogens if the specific tests are in the purified water specification to support finished product quality. The species specific tests should follow a compendial method.

Packaging Material Testing - C.02.016 & C.02.017

Q.1 What is the Inspectorate's position on 2-mercaptobenzothiazole (MBT) in rubber closures?

A.1 MBT is sometimes used in the manufacture of rubber stoppers used as closures for vials or as components of syringes. Due to the concerns about the potential toxicity of MBT, its use in the manufacture of packaging materials that are in direct contact with injectable drugs is not permitted.

Q.2 Is it necessary to include a chemical identification test in a specification for a packaging component (such as a plastic bottle)? Must this chemical identification (ID) be conducted for each lot received? Would vendor certification be considered an acceptable substitution for testing upon receipt?

A.2 If the type of material is described on the Certificate of Analysis (C of A) and if a specific test has been performed by the fabricator of the packaging materials confirming the identity of the starting polymer used to manufacture a specific lot, it is not necessary to repeat the chemical ID (such as Infra-Red). But each lot of packaging materials should be visually examined to confirm the identity.

Q.3 Can industrial grade nitrogen be used as a blanketing agent during the manufacture of a drug product?

A.3 No. Any gas used as a blanketing agent should be of compendial standard.

Q.4 If nitrogen is used as blanket in the manufacturing/ filling of parenteral drugs, is it required to test the identity of all the cylinders if the nitrogen supplier has been audited?

A.4 Interpretation 6.1 under C.02.009 Raw Material Testing of the " Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)", specifies that each container of a lot of a raw material is tested for the identity of its contents using a specifically discriminating identity test. Interpretation 6.3 allows for testing only a proportion of the containers however Interpretation 6.3.2 specifies that Interpretation 6.3 does not apply when the raw material is used in parenterals. Therefore, in response to the question, yes, it is required to test the identity of all the cylinders of nitrogen used as a blanket agent in the manufacturing/filling of parenterals drugs.

Finished Product Testing - C.02.018 & C.02.019

Q.1 Do bacteriostasis and fungistasis testing have to be performed for each lot of product in reference to the United States Pharmacopoeia (USP) sterility test?

A.1 No. This needs to be established only once for a specific formulation to determine the suitable level of inoculate for that product. If the formulation has not changed for a number of years, periodic verification can be done as microorganisms become resistant to preservatives in a formulation.

Q.2 Does the Inspectorate encourage the use of environmental isolates for preservative effectiveness testing?

A.2 While the use of environmental isolates in addition to the specified compendia cultures is acceptable, the use of environmental isolates alone is not acceptable.

Q.3 What are the Inspectorate's expectations for process parametric release for foreign and Canadian manufacturers?

A.3 Further information is available in the document entitled "Annex 17 of the Current Edition of the Good Manufacturing Practices Guidelines - Guidance on Parametric Release (GUI-0046)". Please note that requests will be considered only for terminally sterilized drugs in their immediate containers and following submission and approval of evidence acceptable according to this guidance.

Q.4 Should an inspector observe and question a technician's analytical work?

A.4 An inspector may verify if the laboratory staff is qualified to carry out the work they undertake. This could occasionally include the observation of what the laboratory technicians are performing and question their actual analytical work in conjunction with standard operating procedures (SOP), methods or equipment used.

Also, inspectors will frequently examine testing data from the laboratory for format, accuracy, completeness, and adherence to written procedures. These matters would usually be regarded as requirements under Section C.02.015 Quality Control Department. The general requirements are outlined in Interpretation 6. Laboratory supervisors must sign off subordinates work as per Interpretation 6.3.

Q.5 Does the official method DO-25 apply to tablets labelled as being professed or as manufacturer's standard?

A.5 Section C.01.015 of the *Food and Drug Regulations* specifies requirements relating to tablet disintegration times. These regulations require that all drugs in tablet form, intended to be swallowed whole, disintegrate in not more than 60 minutes when tested by the official method.

The regulations also prescribe a specific disintegration requirement and test for tablets which are enteric coated. Subsection (2) specifies conditions where subsection (1) requirements for DO-25 are not required, i.e., (e) drug demonstrated by an acceptable method to be available to the body, and (f) tablets which are for example extended release. Refer to C.01.011 and C.01.012.

The Inspectorate has no objection to the use of an alternate disintegration or dissolution method to demonstrate compliance with the prescribed release requirements provided that the method had been properly validated. It is understood the DO-25 is not generally used for new drugs.

Q.6 Do tests for impurities have to be repeated for finished products if they have been done on the raw materials?

A.6 The sponsor may have evidence that a related impurity present in the drug product is a previously identified/qualified synthetic impurity. In this case, no further qualification for that impurity is required at the drug product stage. The concentration reported for the established synthetic impurity may be excluded from the calculation of the total degradation products in the drug product, and should be clearly indicated as such in the drug product specifications. Evidence should be provided in the submission demonstrating the related impurity is indeed a synthetic impurity (e.g., by showing constant levels during accelerated and/or shelf-life stability studies and confirmation by providing chromatograms of spiked samples). In cases where the methodology applied to the drug substance and drug product differs, the claim should be confirmed by appropriate studies and the results submitted (e.g., using actual reference standards for that compound).

For further information regarding the control of impurities, please consult Impurities in New Drug Substances - ICH Q3A (R) and Impurities in New Drug Products - ICH Q3B (R).

Q.7 What are the minimum testing requirements for solid dosage drugs?

A.7 The testing requirements for solid dosage form products include description, identification, purity, and potency and other applicable quality tests depending on the dosage form (e.g., dissolution/disintegration/drug release, uniformity of dosage units, etc.).

For new drugs, the minimum testing requirements have to be approved by the review Directorates.

Q.8 What are the standards other than the United States Pharmacopoeia (USP) that have official status in Canada?

A.8 The acceptable standards are described in Schedule B of the *Food and Drugs Act* ;

European Pharmacopoeia (Ph.Eur.)
Pharmacopée française (Ph.F.)
Pharmacopoeia Internationalis (Ph.I.)
The British Pharmacopoeia (B.P.)
The Canadian Formulary (C.F.)
The National Formulary (N.F.)
The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals
The United States Pharmacopoeia (U.S.P.)

Trade standards are also acceptable under certain conditions.

Q.9 Should compendial test methods be validated?

A.9 Since compendial methods cannot encompass all possible formulations of a drug product, the applicability of a compendial method to a company's particular formulation of a drug product must be demonstrated. It must be determined that there is nothing in the product that causes an interference with the compendial method or affects the performance of the method. It must also be established that the impurities that would be expected from the route of synthesis or formulation are controlled by the compendial method.

The main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose.

For guidance on validation of analytical procedures, please refer to Text on Validation of Analytical Procedures - ICH Q2A and Validation of Analytical Procedures - ICH Q2B.

Q.10 Must all identification tests stated in a compendial monograph be performed?

A.10 Yes, all tests stated in the monograph must be performed.

Q.11 Are solid dosage drugs exempted from dissolution testing if sold under a manufacturer's standard?

A.11 No, solid dosage drugs should include a routine test for monitoring release characteristics (e.g., dissolution).

Q.12 Do products labelled as United States Pharmacopoeia (USP) have to be tested as per the USP test methods?

A.12 No. An alternate method can be used, but the distributor must demonstrate that USP drugs comply with USP specifications when tested by USP methods. If an alternate method is used, it must be fully validated and results from a correlation study should be available.

Q.13 What should be the calibration frequency for a dissolution apparatus used with both baskets & paddles?

A.13 The "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)" call for equipment calibration at suitable intervals. Although specific time periods are not given, equipment should be calibrated at a frequency necessary to ensure reliable and reproducible results and covered in the firm = s standard operating procedures (SOP). The firm may consult the apparatus manufacturer's manual for guidance. Historical or validation data may also be used by the firm to support an appropriate calibration frequency.

In case of any event that might change operating characteristics of equipment, such as maintenance or moving it, it should be calibrated as required.

Q.14 In performing system suitability as per United States Pharmacopoeia (USP) <621>, do all replicate injections have to be completed before any analyte sample injections are made?

A.14 No.

Q.15 Is routine product pH testing required for endotoxin (*limulus amebocyte lysate* - LAL) testing?

A.15 No, provided that the method is validated and the firm has not committed to such testing in a new drug submission.

Q.16 Is the use of recycled solvents for high performance liquid chromatography (HPLC) columns acceptable?

A.16 Yes, provided that appropriate validation studies have been performed.

Q.17 If one lot of a product made in a Mutual Recognition Agreement (MRA) country is split into two separate shipments, is it mandatory for the importer to obtain separate manufacturer's batch certificate for each shipment?

A.17 No. However, the importer should demonstrate that the conditions of transportation and storage applicable to this product have been met for each shipment.

Q.18 Is it acceptable to perform the testing, including the potency, before packaging or is it mandatory to perform this testing after packaging?

A.18 Other than the Identity testing which must be performed after packaging, as per Interpretation 1 under C.02.019 Finished Product Testing, there is no specific requirement to perform the other tests after packaging including potency. In such cases, the manufacturing process must be validated to demonstrate that the packaging / filling operation does not alter the quality of the product (including potency). These validation data must also demonstrate that the homogeneity of a product is maintained by appropriate means throughout the entire filling process for dosage forms such as lotion, creams or other suspensions. For parenteral, ophthalmic, and other sterile products, at least identity and sterility testing must be performed on the product in the immediate final container.

For the requirement to perform the identity testing after packaging, the unique identifier principle can be used as long as the chemical / biological identity test has been performed after the unique identifier is applied to the product.

Q.19 A product is manufactured in a non-Mutual Recognition Agreement (non-MRA) country, then shipped in bulk in a MRA country where it is packaged and tested before being released and exported to Canada. Would the testing exemption provided by Interpretation 4 under C.02.019 Finished Product Testing apply?

A.19 No.

Records - C.02.020, C.02.021, C.02.022, C.02.023 & C.02.024

Q.1 Must standard operating procedures (SOP) referenced in master production documents (MPD) be available at the importer's premises?

A.1 Procedures related to critical processes must be available, whether or not they are referenced in the MPD.

Q.2 Can chromatograms be stored on disc instead of retaining the hard copy?

A.2 Yes, refer to the Interpretation under Section C.02.020 to C.02.024 Records.

Q.3 Does the person in charge of quality control have to sign Quality Control (QC) data and documents?

A.3 QC data and documents must be signed by the person in charge of QC or by a designated alternate as per Interpretation 1.4 of Section C.02.006 Personnel, or Interpretation 2.2 in the case of a wholesaler. The person in charge remains accountable for the tasks delegated and retains the necessary authority.

Q.4 According to Section C.02.020 Records, documents to be kept by the fabricator, packager/labeller, distributor and importer must be stored on their premises in Canada. In the case of a distributor or importer particularly, these documents are sometimes kept only on the premises of a consultant hired to provide Quality Control (QC) services, therefore they are not available on the premises of the distributor or importer at the time of the inspection. Is this practice acceptable?

A.4 No. All documents required under Division 2 of the *Food and Drug Regulations* must be available on the premises of the distributor or importer. Exceptionally, the consultant may bring a file home for a short time to review it but if at the time of the inspection, required documentation are not available on the premises of the distributor or importer, an observation to this effect will be made in the report. In some cases, this could also lead to a non-compliant rating.

Q.5 If electronic signature is not validated, must the signed paper copy be available?

A.5 Yes. The signed paper copy should be available if the electronic signature system has not been validated.

Q.6 Do wholesalers need to validate their computerized systems used for GMP activities (for example, recall)?

A.6 Yes, wholesalers need to validate their computerized systems used for GMP activities. See Interpretation 1 under C.02.020-024 Records of the "***Good Manufacturing Practices, 2009 Edition, Version 2 (GUI-0001)***".

In addition, routine quality system functions carried out in a wholesaling operation are indicated under sections C.02.004 Premises, C.02.006 Personnel, C.02.012 Manufacturing Control, C02.013, C.02.014 and C.02.015 Quality Control Department including:

tracking of customer orders and product distribution for the purpose of carrying out an effective and timely recall
maintaining material status control ie. released, rejected, quarantine, returned and recalled products, etc.
accountability of stock/inventory control (related to recall capability)
expiry date control (to ensure expired or soon to be expired products are not distributed)
proper storage of drug products (environmental control) i.e. temperature mapping, monitoring of storage temperature to ensure drug label storage conditions are met
deviation handling i.e. temperature excursion, temperature alarm and notification, procedure deviation, etc. - processing of returned drugs
complaint handling (product or operation related)
self inspection

Companies may choose to control these functions by means of a computerised system. There is no specific regulation requiring computer validation. However, this requirement is implied. When computer or automated systems are used to control and maintain quality systems functions; to maintain records required by regulations and to demonstrate compliance with regulatory requirements for records (C.02.021,C.02.022,C.02.023,C.02.024), the system must be able to provide and maintain data integrity. Thus, the system should be validated for its intended use. Validation activities and results are to be documented.

Samples - C.02.025 & C.02.026

Q.1 What is considered an adequate sample when tank loads of a raw material is received?

A.1 As per Interpretation 3 under Section C.02.025-C.02.026 Samples, the retained sample should represent at least twice the amount necessary to complete all required tests. For bulk materials received in tankers, the retained sample should be taken before being mixed-up with the unused quantities still present in the storage tank.

Q.2 A pressurized tanker of hydrocarbon raw materials (isobutan, propane, etc.) is normally sampled and approved before pumping. What is the current Inspectorate policy for sample retention given the inherent risks generated by these flammable gases under pressure?

A.2 The intent of regulation C.02.030 is applied to these cases. Samples of pressurized raw materials are not expected to be retained by manufacturers.

Q.3 If a product is fabricated in Canada and exported outside of Canada (the product is not sold on the Canadian market), are samples of this finished product to be retained in Canada?

A.3 No. This Canadian site is a contract fabricator and not a distributor. Subsection C.02.025 (1) of the *Food and Drug Regulations* (FDR) requires that a sample of each lot of the packaged/labelled drug be kept by the distributor and the importer (not the fabricator). This is also applicable if the Canadian fabricator manufactures a product for a Canadian distributor (Drug Identification Number (DIN) owner). While subsection C.02.025(2) of the FDR for retained samples of raw materials, the requirement applies to the fabricator (the person that transforms the raw material into a finished product), not the distributor. Subsection C.02.025(2) of the FDR for retained samples of raw materials, applies to the fabricator (the person that transforms the raw material into a finished product), not the distributor.

Q.4 If a product is fabricated in Canada, and contract packaged by another company in Canada and then exported outside of Canada (the product is not sold on the Canadian market), who is responsible for retaining samples of the finished products?

A.4 The Canadian fabricator and the Canadian packager/labeller are not responsible for retaining samples of the finished product. Subsection C.02.025 (1) of the *Food and Drug Regulations* (FDR) requires that a sample of each lot of the packaged/labelled drug be kept by the distributor and the importer (not the fabricator). This is also applicable if the Canadian fabricator manufactures a product for a Canadian distributor (Drug Identification Number (DIN) owner). This could vary according to the requirement of each health authority. On the other hand, both parties (Canadian fabricator or packager/labeller) could negotiate a written contract or agreement with the foreign client (the distributor/owner of the product) in order to clearly mention who will be responsible to keep the retained samples of the finished product, as long as this is acceptable to the health authority of that country. Each country could have their own regulatory requirement.

Stability - C.02.027 & C.02.028

Q.1 Do batches have to be tested for preservatives at initial release and then in the continuing stability program?

A.1 Finished products where antimicrobial agents are added to preparations such as multiple dose injections, topical creams, and oral liquids, an assay with limits should be included in the specifications.

An antimicrobial preservative effectiveness testing is performed during the development phase of the product to establish the minimal effective level of preservatives that will be available up to the stated expiry date, and for which a single regular production batch of the drug is to be tested for antimicrobial preservative effectiveness at the end of the proposed shelf life. Once the minimal effective preservative level has been determined, all lots of any preservative containing dosage form included in the stability program must be tested at least once at the expiry date for preservative content. For sterile drugs, the declaration of preservatives on the label is mandatory and those should be treated as for active ingredients (i.e., tested for preservative content at pre-established control points for those batches enrolled in of the continuing stability program). Where the lower limit of the preservative is less than 90 percent of label claim, the challenge test should be performed on samples at or below the lower limit. The challenge test need not be included in the specifications, provided that an assay for the preservative is included.

Q.2 Can it be assumed that United States Pharmacopoeia (USP) chromatographic assay methods are stability indicating?

A.2 No.

Q.3 Is it acceptable to place an expiry date on a bottle cap instead of on the bottle label?

A.3 No. Please refer to Section C.01.004(c)(v) of the *Food and Drug Regulations*. The expiration date must appear on any panel of the inner and outer label.

Q.4 When the labelled expiration date states only the month and year does it mean the end of the month?

A.4 Yes. The product should meet approved specifications up to the last day of the specified month.

Q.5 Can accelerated stability data of less than three months be used?

A.5 Accelerated stability studies of any length are considered as preliminary information only and should be supported by long term testing.

The assignment of expiry dates should be based on long term testing.

Q.6 Should drugs packaged into kits and subsequently sterilized, be tested for stability?

A.6 Yes. These operations are part of manufacturing. For drugs that are packaged into trays or kits and the resulting package is sterilized prior to being marketed, data should be available to demonstrate that the sterilization process does not adversely affect the physical and chemical properties of the drug. The testing should be sensitive enough to detect any potential chemical reactions and/or degradation, and the test results should be compared with test values obtained prior to sterilization.

1.5.2 Sterile Products

Q.1 Does the supervisor of a sterile product manufacturing facility need to have a degree in microbiology?

A.1 Section C.02.029(b) of Division 2 of the *Food and Drug Regulations* requires that "...a drug that is intended to be sterile shall be produced under the supervision of personnel trained in microbiology...". The expression "trained in microbiology" does not mean that this person must have a University degree in microbiology. However, the person must have taken university courses in microbiology.

Q.2 If water that has already been used in compounding is later found to contain endotoxins, what actions need to be taken?

A.2 Water can be used for production prior to obtaining microbiological testing results but the results of these tests must be available prior to final release of the product. Good Manufacturing Practices permit release only after raw material and finished product testing is completed and results demonstrate compliance of the product with its specifications.

The appropriate action would include an investigation into:

i. the potential sources of endotoxins;
ii. the sanitation and maintenance of the water system.

Q.3 Are sterile products in amber glass and plastic ampoules exempt from 100% visual inspection?

A.3 No. Each final container of injections must be subjected to a visual inspection. The 100% visual inspection test does not limit itself to particulate matter but includes sealing defects, charring, glass defects, underfills and overfills, missing print, etc. Please refer to Interpretation 84 under Section C.02.029 Sterile Products. For parenterals, there are additional requirements for packaging (i.e., the immediate container shall be of such material and construction that visual or electronic inspection of the drug is possible). Please refer to Section C.01.069 of the *Food and Drug Regulations*.

Q.4 What are the requirements in terms of monitoring/testing for the release of sterile gowns to be used in a controlled environment (Grades A or B) when those are obtained from a supplier?

A.4 There is no specific requirements in the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)" for the sterility testing of the protective garments to be worn in Grades A and B areas. However, the sterility cycle used by an outside supplier to sterilize these garments should have been validated according to scientifically sound procedures. Among other aspects, validation should address penetration/distribution studies of the sterilizing medium (gas, radiation, heat, etc.), load patterns of the sterilizers, determination of the Sterility Assurance Level with Bio indicators, etc. Also, the integrity of the outside wrapping in order to maintain sterility should be demonstrated.

Q.5 What are the room classification requirements for the preparation of containers and other packaging materials to be used in the fabrication of sterile products?

A.5 The preparation (cleaning, washing, etc.) of containers and packaging materials is normally performed in a "clean" room (Grades C or D). After these operations, the containers and materials used for drugs sterilized by filtration (and not further subjected to terminal sterilization in their final containers) must be depyrogenated and sterilized before being introduced in the aseptic rooms by the use of double-ended sterilizers or any other validated method. The depyrogenation step can be done using pyrogen-free water for injection (WFI) for the last rinse prior sterilization or by performing the depyrogenation and sterilization in one operation using a dry heat oven. Filling of these products normally takes place in a Grade A with a Grade B background.

For products submitted to terminal sterilization, it is not mandatory to use containers and packaging materials that are sterile but those that are in direct contact with the product should be free of pyrogen. This is usually achieved by using pyrogen-free WFI for the last rinse of these materials unless they are subsequently depyrogenated by another method (e.g., dry heat oven).

In addition, the initial bioburden of these materials should meet pre-established limits (that are based on sound science) and the risk of contamination during their introduction in the filling areas should be kept to a minimum.

Q.6 For the validation of moist heat sterilization cycles, will the new standards include the use of prions as the organism of choice instead of *Bacillus stearothermophilus* ?

A.6 At the present time, it is recognized in the scientific and pharmaceutical community that the spores of *Bacillus stearothermophilus* are the organisms of choice for the validation of moist heat sterilization cycles. Validation of such cycles is based on biological indicators containing a known count of organisms in order to determine a lethality factor for a given cycle. Those studies are based on parameters such as the "D" value of certain organisms and also imply a microbiological testing of these indicators at the end of the cycle in order to establish a survival rate. The use of prions (infectious proteins) could be inadequate in that their detection and quantification, which is based on animal models, is very difficult. Moreover, these proteins are very difficult to destroy and could present a danger should they accidentally be spread in a plant.

Q.7 According to the monograph on parenteral products (0520) of the 4th edition (2002) of the European Pharmacopeia (Ph. Eur.), injections for veterinary use with a volume dose of less than 15 mL are exempted from bacterial endotoxins/pyrogen testing by the European Union (EU). Is this interpretation correct? If so, would this EU exemption be applicable in Canada?

A.7 Yes, this interpretation is correct but this exemption is not applicable in Canada.

As per Section C.01.067(1) of the *Food and Drug Regulations*, it is required that each lot of a drug for parenteral use be tested for the presence of pyrogens using an acceptable method and be found to be non-pyrogenic. The Bacterial Endotoxins and Pyrogen test methods described in the United States Pharmacopoeia (USP) and Ph. Eur. are considered acceptable methods for that purpose. For all parenteral drug products, the Bacterial Endotoxins test should be preferred over the Pyrogen test unless the latter is demonstrated to be justified (more appropriate) or has been approved by a review Directorate. Therefore, the specification of all drug products for parenteral use intended for the Canadian market should include a test for Bacterial Endotoxins or Pyrogens and the EU current "15 mL exemption" is not applicable in Canada.

The only acceptable exemptions are those provided by Section C.01.067(2) (i.e., for parenteral drug products inherently pyrogenic or those which cannot be tested for the presence of pyrogens by either test methods). In other words, not testing a parenteral drug product for the presence of pyrogens would be considered acceptable only if documentation is available demonstrating that the parenteral drug product is inherently pyrogenic or that it cannot be tested by any of the methods.

Q.8 For radiopharmaceuticals, can it be acceptable to verify the integrity of the sterilizing filter only after use and to not perform the pre-filtration integrity testing?

A.8 As per Interpretation 4.7 under Section C.02.029 Sterile Products, the integrity of the sterilizing filter must be verified before and after use. However, the pre-filtration integrity testing for that type of products could lead to radioactive contamination as a result of the venting process of the filter assembly that must be performed before the start of product filtration. This would pose an unacceptable health risk for the operators and could result in disruption of production until the facility is decontaminated. It is therefore acceptable to use two filters of a minimum filter rating of 0.22 micron and to verify the integrity of the sterilizing filters after use only for these products. However, data should be available from the filter manufacturer that the filters are supplied pre-assembled and individually integrity tested by the filter manufacturer.

Q.9 What is the Inspectorate's position on pooling of samples within the same batch (e.g., 7 samples in one pool) for testing for sterility? The European Pharmacopoeia (Ph. Eur.) does not mention explicitly a pooling of samples for testing for sterility.

A.9 It is acceptable if companies pool samples for sterility testing with the membrane filtration method. However, it is not acceptable to pool samples when the direct inoculation method is used. Exceptions can be tolerated, when the volume of the sample-pool does not exceed 10% of the culture medium volume.

1.6. TGA Australia

1.6.1 General Issues

1. Why is the Code of GMP changing from time to time?

The TGA uses internationally harmonised manufacturing standards to allow manufacturers to operate in an international environment. The TGA maintains its GMP standards in line with updates issued through the PIC/S. Regular updates are necessary to maintain mutual confidence with regulators overseas and to promote quality assurance of inspections and harmonisation of technical standards and procedures with international inspection standards for the production and testing of medicinal products.

Australian manufacturers benefit from reduced regulatory burden where the TGA is able to adopt harmonised international standards and establish mutual recognition agreements and cooperation arrangements with comparable overseas regulatory authorities.

2. When did the current Code of GMP become mandatory?

The current Code of GMP was introduced on 29 July 2009 with a transition period up to 30 June 2010. It became mandatory from 1 July 2010.

3. What are the main new requirements introduced by the 2009 Code?

The most significant changes for manufacturers of medicinal products were:

- The requirement to prepare annual Product Quality Reviews
- The requirement to use quality risk management
- Detailed procedures on stability testing
- Detailed procedures on reference and retention samples, and
- Several changes for the manufacture of sterile medicinal products are also included in Annex 1.

Where relevant, annexes also apply to the manufacture of APIs.

4. What are the implications of the 2009 Code on products being imported into Australia?

There are no impacts on imports, cleared by GMP certificates and other evidence of GMP compliance as outlined in the Guidance on Clearance of Overseas Manufacturers. From 1 July 2010, the TGA has conducted its overseas inspections according to the 2009 Code. This includes inspections of US manufacturers of herbal & vitamin preparations that are not inspected by the US FDA according to medicinal GMP requirements.

5. PIC/S GMP Annexes 4 and 5 are not adopted in Australia. If a domestic veterinary manufacturer is inspected by the TGA under the EU MRA, what role will Annexes 4 and 5 play?

If the TGA inspects and grants an 'MRA certificate' to a veterinary product manufacturer to enable their product to be exported to Europe, the TGA will use the relevant parts and Annexes of the 2009 Code, as well as Annexes 4 and 5.

6. Will the Australian Pesticides and Veterinary Medicines Authority (APVMA) accept TGA inspections as applicable for veterinary manufacture where a company manufactures both medicines and veterinary products?

Yes, the APVMA will accept TGA inspections of veterinary manufacture. However, requests for inspections of veterinary medicinal products in addition to human medicinal products must be conveyed to the TGA inspector prior to the commencement of the scheduled inspection.

7. What sunscreens are required to be manufactured in compliance with the 2009 Code?

Sunscreens with an SPF claim of 4 or over are required to be manufactured in compliance with GMP.

Note that cosmetic preparations which contain a sunscreen for a secondary purpose are under certain circumstances excluded from medicines regulation and regulated as cosmetics. More details are given in the Australian Regulatory Guidelines for Sunscreens (ARGS).

8. Can the Technical Guidance documents that are available for Listed Complementary medicines manufacturers also be applied for sunscreen manufacturers?

Yes, the Technical Guidance documents for Listed Complementary medicines are baseline documents, elements of which can also be applied to other medicines if justified.

9. What are the implications of the 2009 Code for medicinal gases manufacturers?

The implications for medicinal gases manufacturers are similar to those for other medicines manufacturers. The Guide for interpreting the 2002 Code for manufacturing medicinal gases has been revised to reflect the 2009 Code.

10. Has there been an assessment of the financial impact of the introduction of the 2009 Code?

The TGA prepared a preliminary assessment which was reviewed by the Office of Best Practice Regulation. The preliminary assessment recognised the impacts would vary for different classes of manufacturers, and that for many Australian manufacturers exporting abroad or who were part of a multinational group of companies, there would be no impact at all. Overall, the TGA assessed the financial impact as low.

Quality management (Chapter 1)

11. What is meant by 'marketing authorisation'?

Marketing Authorisation is a set of regulatory requirements specified on the ARTG and any other requirements imposed by a relevant Delegate of the Secretary upon product listing or registration.

Examples of regulatory requirements include, but are not limited to, compliance with registered formulations, special storage and transportation conditions, shelf life, labelling, batch release testing requirements etc.

The Marketing Authorisation is equivalent to a Certificate of Registration or a Certificate of Listing for a medicinal product under the *Therapeutic Goods Act 1989*.

12. Is the holder of the Marketing Authorisation the product sponsor?

Yes.

13. Can a sponsor perform release for supply?

Release for supply is defined as a manufacturing step for which a TGA licence is required. For this reason, a sponsor can only perform release for supply if the sponsor holds a TGA manufacturing licence. Refer to clause 1.1vii. of the 2009 Code.

14. Can a manufacturer have more than one authorised person to perform release for supply?

Yes - a manufacturer is allowed to have more than one authorised person to perform release for supply.

15. If a sponsor has multiple manufacturers for a product, who should be responsible for release for supply?

The Authorised Person of the manufacturer responsible for release for supply should have a full overview of all manufacturing steps, including the ones performed by other manufacturers. Consequently, in most cases it would make sense to make the last manufacturer in the supply chain for each batch of product responsible for release for supply. However, for example where the last manufacturer in the supply chain only performs secondary packaging it would probably be better to have the responsibility for release for supply with the manufacturer performing the more crucial steps in manufacture. It could be any of the manufacturers, as long as the manufacturer's Authorised Person has full overview of all steps performed in the manufacture of the batch involved and has full access to all details of the marketing Authorisation.

16. What is the TGA's expectation during inspection in relation to marketing authorisation (regulatory compliance) of products?

The TGA expects that an authorised person must carry out release for supply to ensure the products meet all regulatory requirements. Release for supply must include assurance of compliance with the marketing authorisation, as well as meeting GMP requirements, such as assessing Product Quality Reviews and the effectiveness of the on-going stability program. This applies to both local and overseas manufacturers.

17. Does the inspection of a manufacturer's compliance with marketing authorisation refer only to products manufactured at the site of inspection, products manufactured by a third party, imported products, or all products?

Where the manufacturer being inspected is responsible for the release for supply of the product, the inspection scope includes products manufactured by that manufacturer, irrespective of whether the products are manufactured in-house (where the manufacturer is the sponsor) or whether the products are manufactured under contract. This applies to both Australian and overseas manufacturers.

Where another regulatory authority certifies an overseas manufacturer as being compliant with the PIC/S or EU GMP requirements, it will be presumed that the manufacturer meets all requirements and ensures that the marketing authorisations have complied with GMP requirements for all manufactured products.

18. Do distribution records require batch numbers?

According to Clauses 1.3(vii) and 8.13 the recording of batch numbers in distribution records is mandatory.

19. What is meant by 'all licensed products' in the first sentence of Clause 1.4, stating that Product Quality reviews (PQRs) should be conducted for all licensed products?

This refers to the manufacturing licence or, in case of overseas manufacturers, the applicable GMP clearances. This implies that domestic manufacturers are expected to conduct PQRs for all medicinal products manufactured under the manufacturing licence and overseas manufacturers are expected to

conduct PQRs for all medicinal products for which a clearance is granted. Where no marketing authorisation is available, clauses 1.4.vi and 1.4.x do not apply.

20. Do Product Quality Reviews (PQRs) have to be conducted yearly?

Yes. However, if very few batches of one product are manufactured in one year, it may also be acceptable to conduct a two yearly PQR providing a rationale is documented and scientifically justified. The justification for a reduction in the frequency of reviews should consider whether the medicines are registered, listed or complementary, the number and size of batches manufactured, whether grouping is utilised (see question 19) and the method of manufacture, together with an assessment of the risk associated with the product. The approach taken by the manufacturer will be assessed on a case-by-case basis.

21. Can one Product Quality Review (PQR) be prepared for a group of products?

Grouping (sometimes referred to as bracketing or matrixing) of products for the preparation of PQRs may be acceptable, if adequately justified. It is usually only acceptable if the amount of batches manufactured annually for each product within the group is low, the grouped products are of the same pharmaceutical form containing the same or very similar active ingredients and are manufactured using the same equipment. Acceptability will be assessed during inspections on a case-by-case basis.

22. Do all batches for which manufacture has commenced have to be included in Product Quality Reviews (PQR)s?

Yes. For example, also all batches for which the manufacture was terminated, delayed or has failed are expected to be included in the PQRs. When grouping is applied, all batches of all products in each group are expected to be included in the PQR.

23. If a company has multiple contract manufacturers, how are they supposed to perform a Product Quality Review (PQR)? Are sponsors required to obtain any evidence from overseas manufacturers?

The preparation of PQRs is a shared responsibility between the sponsor and the manufacturer(s) of a product. PQRs are expected to be available for review during inspections of manufacturers of products for which the manufacturer is responsible for release for supply. Sponsors are also expected to have access to the PQRs, to ensure product compliance with the marketing authorisation.

24. When the 2009 Code became mandatory from 1 July 2010, did the TGA expect to see PQRs readily available during inspection?

The TGA expects PQRs to be prepared as of 2011.

25. Are the TGA's expectations for PQRs for listed complementary medicines similar to those for other medicines?

Yes. A separate guidance document on this issue is available on the Technical working groups page.

26. What are the requirements for Product Quality Review (PQR) for products that are for export only?

The PQR requirements for products that are for export only are the same as the PQR requirements for all other products.

27. Why is it that Quality Risk Management is mandatory whereas Annex 20 is voluntary?

Clauses 1.5 and 1.6 of the 2009 Code make it a mandatory requirement for manufacturers to have an operational Quality Risk Management system in place to ensure that the evaluation of a risk to

product quality is based on a sound, scientific basis and that risk assessments are appropriately documented. Annex 20 provides guidance only on Quality Risk Management tools that may be applied by a manufacturer when assessing the risk to product quality.

28. What is the difference between a regulated change and a change that can be made through risk assessment?

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM), OTC Medicines (ARGOM) and Complementary Medicines (ARGCM) each include requirements for changes to medicines in the ARTG. These requirements are mandatory and cannot be overridden by the 2009 Code. The requirements within the 2009 Code in relation to change control and risk assessment apply to both regulated and other changes.

Personnel (Chapter 2)

29. What does 'necessary qualifications' mean in clause 2.1?

'Necessary qualifications' mean having the education, training, experience and skills or any combination of these elements that will ensure that staff can perform assigned duties and functions at an acceptable level.

30. What are the training requirements for personnel (clauses 2.8-2.12)?

Training and assessment should be carried out by persons with relevant training, qualifications and experience in the subject matter and training personnel should preferably have been formally qualified in training and assessment.

Training should be given to all people affected by significant change in the Quality Management System, e.g. when SOPs or methods of manufacture change. The requirement for initial and ongoing training should be reflected in procedures, and training records should be generated and kept.

There are a number of people who have a direct bearing on quality outcomes. These include contractors, consultants and casual employees. Therefore, appropriate training and assessment should be provided and recorded.

31. What are language requirements for personnel?

Manufacturers should define language requirements or standards and ensure personnel are proficient in the required language for their allocated tasks, particularly in relation to documenting and recording. Procedures employed to overcome identifiable deficiencies should also be documented.

Premises and equipment (Chapter 3)

32. What environment (including air supply) is required for sampling of non-sterile starting materials?

Clause 3.9 describes the physical requirements for the area being used to sample non-sterile starting materials. This sampling should be carried out in a separate room, or appropriately qualified sampling hood, under a filtered air supply to protect product from contamination. The sampling area should be designed with dust extraction or equivalent controls to prevent contamination of adjacent areas.

Sampling hoods may be used provided there are adequate controls in place to ensure that materials are contained. Consideration should be given to the use of appropriate extraction/de-dusting facilities, the qualification of the hood, the possibility of contaminating the sampled material and adjacent storage area and whether materials sampled are hazardous.

33. What environment is required for sampling primary packaging materials for non-sterile products? Can they be sampled in the warehouse?

Clause 3.9 also describes the physical requirements for the area being used to sample primary packaging material for non-sterile products. As product contact components, primary packaging materials should be sampled within an environment that adequately protects the packaging from contamination. The standard of air quality is optional and HVAC is not expected. However, sampling of primary packaging materials in an open warehouse would not be allowed.

34. What is the definition of 'campaign' manufacture?

Clause 5.19 defines campaign manufacture as being a separation in time of production. That is, manufacturing a series of batches of the same product in sequence in a given period of time and/or maximum number of batches followed by an appropriate (validated) cleaning procedure.

35. The Code does not reference a specific standard for air quality for non-sterile manufacturing areas. What is the relevant Australian or ISO standard to be applied?

There are no standards specific to non-sterile medicine manufacture. Manufacturers are required to demonstrate that the manufacturing environment for non-sterile products affords appropriate protection to the products, and prevents contamination. Through qualification, validation and monitoring processes manufacturers should justify that the air quality is sufficient for their non-sterile manufacturing areas. Manufacturers may wish to consult the World Health Organisation's 'Good manufacturing practice: main principles for pharmaceutical products - Heating, ventilation and air conditioning systems for non-sterile pharmaceutical dosage forms' which provides additional guidance in relation to recommended levels of air filtration.

36. What does 'certain' (as per certain additional products, certain antibiotics, certain hormones etc) in clause 3.6 of the Code mean?

'Certain' refers to materials known to cause specific (side) effects in low doses. For example, 'certain antibiotics' refers to antibiotics, usually of the beta lactam group, which are known to cause allergic reactions. 'Certain hormones' refers to hormones that can have pharmacological effects if trace amounts cross-contaminate other products. Examples are estrogens and some progesterone-like hormones. Manufacturers should evaluate materials that are processed and ensure that adequate control measures are in place.

37. The Code appears to contain very little detail on requirements for cleaning and sanitisation. What will the TGA consider an acceptable standard for these requirements?

The Code is not prescriptive on cleaning and sanitisation, as it considers the manufacturer to be responsible for demonstrating that the applied cleaning and sanitisation procedures are suitable for its intended purpose. This can be demonstrated by qualification, validation or monitoring studies. The level of depth of these studies may depend on the nature and types of products manufactured.

38. Is a facility that is used as a warehouse and distribution centre AFTER release of a pharmaceutical product, required to comply with the Code of GMP?

By definition, 'manufacture' includes all steps in bringing the product to its final form and 'release for supply' is considered to be the last step in this process. From a GMP point of view, warehousing and distribution after release for supply and after the product has left the manufacturer's control, is not currently regulated by the TGA. Hence, a licence is not required if a facility is used only for warehousing and distribution. However, there may be State regulatory requirements that are applicable which should be checked with the relevant State Department.

Production (Chapter 5)

39. What are the TGA's expectations on validation for listed complementary medicines manufacture?

A separate guidance document is available for this: Technical guidance on the interpretation of manufacturing standards: Process validation for Listed complementary medicines

40. What are the TGA's expectations on supplier qualification for listed complementary medicines manufacture?

A separate guidance document is available for this: Technical guidance on the interpretation of manufacturing standards: Supplier qualification

41. What are the requirements regarding unique batch numbering? Is a batch number required to only designate one batch of a product from other batches of that product, or is a unique batch number required for each product-and-batch combination?

The issue of batch numbering is dealt with in Therapeutic Goods Order No. 69 General Requirements for Labels for Medicines. The system that a manufacturer adopts for batch numbering may include numerals, letters or symbols (or any combination of these) and must effectively serve to uniquely identify a batch of product, and from which it is possible to trace that batch through all stages of manufacture and distribution. The manufacturer should be able to demonstrate that the system for batch numbering meets these requirements and is effective.

Unpacked bulk products, should have a batch number that is unique to both product and batch, to minimise the potential for mix-ups during manufacturing. For finished products which are easily distinguished, a batch numbering system that only designates batches from that product may be acceptable.

42. What are the requirements for label counting and verification?

Roll labels must be counted either on receipt or at issue. Supplier counts are not acceptable unless the supplier is specifically qualified and supplier certifies the exact count for each roll. Supplier numbering of labels is an acceptable alternative.

Cut labels must be counted and effectively verified by the manufacturer because of risks of mix-ups.

Quality control (Chapter 6)

43. What are the TGA's expectations on sampling and testing for listed complementary medicines?

A separate guidance document is available for this: Technical guidance on the interpretation of manufacturing standards: Sampling and testing of complementary medicines

44. Is it necessary to conduct on-going stability studies at a GMP certified laboratory?

No. However, the results from these studies are required to be reliable and meaningful. For that reason, other certificates may be used in lieu of a GMP certification, such as a current Good Laboratory Practice (GLP) certificate or licence issued by a regulatory authority acceptable to the TGA or a current ISO 17025 accreditation certificate. Stability test methods used by the laboratory should be appropriately validated and documented according to the requirements of the Code.

The results from the on-going stability monitoring studies must be considered as part of release for supply, which is the final step in manufacturing.

45. In the case of imported medicines, is the responsibility to conduct an on-going stability monitoring program with the manufacturer or with the sponsor?

The responsibility is with both the manufacturer and the sponsor. The manufacturer who carries out release for supply needs to ensure that the batch meets its Marketing Authorisation, and that an on-going stability monitoring program is conducted and data is available to support the expiry date. The sponsor is responsible for the Marketing Authorisation, ensures an on-going stability testing program is performed and has access to the stability results. In the contract manufacturing agreement, the responsibility for on-going stability may be contracted out to the manufacturer or other parties.

46. Where bulk medicines are imported into Australia to be packaged by a domestic manufacturer, may the on-going stability program of the bulk manufacturer be used?

No. On-going stability is required to be performed in the packaging material in which the product is marketed in Australia. The overseas bulk manufacturer will use different packaging equipment and processes although the packaging materials might be the same.

47. Are the TGA's expectations for on-going stability studies for listed complementary medicines similar to those for other medicines?

Yes. A separate guidance document on this issue is available on the Technical working groups page.

48. Is grouping of products in the on-going stability program acceptable?

Grouping or bracketing could be acceptable, if appropriately scientifically justified and if the formulation is (nearly) identical. This will be assessed during inspections on a case-by-case basis.

49. Are on-going stability data reviewed during inspections?

Yes. During inspections, the operation of an appropriate on-going stability program are reviewed, including the results of on-going stability studies, where appropriate. If there are any concerns, the inspector can refer the evaluation to the regulator.

50. In which cases are the outcomes of the on-going stability program to be communicated to the regulator?

Although it is acknowledged that some normal variability in the results of on-going stability studies can be expected, all statistically significant departures from established stability profiles must be notified to the regulator.

51. Should the results of the on-going stability program be part of the release for supply process?

Yes, the results of the on-going stability program are expected to be available to the Authorised Person who should consider those before releasing a batch for supply.

Complaints and product recall (Chapter 8)

52. What requirements are included in the 2009 Code regarding counterfeit products?

Clauses 8.7 and 8.8 require that the procedures on complaints handling should include an assessment for counterfeit products. If counterfeiting is detected the TGA must be notified.

1.6.9 Reference and retention samples (Annex 19)

74. What is the difference between a reference sample and a retention sample?

A reference sample is a sample for the purpose of future analysis, which could refer to starting materials, packaging materials or finished products.

A retention sample is a sample representing the batch of finished product as distributed.

75. Can items from the stability program be used as retention samples?

No.

76. For multipack products, do the complete multipacks need to be retained as samples?

Not necessarily. The requirement is that the amount of retention samples is sufficient to carry out analytical work during the entire shelf life of the product.

1.7 ICH

1.7.1 ICH: Q8, Q9 and Q10

A. For General Clarification (1.1)

Q1: Is the minimal approach accepted by regulators?
A1: Yes. The minimal approach as defined in Q8(R2) (sometime also called "baseline" or "traditional" approach) is the expectation that is to be achieved for a fully acceptable submission. However, the "enhanced" approach as described in ICH Q8(R2) is encouraged (Ref. Q8(R2) Annex, appendix 1). (Approved June 2009)

Q2: What is an appropriate approach for process validation using ICH Q8, Q9, and Q10?
A2: The objectives of process validation are unchanged when using ICH Q8, Q9, and Q10. The main objective of process validation remains that a process design yields a product meeting its predefined quality criteria. ICH Q8, Q9, and Q10 provide a structured way to define product critical quality attributes, design space, the manufacturing process, and the control strategy. This information can be used to identify the type and focus of studies to be performed prior to and on initial commercial production batches. As an alternative to the traditional process validation, continuous process verification (see definition in ICH Q8(R2) glossary) can be utilized in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle. (Approved October 2009)

Q3: How can information from risk management and continuous process verification provide for a robust continual improvement approach under ICH Q8, Q9 and Q10?
A3: Like the product itself, process validation also has a lifecycle (process design, process qualification and ongoing process verification). A risk assessment conducted prior to initial commercial validation batches can highlight the areas where particular focus and data collection could demonstrate the desired high level of assurance of commercial process robustness. Continual monitoring (e.g., via continuous process verification) can further demonstrate the actual level of assurance of process consistency and provide the basis for continual improvement of the product. Quality Risk Management methodologies of ICH Q9 can be applied throughout the product lifecycle to maintain a state of process control. (Approved October 2009)

B. Quality by Design (QbD) Topics (2)

Q1: Is it always necessary to have a design space (DS) or real-time release (RTR) testing to implement QbD?
A1: Under Quality by Design, establishing a design space or using real-time release testing is not necessarily expected (ICH Q8(R2)). (Approved April 2009)
1. Design Space (2.1)

Q1: Is it necessary to study multivariate interactions of all parameters to develop a design space?
A1: No, the applicant should justify the choice of material attributes and parameters for multivariate experimentation based on risk assessment and desired operational flexibility. (Approved April 2009)

Q2: Can a design space be applicable to scale-up?
A2: Yes, when appropriately justified (for additional details, see Q8(R2) Annex section II.D.4 (2.4.4)). An example of a scale-independent design space is provided in the European Federation of Pharmaceutical Industries and Associations (EFPIA) Mock P2 document (EFPIA Mock P2 submission on "Examplain": Chris Potter, Rafael Beerbohm, Alastair Coupe, Fritz Erni, Gerd Fischer, Staffan Folestad, Gordon Muirhead, Stephan Roenninger, Alistair Swanson, A guide to EFPIA's "Mock P.2" Document, Pharm. Tech. (Europe), 18, December 2006, 39-44).
This example may not reflect the full regulatory requirements for a scale-up. (Approved April 2009)

Q3: Can a design space be applicable to a site change?
A3: Yes, it is possible to justify a site change using a site independent design space based on a demonstrated understanding of the robustness of the process and an in depth consideration of site specific factors (e.g., equipment, personnel, utilities, manufacturing environment, and equipment). There are region specific regulatory requirements associated with site changes that need to be followed. (Approved April 2009)

Q4: Can a design space be developed for single and/or multiple unit operations?
A4: Yes, it is possible to develop a design space for single unit operations or across a series of unit operations (see Q8(R2) Annex, section II.D.3 (2.4.3)). (Approved April 2009)

Q5 Is it possible to develop a design space for existing products?
A5: Yes, it is possible. Manufacturing data and process knowledge can be used to support a design space for existing products. Relevant information should be utilized from e.g., commercial scale manufacturing, process improvement, corrective and preventive action (CAPA), and development data.
For manufacturing operations run under narrow operational ranges in fixed equipment, an expanded region of operation and an understanding of multiparameter interactions may not be achievable from existing manufacturing data alone and additional studies may provide the information to develop a design space. Sufficient knowledge should be demonstrated, and the design space should be supported experimentally to investigate interactions and establish parameter/attribute ranges. (Approved April 2009)

Q6: Is there a regulatory expectation to develop a design space for an existing product?
A6: No, development of design space for existing products is not necessary unless the applicant has a specific need and desires to use a design space as a means to achieve a higher degree of product and process understanding. This may increase manufacturing flexibility and/or robustness. (Approved April 2009)

Q7: Can a design space be applicable to formulation?
A7: Yes, it may be possible to develop formulation (not component but rather composition) design space consisting of the ranges of excipient amount and its physicochemical properties (e.g., particle size distribution, substitution degree of polymer) based on an enhanced knowledge over a wider range of material attributes. The applicant should justify the rationale for establishing the design space with respect to quality attributes such as bioequivalence, stability, manufacturing robustness etc. Formulation adjustment within the design space
depending on material attributes does not need a submission in a regulatory
postapproval change. (Approved June 2009)

Q8: Does a set of proven acceptable ranges alone constitute a design space?
A8: No, a combination of proven acceptable ranges (PARs) developed from univariate experimentation does not constitute a design space (see Q8(R2) Annex, section
II.D.5 (2.4.5)). Proven acceptable ranges from only univariate experimentation may lack an understanding of interactions between the process parameters and/or material attributes. However proven acceptable ranges continue to be acceptable from the regulatory perspective but are not considered a design space (see ICH Q8(R2) Annex, section II.D.5 (2.4.5)).
The applicant may elect to use proven acceptable ranges or design space for
different aspects of the manufacturing process. (Approved June 2009)

Q9: Should the outer limits of the design space be evaluated during process validation studies at the commercial scale?
A9: No. There is no need to run the qualification batches at the outer limits of the design space during process validation studies at commercial scale. The design space should be sufficiently explored earlier during development studies (for scale-up, see also section II.B.1 Design Space (2.1), Q2; for lifecycle approach, see section II.A For General Clarification (1.1), Q3). (Approved November 2010)
2. Real-Time Release Testing (2.2)

Q1: How is batch release affected by employing real-time release testing?
A1: Batch release is the final decision to release the product to the market regardless of whether RTR testing or end-product testing is employed. End-product testing involves performance of specific analytical procedures on a defined sample size of the final product after completion of all processing for a given batch of that product. Results of real-time release testing are handled in the same manner as end-product testing results in the batch release decision. Batch release involves an independent review of batch conformance to predefined criteria through review of testing results and manufacturing records together with appropriate good manufacturing practice (GMP) compliance and quality system, regardless of which approach is used. (Approved April 2009)

Q2: Does real-time release testing mean elimination of end-product testing?
A2: Real-time release testing does not necessarily eliminate all end-product testing. For example, an applicant can propose RTR testing for some attributes only or not all. If all critical quality attributes (CQAs) (relevant for real-time release testing)
are assured by in-process monitoring of parameters and/or testing of materials, then end-product testing might not be needed for batch release. Some product testing will be expected for certain regulatory processes such as stability studies or regional requirements. (Approved April 2009)

Q3: Is a product specification still necessary in the case of RTR testing?
A3: Yes, product specifications (see ICH Q6A and Q6B) still need to be established and met, when tested.[3] (Approved April 2009)

Q4: When using RTR testing, is there a need for stability test methods?
A4: Even where RTR testing is applied, a stability monitoring protocol that uses stability indicating methods is required[4] for all products regardless of the means of release testing (see ICH Q1A and ICH Q5C). (Approved April 2009)

Q5: What is the relationship between control strategy and RTR testing?
A5: RTR testing, if utilized, is an element of the control strategy in which tests and/or monitoring can be performed as in-process testing (in-line, on-line, at-line) rather than tested on the end product. (Approved April 2009)

Q6: Do traditional sampling approaches apply to RTR testing?
A6: No, traditional sampling plans for in-process and end-product testing involve a discrete sample size that represents the minimal sampling expectations. Generally, the use of RTR testing will include more extensive on-line/in-line measurement. A scientifically sound sampling approach should be developed, justified, and implemented. (Approved April 2009)

Q7: If RTR testing results fail or trending toward failure, can end-product testing be used to release the batch?
A7: No, in principle the RTR testing results should be routinely used for the batch release decisions and not be substituted by end-product testing. Any failure should be investigated and trending should be followed up appropriately. However, batch release decisions should be made based on the results of the investigations. In the case of failure of the testing equipment, please refer to the previous question. The batch release decision should comply with the content of the marketing authorization and GMP compliance. (Approved April 2009)

Q8: What is the relationship between in-process testing and RTR testing?
A8: In-process testing includes any testing that occurs during the manufacturing process of drug substance and/or finished product. Real-time release testing includes those in-process tests that have a direct impact on the decision for batch release through evaluation of critical quality attributes. (Approved June 2009)

Q9: What is the difference between "real time release" and "real-time release testing"?
A9: The definition of *real-time release testing* in Q8(R2) is "the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls."
The term *real time release* in the Q8(R2), step 2 document was revised to "realtime release testing" in the final Q8(R2) Annex to fit the definition more accurately and thus avoid confusion with batch release. (Approved June 2009)

Q10: Can surrogate measurement be used for RTR testing?
A10: Yes, RTR testing can be based on measurement of a surrogate (e.g., process parameter, material attribute) that has been demonstrated to correlate with an in-process or end-product specification (see ICH Q8(R2); Annex, section II.E (2.5)). (Approved June 2009)

Q11: What is the relationship between RTR testing and parametric release?
A11: Parametric release is one type of RTR testing. Parametric release is based on process data (e.g., temperature, pressure, time for terminal sterilization, physicochemical indicator) rather than the testing of material and/or a sample for a specific attribute. (Approved October 2009)
3. Control Strategy (2.3)
Refer to the definition of *control strategy* provided in the ICH Q10 glossary:
A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Q1: What is the difference in a control strategy for products developed using the minimal approach vs. "quality-by-design" approach?
A1: Control strategies are expected irrespective of the development approach. Control strategy includes different types of control proposed by the applicant to assure product quality (ICH Q10, section IV.B.1 (3.2.1)), such as in-process testing and end-product testing. For products developed following the minimal approach, the control strategy is usually derived empirically and typically relies more on discrete sampling and end-product testing. Under QbD, the control strategy is derived using a systematic science and risk-based approach. Testing, monitoring, or controlling is often shifted earlier into the process and conducted in-line, online, or at-line testing. (Approved April 2009)

Q2: Are GMP requirements different for batch release under QbD?
A2: No, the same GMP requirements apply for batch release under minimal and QbD approaches. (Approved April 2009)

Q3: What is the relationship between a* design space *and a* control strategy*?
A3: A control strategy is required for all products.[5] If a design space is developed and approved, the control strategy (see ICH Q8(R2), Annex, section IV (4)) provides the mechanism to ensure that the manufacturing process is maintained within the boundaries described by the design space. (Approved April 2009)

Q4: What approaches can be taken in the event of on-line/in-line/at-line testing or monitoring equipment breakdown?
A4: The control strategy provided in the application should include a proposal for use of alternative testing or monitoring approaches in cases of equipment failure. The alternative approach could involve use of end-product testing or other options, while maintaining an acceptable level of quality. Testing or monitoring equipment breakdown should be managed in the context of a deviation under the quality system and can be covered by GMP inspection. (Approved June 2009)

Q5: Are product specifications different for minimal versus QbD approaches?
A5: In principle no, product specifications are the same for minimal and QbD approaches. For a QbD approach, the control strategy can facilitate achieving the end product specifications via real time release testing approaches (see ICH Q8(R2) Annex, appendix 1). Product must meet specification, when tested.[6] (Approved October 2009)

Pharmaceutical Quality System (3)

Q1: What are the benefits of implementing a pharmaceutical quality system (PQS) (in accordance with ICH Q10)?

A1: The benefits are:

- Facilitated robustness of the manufacturing process, through facilitation of continual improvement through science and risk-based postapproval change processes
- Consistency in the global pharmaceutical environment across regions
- Enable transparency of systems, processes, and organizational and management responsibility
- Clearer understanding of the application of a quality system throughout product lifecycle
- Further reducing risk of product failure and incidence of complaints and recalls, thereby providing greater assurance of pharmaceutical product consistency and availability (supply) to the patient
- Better process performance
- Opportunity to increase understanding between industry and regulators and more optimal use of industry and regulatory resources; enhance manufacturer's and regulators' confidence in product quality
- Increased compliance with GMPs, which builds confidence in the regulators

and may result in shorter inspections (Approved April 2009)

Q2: How does a company demonstrate implementation of PQS in accordance with ICH Q10?

A2: When implemented, a company will demonstrate the use of an effective PQS through its documentation (e.g., policies, standards), its processes, its training/qualification, its management, its continual improvement efforts, and its performance against pre-defined key performance indicators (see ICH Q10 glossary on *performance indicator*).

A mechanism should be established to demonstrate at a site how the PQS operates across the product lifecycle, in an easily understandable way for management, staff, and regulatory inspectors, e.g., a quality manual, documentation, flowcharts, procedures. Companies can implement a program in which the PQS is routinely audited in-house (i.e., internal audit program) to ensure that the system is functioning at a high level. (Approved April 2009)

Q3: Is it necessary to describe the PQS in a regulatory submission?

A3: No, however relevant elements of the PQS (such as quality monitoring system, change control, and deviation management) can be referenced as part of the control strategy as supporting information. (Approved April 2009)

Q4: Will there be certification that the PQS is in accordance with ICH Q10?

A4: No. There will not be a specific ICH Q10 certification program. (Approved April 2009)

Q5: How should the implementation of the design space be evaluated during inspection of the manufacturing site?

A5: Inspection should verify/assess that manufacturing operations are appropriately carried out within the design space. The inspector in collaboration with the assessor, where appropriate, should also verify successful manufacturing operations under the design space and that movement within the design space is managed within the company's change management system (see ICH Q10, section IV. B.3 (3.2), Table III). (Approved April 2009)

Q6: What should be done if manufacturing operations run inadvertently outside of the design space?

A6: This should be handled as a deviation under GMP. For example, unplanned "oneoff" excursions occurring as a result of unexpected events, such as operator error or equipment failure, would be investigated, documented, and dealt with as a deviation in the usual way. The results of the investigation could contribute to the process knowledge, preventive actions, and continual improvement of the product. (Approved April 2009)

Q7: What information and documentation of the development studies should be available at a manufacturing site?

A7: Pharmaceutical development information (e.g., supporting information on design space, chemometric model, risk management) is available at the development site. Pharmaceutical development information that is useful to ensure the understanding of the basis for the manufacturing

process and control strategy, including the rationale for selection of critical process parameters and critical quality attributes, should be available at the manufacturing site.
Scientific collaboration and knowledge sharing between pharmaceutical development and manufacturing is essential to ensure the successful transfer to production. (Approved June 2009)

Q8: Can process parameters be adjusted throughout the product lifecycle?
A8: Process parameters are studied and selected during pharmaceutical development and monitored during commercial manufacturing. Knowledge gained could be utilized for adjustment of the parameters as part of continual improvement of the process throughout the lifecycle of the drug product (see ICH Q10, section IV (3)). (Approved June 2009)

D. Impact of New ICH Quality Guidance on GMP Inspection Practices (4)

Q1: How will* product-related *inspections differ in an ICH Q8, Q9 and Q10 environment?
A1: In the case of product-related inspection (in particular, preauthorization) depending on the complexity of the product and/or process, greater collaboration between inspectors and assessors could be helpful (for example, for the assessment of development data). The inspection would normally occur at the proposed commercial manufacturing site, and there is likely to be greater focus on enhanced process understanding and understanding relationships, e.g., critical quality attributes (CQAs), critical process parameters (CPPs). The inspection might also focus on the application and implementation of quality risk management principles, as supported by the pharmaceutical quality system (PQS). (Approved April 2009)

Q2: How will* system-related *inspections differ in an ICH Q8, Q9, and Q10 environment?
A2: The inspection process will remain similar. However, upon the implementation of ICH Q8, Q9, and Q10, inspections will have greater focus on (but not only focus on) how the PQS facilitates the use of e.g., quality risk management methods, implementation of design space, and change management (see ICH Q10). (Approved April 2009)

Q3: How is control strategy approved in the application and evaluated during inspection?
A3: Elements of control strategy submitted in the application will be reviewed and approved by the regulatory agency. However, additional elements are subject to inspection (as described in Q10). (Approved October 2009)

E. Knowledge Management (5)

Q1: How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?
A1: Q10 defines *knowledge management* as: "Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components."
Knowledge management is not a system; it enables the implementation of the concepts described in ICH Q8, Q9 and Q10.
Knowledge management is not a new concept. It is always important regardless of the development approach. Q10 highlights knowledge management because it is expected that more complex information generated by appropriate approaches (e.g., QbD, process analytical technology (PAT), real-time data generation, and control monitoring systems) should be better captured, managed, and shared during product life-cycle.
In conjunction with quality risk management, knowledge management can facilitate the use of concepts such as prior knowledge (including from other similar products), development of design space, control strategy, technology transfer, and continual improvement across the product life cycle. (Approved April 2009)

Q2: Does Q10 suggest an ideal way to manage knowledge?
A2: No. Q10 provides a framework and does not prescribe how to implement knowledge management. Each company decides how to manage knowledge, including the depth and extent of information assessment based on its specific needs. (Approved April 2009)

Q3: What are potential sources of information for knowledge management?
A3: Some examples of knowledge sources are:

- Prior knowledge based on experience obtained from similar processes (internal knowledge, industry scientific and technical publications) and published information (external knowledge: literature and peer-reviewed publications)
- Pharmaceutical development studies
- Mechanism of action
- Structure/function relationships
- Technology transfer activities
- Process validation studies
- Manufacturing experience, e.g.,
    - Internal and vendor audits
    - Raw material testing data
- Innovation
- Continual improvement
- Change management activities
- Stability reports
- Product quality reviews/annual product reviews
- Complaint reports
- Adverse event reports (patient safety)
- Deviation reports, recall Information
- Technical investigations and/or CAPA reports
- Suppliers and contractors
- Product history and /or manufacturing history
- Ongoing manufacturing processes information (e.g., trends)

Information from the above can be sourced and shared across a site or company, between companies and suppliers/contractors, products, and across different disciplines (e.g., development, manufacturing, engineering, quality units). (Approved April 2009)

Q4: Is a specific dedicated, computerized information management system required for the implementation of knowledge management with respect to ICH Q8, Q9, and Q10?
A4: No, but such computerized information management systems can be invaluable in capturing, managing, assessing, and sharing complex data and information. (Approved April 2009)

Q5: Will regulatory agencies expect to see a formal knowledge management approach during inspections?
A5: No. There is no added regulatory requirement for a formal knowledge management system. However, it is expected that knowledge from different processes and systems will be appropriately utilized.
Note: "formal" means: it is a structured approach using a recognized methodology or information technology (IT) tool, executing and documenting something in a transparent and detailed manner. (Approved June 2009)

F. Software Solutions (6)

Q1: With the rapid growth of the new science and risk-based quality paradigm coupled with the IWG efforts to facilitate globally consistent implementation of Q8, Q9, and Q10, a number of commercial vendors are now offering products that are being marketed as "ICH compliant solutions" or ICH Q8, 9, and 10 Implementation software, etc. Is it necessary for a pharmaceutical firm to purchase these products to achieve a successful implementation of these ICH guidances within their companies?
A1: No. The ICH Implementation Working Group has not endorsed any commercial products and does not intend to do so. ICH is not a regulatory agency with reviewing authority and thus does not have a role in determining or defining "ICH compliance" for any commercial products. While there will likely be a continuous proliferation of new products targeting the implementation of these ICH guidances, firms should carry out their own evaluation of these products relative to their business needs. (Approved April 2009)

1.7.2 FDA and EMA on Design Space Verification

1. Why would a design space be verified during the product lifecycle?
In both Agencies' experience, the design space verification at commercial scale is not necessarily complete at the time of submission of the application but should occur over the lifecycle of the product and process. Initial design space verification often occurs solely at or near the target operating ranges. However, movements from one area to another area within the design space (e.g., re-establishing the Normal Operating Ranges (NOR)) within the approved design space in an unverified area) may pose higher or unknown risks due to potential scale –up effects and/or model assumptions. It is important that these risks are understood and evaluated utilizing an appropriate control strategy, including but not restricted to the controls submitted in the dossier. It is understood that when an applicant demonstrates that a design space is scale independent, then additional risk mitigation steps are not necessary for design space verification.

2. What is the purpose of design space verification at commercial scale?
Design space verification demonstrates that within design space boundaries scale-up effects are under control and do not adversely affect the expected product quality at commercial scale.

3. How is a design space initially developed and verified at commercial scale?
Both Agencies acknowledge that when a design space is established at early stages of product development, it is typically developed based on experiments conducted at laboratory or pilot scale. The confidence in the design space at commercial scale can vary depending on the amount and type of development data generated and the knowledge of the scalability (i.e., the degree of scale dependency of the design space). Design space limits at commercial scale can be based on scale-up correlations demonstrated during development studies and/or experimentation. In addition, design space limits can be challenged with computational simulations. The Agencies further acknowledged that the commercial process is generally operated in a specific
area of the design space, sometimes called the NOR (Normal Operating Range). The NOR describes a region around the target operating conditions that contains typical operational variability. Initial process verification often occurs solely within the NOR at commercial scale.

4. How can a design space be verified at commercial scale?
It is not necessary to repeat at commercial scale the experiments initially conducted to define a design space at lab or pilot scale. Furthermore, it is neither necessary to verify entire areas of design space nor to identify the edge of failure. In principle, more than one area of a design space may be verified at the time of submission but the design space can, as appropriate, also be further verified over the product lifecycle. The approach to design space verification over the product lifecycle can be guided by the results of risk assessment on the potential effect of changes to scale dependent parameters on product quality. Depending on the specific change, the potential impact to the product quality, and the ability of the control strategy to detect product failures, the management of the risk can include additional monitoring of quality attributes and/or process parameters not included in the routine control system.

5. How should design space verification protocol be addressed in the submission?
In principle, a design space verification protocol could include the following: list of scale dependent parameters whose impact on the CQAs has not been verified at commercial scale, definition of the potential scale-up risks to the CQAs, discussion of whether the control strategy can address these risks, and description of any additional controls, as needed. EU authorities' expectation is that a protocol for design space verification be submitted in section 3.2.R of the application. At the time of submission, a proposed design space not verified at commercial scale should be accompanied by an appropriate verification protocol. The protocol would be assessed at the time of review. Verification data are managed and documented in the site change management system.
FDA's expectation is that any plans for design space verification be available at the manufacturing site as an element of the change control, validation, and/or knowledge management strategy. Providing data for initial design space verification and a high-level overview of the plan for design space verification over the product lifecycle can be beneficial to the review of the application.

6. What if unexpected results/events are obtained during the design space verification studies?
If the verification studies prove the process does not meet the predefined product quality attributes in a new region of the approved design space, this may indicate an underlying issue with the design space or a flaw in the assessment or verification plan. Changes to the boundaries or description of the design space and any required changes to design space verification protocol should be reported to the Agencies, using appropriate notification categories, in accordance with regional requirements.
Appendix 1 and 2 address regional expectations and regulations
Appendix 1: EU's expectations

7. How can a design space be verified at commercial scale for biological products?
Principles laid down for chemical products are applicable to biological products. In addition, verification studies should provide evidence that the quality attributes of the product are comparable prior to and after the change. This could include a proposal for modular sets of tests and acceptance criteria to be deployed, taking into account the nature of the change and its associated risk.

8. What is the difference between process validation and design space verification?
Design space verification should not be confused with process validation. Both take into consideration prior knowledge and development conclusions and are conducted at commercial scale, however the scope of the studies are not the same. Whereas process validation demonstrates consistency of the process at normal operating ranges, design space verification demonstrates that scale effect and or model assumptions are under control in the new area of design space and do not affect product quality. Unlike validation which covers all the steps of the manufacturing process, verification studies refer only to those operations where a design space has been proposed. In order to address the risks identified during the risk assessment of operating in the unverified area of the design space the verification studies may also include testing / monitoring of additional parameters or at an increased frequency as compared to the routine control strategy. When verification data proves that the extent of movement within the design space is of high risk (e.g. critical quality attributes are met but close to edge of failure identified at laboratory/pilot scale), process validation (consistency of the process) in the new area of design space (new NOR) should also be considered. A protocol for design space verification should be submitted in section 3.2.R. irrespective of the validation approach. When a strategy for continuous verification is envisaged, where relevant, the elements of design space verification should be included as part of the continuous verification protocol. It is understood that when an applicant can demonstrate that the design space is scale independent then a verification protocol is not requested in the dossier. NB: Continuous Process Verification is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8).
Appendix 2: FDA expectations

9. How should design space verification approach be addressed in the pharmaceutical quality system?
FDA recommends that firms have a written plan for when and how to evaluate the need for design space verification under their pharmaceutical quality system. FDA's expectation is that such plans for design space verification be available at the manufacturing site. Additionally, it can be beneficial to the review of the application for the applicant to include in the initial submission a high-level overview of the plan for design space verification over the product lifecycle.

2 GMP for Medicinal Products

2.1 EU GMP (EMA)

European Union (EU) GMP guide part I: Basic requirements for medicinal products: Chapter 5: Qualification of suppliers

1. Is an audit performed by a third party acceptable? H+V July 2006
The document 'guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials published as part of the Community procedures, states that it is expected that manufacturing-authorisation holders will gain assurance that the active substances they use are manufactured in accordance with GMP through audit of the active-substance suppliers. Small manufacturers may not have the necessary expertise or resource to conduct their own audits.
Section 5.25 of the GMP guideline requires starting materials to be purchased from approved suppliers and about whom the manufacturer has a particular and thorough knowledge.
An audit conducted by the manufacturing-authorisation holder itself should be integral to the manufacturer's quality-assurance system and subject to the basic GMP requirements, i.e. conducted by properly qualified and trained staff, in accordance with approved procedures. It should be properly documented. These aspects can be inspected as necessary by the competent authorities.
If a third party is involved, the arrangements should be subject to chapter 7 of the GMP guideline. There should be evidence that the contract-giver has evaluated the contract-acceptor with respect to the aspects described above.
All parties involved should be aware that audit reports and other documentation relating to the audit will be made available for inspection by the competent authorities if requested. This should normally provide sufficient assurance that the results of an audit carried by the third party are credible, thus waiving the need for an audit conducted by the manufacturing-authorisation holder itself. However, it must also be satisfactorily demonstrated that there are no conflicts of interests. Conflicts of interests could arise for example from:

- a commercial relationship between the organisation performing the audit and the organisation being audited;
- a personal conflict on the part of the auditor where he / she has been employed by the organisation being audited in the recent past (i.e. within the last three years) or has a financial interest in it.

This topic should also be addressed in the technical contractual arrangements. Any measures taken by the contract-giver should be documented, e.g. signed undertakings by the auditors.
Similarly, the principles outlined above could be used to allow sharing of audit reports between different manufacturing-authorisation holders using the same active substance supplier, provided that the scope of the audits can be shown to be applicable to the active substances of mutual interest.

2. Is it possible to use multiple batch numbers in packaging of medicinal products? H+V January 2005

Manufacture of the medicinal products - Process control
1. When validating a manufacturing process, if a common bulk is used to manufacture a series of products, how should the pilot batch size be decided upon? H+V September 2007
It is the applicant's responsibility to select and justify the pilot batch size.
The joint Committee for Medicinal Products for Human Use and Committee for Medicinal Products for Veterinary Use guideline on process validation (CPMP/QWP/848/96, CVMP/598/99) states that, "pilot-batch size should correspond to at least 10% of the future industrial scale batch i.e. such that the multiplication factor for scale-up does not exceed 10. For oral solid dosage forms this size should be at least 10% or 100,000 units whichever is greater* unless otherwise justified".
The guideline does not dictate that the 10% figure should always be linked to the scale of manufacture of individual product presentations. In addition, it allows for departures from the guidance where this is justified. Furthermore, the guideline does not preclude the use of bracketing. Certain bulk products are used to produce a series of presentations, for example a bulk powder blend may be used to produce 50-mg, 100-mg and 200-mg direct compression tablets with the same percentage composition. In such instances, as long as the applicant can demonstrate a satisfactory link between the pilot batch size used for validation and the routine production batch size, it will

usually be acceptable to define the pilot batch size as 10% of the planned production scale for the bulk product. During the process validation study, the complete pilot scale bulk batch should be used to manufacture the individual presentations. The division of the bulk batch between the different presentations should also be justified.
*In the case of veterinary medicinal products, the minimum pilot size may be smaller than 100,000 units where justified.

Variation
What is understood by "manufactured by complex manufacturing processes" in change code B.II.b.4 (change in batch size of the finished product)? H+V October 2010

Appearance of tablets of different strengths
1. If the applicant wishes to apply for more than one tablet strength, what level of difference in the appearance between the different tablet strengths would be required? H+V June 2011
In the case of applications for more than one tablet strength, the different tablet strengths should be distinguishable at a level sufficient to avoid mistakes between the different strengths by the final user. Distinguishing tablet strengths by colour / shape and marking / embossing is preferable.

Packaging
1. No specific requirements or recommendations are provided in the European Union guideline on plastic immediate packaging materials, CPMP/QWP/4359/03 and EMEA/CVMP/205/04, in regard to acceptable quality standards for plastic materials to be used for containers for solid oral dosage forms and solid active substances. Should the materials always comply with the specifications in the European Pharmacopoiea and if not, which quality standards are considered to be acceptable? H+V January 2009
The chapters of the European Pharmacopoeia (Ph. Eur.) that describe materials and containers are not exhaustive with regard to all different types of plastic materials and additives. Reference to the specifications published in the Ph. Eur. is therefore not always possible. As outlined in the Ph. Eur. general notices 1.3, it is not obligatory that only materials complying with a given specification in a chapter of the Ph. Eur. can be used as immediate packaging materials. Materials with a different formulation, complying with a different specification may be used, if justified, and subject to agreement by the competent authority.
For solid oral dosage forms and solid active substances, it has been agreed by the Joint Committee for Medicinal Products for Human Use / Committee for Medicinal Products for Veterinary Use Quality Working Party that plastic materials compliant with the relevant European Union (EU) food legislation relating to plastic materials and articles intended to come into contact with foodstuffs are considered acceptable. A specification elaborated in accordance with the provisions described in the EU guideline on plastic immediate packaging materials (CPMP/QWP/4359/03) should be laid down.
2. Does the European Medicines Agency / Committee for Medicinal Products for Veterinary Use guideline on development pharmaceutics for veterinary medicinal products and its annex decision trees for the selection of sterilisation methods prevent the use of heat-labile plastic packaging materials and aseptic processing for sterile veterinary medicinal products? V February 2012
Ensuring the sterility of medicinal products is the main issue when considering the packaging for sterile products, and therefore the method of choice for the production of any sterile products should be terminal sterilisation.
The European Medicines Agency / Committee for Medicinal Products for Veterinary Use guideline on development pharmaceutics for veterinary medicinal products and its annex decision trees for the selection of sterilisation methods currently state in the introduction to the annex that, "the use of an inappropriate heat-labile packaging material cannot in itself be the sole reason for adoption of aseptic processing. Manufacturers should choose the best sterilisation method achievable for a given formulation and select the packaging material for the product accordingly. However, it may be that the choice of a packaging material for a given product has to take into account factors other than the method of sterilisation. In such cases these other factors need to be clearly documented, explained and scientifically justified in the marketing authorisation dossier."
Aseptic processing cannot be considered as a simple replacement for terminal sterilisation. The European Pharmacopoeia (Ph. Eur.) general text 5.1.1: methods of preparation of sterile products states that, "wherever possible, a process in which the product is sterilised in its final container (terminal sterilisation) is chosen," and that, "if terminal sterilisation is not possible, filtration through a bacteria-retentive filter or aseptic processing is used; wherever possible, appropriate additional treatment of the product (for example, heating of the product) in its final container is applied." Such a

combination of aseptic processing with non-standard lower temperature heat treatments, either before aseptic filling, or after aseptic filling, should be pursued where possible in line with the recommendations of the Ph. Eur.
The guideline therefore does not prevent the use of heat-labile packaging materials for sterile products, but there must be justified reasons for having such packaging for sterile products, and these must be supported by the overall benefit:risk balance of the product.

Quality by design - Cooperation between assessors and inspectors when real-time release testing (RTRT) is applied - New June 2013

1. Are good-manufacturing-practice (GMP) inspectors involved in approval of RTRT submissions? H+V June 2013
The level of interaction during (and possibly after) the assessment process will depend upon what is actually proposed, which could be quite varied and of different levels of complexity. Where needed, a discussion between assessor and inspector is important to achieve a common understanding of the applicant's proposal and its potential impact on the marketing-authorisation dossier and on-site situation.
The potential requirement for an inspection will depend upon the applicant's approach to and justification for RTRT and on existing experience of the manufacturer with this approach, i.e what the basis is for RTRT and what in-process controls will be applied and how this will be done e.g. the technology applied. If complex technology (such as near-infrared or Raman spectroscopy) is used for RTRT for the first time at a manufacturing site, a product-specific inspection is likely to be requested. If the RTRT approach merely involves an increased level of at line testing in lieu of finished product testing, then this would not necessarily require a product-specific inspection prior to approval, but will be taken into consideration as part of a future routine GMP inspection.

2. When should collaboration between inspector and assessors in relation to RTRT start? H+V June 2013
Collaboration between inspectors and assessors on RTRT may be initiated by inclusion of a proposal for introduction of RTRT in a new marketing-authorisation (MA) or variation application. In such cases, the assessor should contact the relevant supervisory authority at the earliest opportunity in the assessment procedure to discuss the potential implications for the MA dossier and discuss the need to trigger a GMP inspection. When an inspection is triggered for a specific product, the timing of the inspection will depend on the availability of relevant data generated at the commercial scale.

3. Are data generated during the running in period (parallel testing) requested before approval of RTRT? H+V June 2013
For biological products or when models (design-space or calibration models for complex technology such as near infrared, etc.) are part of the RTRT scheme, results of parallel testing on commercial-scale batches should normally be included in the MA or variation submission.
In event that parallel testing of a sufficient number of batches is not complete at the time of submission or approval, this may be completed by inclusion in a post-approval change-management protocol and the MA can be granted on the grounds of finished product testing.
Once parallel testing is complete, RTRT may be implemented by either notification to (type IA), or approval by, the competent authority (type IB) as appropriate. The route for implementation will be indicated to the applicant during the assessment of the initial application.

Reduced testing of starting materials
1. What information should be included in marketing-authorisation dossiers regarding the actual testing that is carried out on any starting materials, e.g. active substances, excipients and packaging materials, on receipt by a finished product manufacturer? H+V June 2011
Although some parameters should always be tested on receipt by the finished product manufacturer e.g. diethylene glycol in glycerol, what is actually tested on receipt is fully covered under good manufacturing practice and should be justified based upon risk assessments, based on historical data backed by supplier audit. Consequently, the relevant registered specifications in the marketing-authorisation application should not include any reference at all to reduced testing on receipt by the finished product manufacturer.

Setting specifications for impurities in veterinary medicinal products

1. Different positions regarding the setting of specifications for both single identified and unidentified impurities observed below 1.0% in the finished product specifications (release and shelf-life), in veterinary medicinal products, appear to have arisen from the wording of VICH Guidelines GL11 and GL39 (mainly decision tree 2) being interpreted in two different ways. What limits should therefore be applied for impurities in veterinary medicinal products? Should these limits be set to < 1.0% (the VICH guideline GL11 identification threshold limits) regardless of the batch analyses and stability study data? Or should they be set based on the results observed in the batch analyses and stability studies? V July 2013

Individual impurities:

- the limits for individual impurities can be set by applying the VICH GL11 identification/qualification threshold of 1.0% (for impurities for which there are no specific safety concerns) irrespective of batch data results. Lower limits for individual impurities (e.g., 0.4%) are however also acceptable if proposed by the applicant and supported by batch data.It should be noted however, that individual impurities observed at levels greater than 0.3% should be reported, in accordance with VICH GL11.

Total impurities:

- the limits for total impurities should be based on batch results, nevertheless where limits of 1.0% have been accepted for individual impurities, a limit for total impurities of less than 1.0% should not be requested by competent authorities, irrespective of the batch data results.

Specific type of products – Dry product inhalers

1. Should dropping of an inhalation device be investigated during development? H June 2012

Dropping of the device should be investigated as part of the robustness study defined in the guideline on the pharmaceutical quality of inhalation and nasal products (section 4.2.18).
The product performance should be investigated under conditions to simulate use by patients.
The delivery device should be carried between use and actuated at the frequency indicated in the instructions for use. Simulation of dropping the delivery device and the robustness of any lockout mechanism should be investigated. The dropping simulation should be performed towards the end of the life of the product (e.g. at dose 180 for a 200-dose product) in order to assess the effect of drug accumulated on the mouthpiece, or any other part of the device, during the lifetime of the device being dislodged. If the device is designed to have the mouthpiece removed for periodical cleaning, testing should be performed both with the mouthpiece removed and cleaned in accordance with instructions for use during the test, and, as a worst case, without removal and cleaning. Significant variations in the delivered dose and/or fine particle mass should be fully discussed in terms of the safety and efficacy of the product. Appropriate handling instructions to the patients should be established, based on the results obtained.

Specific types of product - Graduation of measuring devices for liquid dosage forms

1. What are the requirements for the graduation of measuring devices for liquid dosage forms of medicinal products for human use, in particular in relation to the suitability of the graduation of the measuring device regarding dosing accuracy and dosing precision of the related product and the suitability of the measuring device for the related product? H September 2006

The points discussed below are applicable to new marketing-authorisation applications or fully reformulated existing medicinal products. These points should be considered referring to the graduation of a measuring device for a liquid dosage form of a medicinal product for human use, such as solutions, suspensions and emulsions, in section 3.2.P.2: pharmaceutical development of the Common Technical Document. They should be part of the justification of the suitability of the graduation of the measuring device for dosing the medicinal product under application. The measuring device shall comply as well with the relevant parts of the requirements given in the Medical Device Directive 93/42/EEC and with International Organization for Standardization (ISO) standards, as applicable.
Measuring devices may be required to deliver oral, parenteral, nasal, vaginal, and rectal liquid dosage forms to patients. The measuring device can be marketed together with the medicinal product, e.g. syringes without needles to administer oral liquid preparations, measuring cups, spoons or beakers,

pipette applicators, or can be incorporated as integral part of the medicinal product, e.g. prefilled syringes.

Manner of graduation: The graduation should be applied to the measuring device in such a manner that accurate and precise dosing is guaranteed. The graduation can be embossed in the material. The graduation can also be printed on the material of the measuring device.
This precision and accuracy of dosing should be guaranteed from release throughout storage until the end of shelf life and also during the use of the particular measuring device under the conditions recommended in the summary of product characteristics (SmPC). Attention should be paid to the possibility of fading of the printing ink. Glueing of a label with a printed graduation to the measuring device is not generally favoured, because of the potential for dislocation of the glued label during storage and use. If a glued label is used, the effectiveness of the adhesive / label system under normal conditions of storage and use should be demonstrated.

Graduated scale: The graduated scale should correspond with the dosing advice as stated in section 4.2: posology and method of administration of the SmPC. This applies in principle to all measuring devices. Attention should among others be paid to the following items:

- possibility of the measuring device to supply the minimal and maximal dose per single dose (nominal capacity);
- suitability of the scale intervals in relation to the dosing advice or the dosage range when posology is stated per kilogram bodyweight or square metre body surface;
- ease of interpretation of the graduated scale: readability of the graduation numbers and the graduation lines, and distinction between the intervals of the scale.

European or international standards (European Committee for Standardization or ISO) may be available, e.g. for syringes recommendations are given on tolerances, graduated capacity, and graduated scale in ISO standards. These recommendations can be applied without further justification.

Suitability of measuring device for the medicinal product: The suitability of the measuring device for the medicinal product should be addressed. Attention should be paid to the following items:

- dosing accuracy and precision in relation to the therapeutic window of the drug substance;
- the risk of overdosing in relation to the measuring device. If possible, overdosing should be prevented. If the risk of overdosing cannot be avoided, appropriate care should be taken in the design of the scale graduation to prevent overdosing;
- the physical characteristics of the liquid in relation to the measuring device. The combination should assure accurate and precise dosing. Considerations can be for instance the needle diameter and the particle size of suspensions in injectables, the homogeneity (resuspendability) of suspensions and emulsions prior to and during the application of the measuring device, or residual amounts of liquid in the measuring device after administration of the dose to the patient.

Furthermore, suitability of the measuring device and its graduation for the intended patient population should also be taken into account.

Acceptance criteria: The graduation of the measuring device should be suitable to meet the acceptance criteria of the dose of medicinal product under application, as measured with the measuring device under application. These acceptance criteria should be in line with European Pharmacopoeia (Ph. Eur.) requirements, if applicable (for example Ph. Eur. 2.9.27: uniformity of mass of delivered doses from multidose containers), or other accepted pharmacopoeias. For single-dose containers, where not necessarily the whole content of the product needs to be administered to the patient, the same requirements can be applied as for multidose containers.

Specific types of product - Need for in vitro dissolution studies with alcohol for modified-release oral products including opioid drug products

1. What are the likely implications of the various observed in vitro effects of alcohol on the dissolution of different prolonged release opioid products at various concentrations and durations of exposure? H April 2009

In the absence of clinical data, the results of in vitro observations with alcohol (ethanol) may be considered, as a minimum, evidence of a possible physicochemical incompatibility with alcoholic

drinks. The possibility of such an incompatibility with alcoholic drinks should be considered for all modified release products.
The general methods of in vitro release testing are considered capable of providing sufficient evidence of alcohol incompatibility. In the case where in vitro alcohol incompatibility of the drug product is demonstrated, then appropriate warnings should be included in the summary of product characteristics, in line with current guidelines.

2. Is it considered that in future, in vitro studies investigating the effect of alcohol / ethanol on dissolution / release should be required for the following cases? H April 2009
The interaction with alcohol observed in vitro should be considered as a physicochemical incompatibility of the drug product. In line with current regulatory practice, reference to this incompatibility, albeit dietary rather than medicinal, has been included in the product literature to supplement the current pharmacological warning to avoid alcohol.
In vitro studies investigating the effect of alcohol / ethanol on dissolution / release are recommended for all opioid modified-release products where applicants consider the potential for incompatibility with alcohol exists.
To minimise the risk, it is recommended that the product design, if possible and practical, should be such that a physicochemical incompatibility with alcohol is avoided. This advice is especially important for drug substances with a narrow therapeutic index.

3. Is it considered that in vitro studies investigating the effect of alcohol / ethanol on dissolution / release might also be required for oral prolonged release formulations containing active substances other than opioids? If so, should they be required only where rapid dose dumping of the active substance might be expected to cause clinically hazardous overdose, or should they be required for all oral prolonged-release products containing any active substance? H April 2009
Where there are scientific grounds that the defined-release characteristics of the oral drug may be adversely affected by the presence of alcohol, then alcohol physicochemical incompatibility should be considered by the applicant. This would apply to all oral prolonged- (and delayed- and modified-) release products.

4. How might the methodological requirements for in vitro testing of the potential for accelerated release in the presence of alcohol be established, ensuring maximum relevance to the clinical situation? H April 2009
At this point in time, it is not possible to provide authoritative methodological requirements.
In vitro studies are considered sufficient to show evidence of alcohol incompatibility, with a consequential effect on the quality of the drug product, with respect to release performance.
It is noted that in vitro release testing primarily relates to the quality control of drug products, with limits set to be in line with those batches used for clinical studies for which satisfactory safety and efficacy has been established.
Taking this into account, if the presence of alcohol in the dissolution medium of the in vitro release test produces out of specification results, then this may be considered sufficient evidence of an incompatibility with alcohol, i.e. that alcohol adversely affects the quality of the drug product.
In the first instance, the applicant should consider the possibility of physicochemical incompatibility with alcohol. This should include a discussion of the solubility of the release controlling excipients in alcohol and the impact this may have on the in vitro release performance of the drug product. Where solubility or other information cannot exclude the possibility of physicochemical incompatibility with alcohol, then in vitro release data should also be provided to assess the extent of interaction.
The dissolution medium should be the same as that proposed for routine testing, but with a justified range of alcohol added. The range of alcohol in the medium should mimic levels that are likely to be reached in the fluid of the stomach and proximal gastrointestinal tract following alcohol consumption e.g. 5%, 10% and 20%.
The applicant should discuss the significance of any out of specification results, particularly at the early time points, together with consideration of the risks of dose dumping and accelerated release. Appropriate warnings in the summary of product characteristics should be proposed and justified.

5. Are further measures needed to gain better understanding of the release characteristics of oral prolonged-release products in the presence of alcohol and their relevance to the clinical situation, for example by in vitro – in vivo correlation? If in vitro testing demonstrates a potential for alcohol to enhance opioid / active product release, should the applicant be required to investigate the clinical relevance of the effect in in vivo studies? H April 2009

It should be acknowledged that the clinical relevance of physicochemical incompatibility with co-administered alcohol is debatable, at the present time. The published literature is limited.
Where incompatibility with alcohol is evident, it is currently sufficient to address safety or other concerns by the inclusion of appropriate warnings in the product literature unless serious concerns are raised with respect to efficacy and safety.

Specific types of product - Veterinary medicinal products

1. What limits for microbiological quality are considered appropriate for premixes for medicated feeding stuffs which contain excipients of natural origin (e.g. soya bean husks, maize meal, etc.)? V October 2010

Ideally, compendial grade excipients should be used in new veterinary medicinal products and in these cases compliance with the general chapter 5.1.4: microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use is considered appropriate. For premixes for medicated feeding stuffs for veterinary use containing excipients of natural origin, application of these limits may not be possible. European Pharmacopoeia (Ph. Eur.) 5.1.4: microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use is a general chapter and is not specifically referenced in the Ph. Eur. monograph for premixes for medicated feedingstuffs and is therefore not mandatory.
The general chapter has essentially the same status as a guideline, that is, it represents the preferred option but it should be possible to accept deviation from it where justified. In case of premixes containing excipients of natural origin, the Agency would recommend following criteria as requested under special Ph. Eur. provision for oral dosage forms containing raw materials of natural origin. In exceptional cases, if this cannot be fulfilled, the applicant could apply other limits, e.g. the limits detailed in section C of 5.1.8: microbiological quality of herbal medicinal products for oral use, but only if fully justified.
In cases where an oral powder and a premix for medicated feedingstuffs have the identical composition, it would be expected that the same microbiological limits would be applied to both pharmaceutical forms. In this case the stricter limits are applicable (normally those for oral powders requested in chapter 5.1.4: non-aqueous preparations for oral use).

2. Is it possible to grant a marketing authorisation for a product which is not soluble over the pH ranges described in the guideline on quality aspects of pharmaceutical veterinary medicines for administration via drinking water (EMEA/CVMP/540/03-Rev.)? Could a recommendation be added in the summary of product characteristics / product information that, for solubility reasons, the pH of the drinking water has to be adjusted with acid / base before adding the medicinal product? V October 2010

The guideline on quality aspects of pharmaceutical veterinary medicines for administration via drinking water (EMEA/CVMP/540/03-Rev.1) sets out how the solubility of a product in drinking water should be tested (soft water / low pH with a pH range from 5.0 to 7.0 and hard water / high pH with a pH range from 8.0 to 9.0).
In principle, a veterinary medicinal product can only be authorised if it fully dissolves (and remains in solution) without further aid in drinking water of the usual pH range (which is usually a pH range between 5.0 and 9.0). If a pH adjustment of the drinking water is necessary this should be done with excipients (acid, base or buffer) included as part of the authorised veterinary medicinal product. Exclusions are only acceptable if justified (e.g. it has been shown that other formulation principles have been excluded).
The use of unlicensed acids or alkalis for the pH adjustment of the drinking water before (or after) adding the veterinary medicinal product in order to achieve the necessary solubility is not acceptable unless justified.

3. Is it permitted to have a multidose (parenteral) veterinary medicinal product for use both as an intramuscular injection and also an intramammary preparation? V October 2010

Such an example would be considered to be two different pharmaceutical forms (and also in this specific problem case, routes of administration) and therefore to need two different marketing authorisation (sub)numbers, as well as two different summaries of product characteristics.
In the European Union, different marketing authorisations (sub)numbers are necessary for different pharmaceutical forms. See the guideline on the categorisation of new applications versus variation applications.
Another reason is that using multidose containers for both intramammary and parenteral use may result in an increased risk of microbial contamination of the product in its multidose container.

4. Rubber stoppers (bungs) used for vial closures for multidose veterinary injectables are often punctured many times during use. Therefore suitable criteria regarding fragmentation (and self-sealing) are required. Problems can mainly arise in large multidose injectables, which can be used for different target species and / or ages of animals, but particularly for smaller animals where dose volumes are small, and so the pack could be punctured many times (e.g. in extreme cases in excess of 100 punctures). Should the general chapter on rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders (3.2.9) be applied in these cases? Which criteria for the maximum number of rubber fragments are deemed acceptable for a test design which is a multiple of the number of punctures described by Ph. Eur. 3.2.9? Should a worst-case scenario be used? V October 2010

The general chapter on rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders (3.2.9) is not mandatory on its own. If suitable justification is provided, the requirement (maximum of five fragments) contained in this chapter does not necessarily need to be applied. It is noteworthy that the European Pharmacopoeia (Ph. Eur.) test is designed to demonstrate that a stopper fulfills the general minimum requirements that are expected for rubber stoppers for medicinal products, but this can of course not cover all their potential uses.

The pack concerned should be proven to meet the requirements of the Ph. Eur. test modified to use the maximum number of punctures expected in relation to the target species, dose and route of administration (using the appropriate needle size for that scenario). Note that the maximum number of fragments expected remains exactly as in the Ph. Eur. test.

The summary of product characteristics (SmPC) and other product information should then reflect the number of punctures for which the closure has been demonstrated to meet the requirements of the Ph. Eur. test. For example, if the closure has been shown capable of withstanding X punctures with fragmentation and self-sealing characteristics which meet the relevant Ph. Eur. requirements. That is, with no additional increase in fragments for the increased number of punctures.

Risk management tools

Some examples of advice (if necessary in combination) which could be included in the SmPC (section 4.9) and other product literature to reduce potential damage to the stopper from excessive numbers of punctures:

- "The cap may be safely punctured up to X times."
- "When treating groups of animals in one run, use a draw-off needle that has been placed in the vial stopper to avoid excess broaching of the stopper. The draw-off needle should be removed after treatment."
- "Only the xx ml vial should be used to treat small piglets."
- "As the vial should not be broached more than X times the user should select the most appropriate vial size according to the target species to be treated."
- "When treating large groups of animals use only an automatic dosing device (with vented draw off apparatus when using the xx ml vial)."
- "For xxx pack sizes, use only automatic syringe equipment." (Applicable for large collapsible packs where a large number of doses may be withdrawn from the vial and concern about the stopper integrity exist.)
- "For xxx pack sizes, use of a multiple dose syringe is recommended." (Applicable for large non-collapsible packs where a large number of doses may be withdrawn from the vial and concern about the stopper integrity exist.)

Stability - Article-58 products

1. What kind of stability data are required for applications according to Article 58 of Regulation EC/726/2004? H July 2006

Article 58 of Regulation (EC) 726/2004 widens the scope of the European Medicines Agency and the Committee for Medicinal Products for Human Use to include applications for certain medicinal products intended exclusively for markets outside the Community, e.g. for antiretroviral therapy:

"1. The Agency may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 65. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organization, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply."

For these applications, it is of great importance to apply standards that ensure the same adequate product quality as for products to be marketed in the European Union (EU). In this context, stability data need to be submitted by the applicant that demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries, i.e. countries in climatic zones III and IV. Merely applying the same requirements as for the use in the EU, i.e. countries in climatic zone I / II, could potentially lead to substandard products when marketed in climatic zones III and IV.
The guideline stability data package for registration in climatic zones III and IV (ICH Q1 F) was officially withdrawn by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) steering committee in June 2006 due to controversial discussions about the adequacy of storage conditions defined. The World Health Organization (WHO) expert committee on specifications for pharmaceutical preparations has decided to split climatic zone IV into zone IVa (hot and humid) with storage conditions of 30°C/65% relative humidity (RH) and zone IVb (hot and extremely humid) with storage conditions of 30°C/75% RH; the WHO stability guideline will be revised accordingly.
When evaluating applications under Article 58 of Regulation EC/726/2004, it has to be assumed that the respective medicinal product will be used in all sub-zones of climatic zones III and IV, unless otherwise confirmed by the applicant. Therefore, in order to safeguard product quality throughout its entire intended shelf-life, stability studies under the conditions defined for climatic zones IVb need to be performed, i.e. the shelf-life needs to be established based on long-term data at 30°C/75% RH, supported by SIX months of data at 40°C/75% RH. The principles of extrapolation described in the note for guidance on evaluation of stability data (CPMP/ICH/420/02) as well as reduced testing designs as described in the note for guidance on bracketing and matrixing designs for stability testing of drug substances and drug products (CPMP/ICH/4104/00) may be applied. In cases where these data demonstrate stability over the required period of time, no special storage conditions need to be labelled.
If an application under Article 58 of Regulation EC/726/2004 only contains data adequate for climatic zones I / II, the list of questions should request the respective data appropriate for climatic zones III and IV. If the data show stability problems at 30°C/75% RH with regard to humidity, the circulation and use of the product should preferably be restricted to those countries and regions that are covered by data, e.g. the product should only be used in countries within climatic zones III and IVa. As an alternative, storage conditions need to be labelled, including humidity, e.g. 'keep protected from ambient humidity' as, especially for climatic zone IVb, humidity may be the stability-limiting factor. However, it has to be noted that due to the technical equipment and logistics available in some of the climatic zone-IV countries as well as the education and compliance of patients in the respective area, exposure of medicinal products to higher temperatures and humidity cannot be ruled out. This needs to be taken into account when defining shelf-life and storage conditions. For products to be stored at 'normal conditions', i.e. stable at 30°C, submission of accelerated data, i.e. 40°C/75% RH, can not be waived as they are needed to assess the impact of extreme temperature or humidity conditions that may occur in climatic zone IV, even though a product may not be stable for six months at these storage conditions.
Please note that for aqueous products in semipermeable containers to be marketed in climatic zone III, i.e. regions of extreme temperature, long-term testing should be performed at 30°C/35% RH. As an alternative, the calculation factors described in section 2.2.7.3 'drug products packaged in semi-permeable containers' of the note for guidance on stability testing of new drug substances and products (CPMP/ICH/2736/99) may be applied.

Stability - Declaration of storage conditions

1. What is the declaration of storage conditions to be used in the product information, for products which require to be stored and transported refrigerated? H+V August 2007

As foreseen by the note for guidance on declaration of storage conditions, when a product needs to be stored refrigerated, the wording 'store in a refrigerator' should be used in the labelling, and a reference to the temperature range, e.g. 2°C to 8°C, should be included in the summary of product characteristics (SmPC) and in the package leaflet.
According to the same note for guidance, when the need for refrigerated transport (cool chain), in addition to refrigerated storage, is envisaged, the following statement should be used: 'store and transport refrigerated'.

2. How should expiry dates be calculated and expressed? H+V July 2008
Guidance can be found in the note for guidance on the start of shelf-life of the finished product (CPMP/QWP/072/96 / EMEA/CVMP/453/01) and the Committees for Mutual Recognition and Decentralised Procedures and Quality Review of Documents product information templates. In summary, the expiry date should be calculated from the date of release or in case the period between the date of production and the date of release exceeds 30 days, from the date of production. The expiry date should be expressed as MM/YYYY. The product expires at the end of the specified month. In the worst case, this method of calculation results in an extension of the expiry date of two months:

Table 1: Example of the calculation of the expiry date of a tablet with a shelf life of 24 months

Date of first blending step	Date of packaging	Date of release	Expiry date	Interpretation fit for use	Total time from start of manufacture to end of shelf-life	Recalculated expiry date
28/01/2005	29/01/2005	30/01/2005	01/2007	Until 31 January 2007	2 years 3 days	01/2007
03/01/2005	04/01/2005	05/01/2005	01/2007	Until 31 January 2007	2 years 28 days	12/2006
03/01/2005	19/07/2005*	21/07/2005	01/2007	Until 31 January 2007	2 years 28 days	12/2006[1]
03/01/2005	04/01/2005	01/02/2005	02/2007	Until 28 February 2007	2 years 56 days	01/2007[1]

**The bulk compressed tablets have been stored for six months. It is expected that a shelf life for the intermediate product is detailed in the dossier and stability data to support this are also presented in the dossier.*
Particularly for products with a shelf-life of less than twelve months, this is not considered acceptable. The expiry date should therefore be calculated on a DD/MM/YYYY basis starting from the date of release, or if applicable from the date of production, and rounded up or down to MM/YYYY according to the following example: 14/01/2007 becomes 12/2006 and 15/01/2007 becomes 01/2007. See table 1 for recalculated expiry dates.

[1]Note: This question and answer was first published in July 2008 with a mistake (the recalculated date for examples 3 and 4 were mixed-up). Later the mistake was identified by QWP and in March 2009 the present corrected version was published.

Stability - Endotoxin testing and sterility testing at the end of shelf-life
1. Is endotoxin testing considered essential at the end of shelf life to confirm parenterals to be pyrogen-free?
Endotoxin testing is not requested at the end of shelf life, taking into account the fact that it is not considered a stability-indicating parameter. The shelf-life specification should be completed with a footnote stating that endotoxins are not tested during stability studies.

2. Is sterility testing considered essential at the end of shelf life to confirm parenterals to be sterile? H+V May 2009
Sterility is part of the shelf-life specification.
Sterility testing should be performed at least at the end of shelf life but it can be replaced by testing of the container closure integrity. Depending on the nature of the container, intermittent integrity testing might be envisaged, independent of whether the sterility testing is replaced or not.

Stability - Reduced design in stability studies
1. Can reduced designs be used when performing stability studies on veterinary medicinal products? V October 2006
Yes, as long as the selected design is explained and justified. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline bracketing and matrixing designs for stability testing of drug substances and drug products (CPMP/ICH/4104/00), is applicable to new drug substances and products used in human medicine. However, veterinary companies may elect to follow this guideline. Where the guideline is followed, all aspects of the guideline should be followed.

Stability - Stability issues of pharmaceutical bulk products use in manufacture of the finished product

Background

Finished product stability guidance does not address storage of bulk product during the manufacturing process. The purpose of these questions and answers is to address the information to be provided in the marketing-authorisation dossier to support storage and / or transportation of bulk product during the manufacturing process.

Good-manufacturing-practice guidance indicates that bulk products should be stored under 'appropriate conditions' and therefore, the data provided in the dossier should be aimed to demonstrate the suitability of these conditions in relation to the intended storage and / or transportation arrangements of a bulk product and the effect of these on the quality of the given finished product over its declared shelf-life.

The objective is to increase the transparency of the supporting data required and not to introduce any new regulatory requirements.

The data required will depend on the type of product and the activities performed (i.e. prolonged storage or transportation) and a risk-based approach is encouraged in order to demonstrate the suitability of the data generated in each individual case.

The described framework is intended to cover all pharmaceutical bulk products. However, it is understood that the requirements for some specific types of products (e.g. biological products) may require additional data relevant to the type of product and this should be taken into consideration depending on the characteristics of that particular product.

1. What is the definition of bulk storage? H+V February 2012

The question most frequently arises in relation to solid oral dosage forms (particularly tablet cores before coating or packaging) but could be applicable at any stage in the manufacturing process of any pharmaceutical product where bulk is held in storage prior to further processing (e.g. bulk solution prior to filling, granulates, etc.).

2. What information should be provided on the bulk container? H+V February 2012

In general, the level of information to be provided will be dependent on the nature of the bulk product. The qualitative and quantitative (if required) composition of the bulk container should be described in the dossier and its control specification stated (module 3.2.P.3.4 or part 2.B).

3. What information should be provided on the storage conditions? H+V February 2012

It should be stated whether the bulk product is to be stored (and if relevant, transported) under controlled or non-controlled storage conditions.

4. What information is necessary regarding the transportation of bulk products between manufacturing sites? H+V Feb 2012

Where bulk product is transported between manufacturing sites, the transportation arrangements should be described in general terms (bulk container / storage and transportation conditions / monitoring arrangements) in the dossier (module 3.2.P.3.4 or part 2.B).

According to the guideline on good distribution practice, the following should be taken into consideration:

Principle:

- Good-manufacturing-practice quality should be maintained throughout the distribution network;
- Storage conditions should be observed at all times, including during transportation.

Storage:

- Temperature should be monitored and recorded periodically;
- Records should be reviewed regularly.

5. What data should be provided to support bulk storage and transportation arrangements? H+V February 2012

The maximum storage interval for the bulk product should be declared in the marketing-authorisation dossier, or alternatively, the maximum batch manufacturing time from start of product manufacture to completion of packaging in the final primary container for marketing.

When storage is prolonged (i.e. more than 30 days for solid oral dosage forms; more than 24 hours for sterile products), evidence of the suitability of the proposed container, storage interval or

transportation arrangements should be included in the dossier. The data to be provided will be dependent on results of development studies that represent the conditions proposed.
In line with the principles described for finished products in the relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) or International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH) guidelines, it is expected that data from pilot scale batches (minimum of two batches) stored under conditions that represent the storage conditions for the bulk product will be provided to support the storage of bulk products. Unless provided in the dossier, these data should be verified in post-approval stability commitments on commercial scale batches.
Where transportation of bulk between manufacturing sites is proposed, the impact of excursions outside of the original storage conditions should be discussed and, where necessary, supported by accelerated stability data.

6. How should the calculation of a product's shelf-life be performed? H+V February 2012
Calculation of the product's shelf-life should be in accordance with the Committee for Medicinal Products for Human Use / Committee for Medicinal Products for Veterinary Use note for guidance on the start of shelf-life of the finished dosage form (CPMP/QWP/072/96 / EMEA/CVMP/453/01). If other methods are proposed, these should be declared and justified through inclusion of batches that represent the full proposed holding intervals of the bulk product (intermediate) in the finished product stability programme.

7. Which stability conditions should be chosen to support bulk storage? H+V Feb 2012
It is not necessary to conduct stability studies on bulk according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) or International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH) recommendations (temperature or humidity). Stability studies on bulk should reflect real storage conditions in the standard container foreseen at the manufacturing site.
In the event that more than one manufacturing site is involved, the stability studies should also cover any transportation (duration and conditions).

Storage

1. What are the requirements for storage orientation recommendations in the product information for pressurised metered dose inhalers? H December 2008
During product development, the effect of orientation should be investigated in the priming and repriming studies according to the guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005). If storage orientation has a significant effect on the delivered dose during these studies (i.e. different repriming periods / number of actuations are required for re-priming when stored in different orientations), a storage orientation recommendation should be added to the product information (summary of product characteristics, package leaflet and label). The preferred storage orientation should be detailed.
As it cannot be guaranteed that the product will always be stored in the preferred orientation, the repriming instructions in the product information should be based on the worst-case scenario (i.e. the orientation which requires the shortest repriming period or the highest number of repriming actuations).

Water

1. What is the regulatory consequence of implementing an alternative method for rapid control of microbiological quality of water for injection and purified water? H+V July 2005
According to European Union legislation, pharmaceutical manufacturers are required to use European Pharmacopoeial standard water in the manufacture of medicinal products.
The European Pharmacopoeia (Ph. Eur.) has recently introduced a chapter making reference to the acceptability of rapid microbial methods to replace the standard Pharmacopoeial methods provided appropriate validation has been performed.
Following discussions at the QWP and the ad hoc good-manufacturing-practice inspectors' group, it is suggested that the introduction of such methods might require specific review to ensure that the appropriate validation steps have been followed and that the water continues to meet the Ph. Eur. specifications. Since, in the case of water, the validation will not be product specific, it is suggested that a company could request the supervisory authority to carry out a specific site inspection. The performance of such an inspection would be at the discretion of the supervisory authority and could involve a pharmaceutical assessor where necessary.

Since it is expected that the water will continue to meet Ph. Eur. specifications, if tested, no change to dossier requirements* (variations) would be involved and therefore no regulatory impact on individual products would normally be anticipated.

2.2. TAG Australia

2.2.1 Manufacture of sterile medicinal products (Annex 1)

53. What are the main changes in Annex 1 and how does the TGA interpret these changes?

The PIC/S has prepared and published a recommendation document for interpretative guidance on the revised Annex 1, which is called Technical interpretation of revised Annex 1 to PIC/S GMP Guide, PI 032-2. This document gives both a detailed overview of the most significant changes in Annex 1, as well as a technical interpretation. The document is endorsed by the TGA: Revised technical interpretation of Annex 1 to PIC/S GMP guide.

54. Are negative pressure containment isolators which are used for closed system preparations, considered separate in relation to the preparation of beta lactam antibiotics like penicillins (ref. to Clause 3.6 of the general part)?

Generally, dedicated buildings, facilities and equipment are required for penicillin manufacture. An isolator operating at negative pressure would be regarded as a 'micro-environment' and could be accepted for penicillin manufacture provided that factors such as cleaning, sanitation (noting that if the isolator is opened during cleaning this could present specific concerns), preventative maintenance, environmental monitoring (residues), spillage, etc. are adequately addressed with respect to cross contamination. However, the manufacture of 'other drugs' in the isolator used for penicillin would not be permitted.

55. Where in GMP does clean room apparel fit in? Can manufacturers of such apparel be licensed as a manufacturer of starting material?

Clean room apparel is not a therapeutic good and manufacturers of such apparel are not subject to inspection and licensing under the Therapeutic Goods Act 1989. However, licensed manufacturers of sterile medicinal products should qualify their vendors of critical goods used in the clean rooms, such as clean room apparel.

2.2.2 Manufacture of biological medicinal products (Annex 2)

56. Does the scope of Annex 2 include such things as beta-carotene as extracted from kelp and some of the antibiotics eg Gentamicin, Tobramycin?

As a general guide, the following are considered biological medicinal products under the requirements of Annex 2:

- Animal derived fractionation products
- Antibiotics produced by fermentation
- Antigens
- Antitoxins, antivenenes, enzymes and venoms
- Allergenic products
- Biological therapeutics products
- Cytokines
- Hormones
- Human derived fractionation products
- Immunosera
- Monoclonal antibodies
- Somatic cellular products
- Therapeutic recombinant products
- Toxoids/toxins

Also, as a general guide, although the following could be considered biological medicinal products, the additional requirements of Annex 2 will not be applied:

- Beta-carotene
- Shark cartilage
- Bee propolis
- Green lipped mussel
- Deer antler

57. Is Annex 2 applicable to the manufacture of APIs used in biological medicinal products?

Yes. The manufacture of APIs for biological medicinal products for human use is usually performed in immediate conjunction with the manufacture of the biological medicinal product itself. For that reason, Annex 2 is written to cover both the API and the finished product manufacuring steps of biologicals. Additionally, Part II of the Code is applicable to the manufacture of APIs for biological medicinal products.

2.2.3 Manufacture of radiopharmaceuticals (Annex 3)

58. What are the implications of the new Code for manufacturers of radiopharmaceuticals?

The implications for radiopharmaceuticals manufacturers are similar to those for other medicines manufacturers. The Guide to interpretation of the 2002 Code for manufacturing the PET radiopharmaceutical Fludeoxyglucose [18F] Injection has been revised to reflect the 2009 Code.

59. Are hospitals supplying radiopharmaceuticals to other hospitals required to obtain a TGA licence?

Yes, with one exemption, which is for public hospitals supplying radiopharmaceuticals to other hospitals or public institutions in the same State or Territory. In that case the biomedical engineers, radiochemists and pharmacists employed by those public hospitals are exempted from the requirement to obtain a TGA licence to manufacture radiopharmaceuticals.

60. Are radiopharmaceuticals supplied in a hospital situation required to be entered in the ARTG?

Yes, except for radiopharmaceutical cold kits to which a radioisotope is to be added immediately before injection into patients. Registration is not required if the cold kit is manufactured in a public or private hospital for a patient of that hospital or a patient of another public or private hospital in the same State or Territory.

2.2.4 Manufacture of herbal medicinal products (Annex 7)

61. If actives or 'marker compounds' in herbal products are identified but no primary standards are commercially available, how can assays be conducted?

If a marker compound is selected, a suitable reference material of that compound should be obtained from external or internal sources.

62. Does the TGA interpret 'quantified at input' to be equivalent to 'Standardized to contain' in the context of active claims on herbal medicines?

The TGA position on this issue has not changed. Please refer to the Guidance for the use of the term 'quantified by input' for complementary medicines manufacturers.

2.2.5 Sampling of starting and packaging materials (Annex 8)

63. What constitutes a validated procedure that would permit less than all containers to be sampled and tested for identification purposes?

- Every container of starting material must be identified if the supplier is not classified as reliable and is not validated according to Annex 8.
- Requirements for sampling active materials do not differ from those for excipients.
- The validation of a supplier cannot be accepted without a regular and adequate inspection. Such validation should comprise a number of actions, which may include all or most of the following:

I. The use of a questionnaire prepared by the potential customer and completed by the potential supplier, concerning the supplier's operating Quality System.
II. Approval inspection of the potential supplier's operation by the potential customer, or by a third party on their behalf. For example, a sister company located in the same country as the supplier. Reliance on inspection reports of other regulatory authorities by the potential customer is normally not sufficient, unless it can be demonstrated that the inspection covered the specific operations to be used in the processing of materials for the potential customer.
III. A program to evaluate the quality of each shipment of materials on receipt by the customer. In this regard, sampling of powders should be representative of the container contents. For example, sampling from the top, middle and bottom of drums, in the absence of validated sampling positions. Reduced testing programs should be evaluated by the inspector. Sampling by the suppliers should be validated.
IV. A program for regular re-inspection of the supplier's operation and for ongoing monitoring of the quality of material supplied, for example, through trend analysis of analytical results, periodic full testing.
V. In the case of active ingredients, the use of brokers as sources should be carefully evaluated. The quality of each batch of material should be confirmed through testing of representative samples.

• Certification e.g. a Certificate of Suitability of Monographs of the European Pharmacopoeia, does not replace an inspection.

64. In what cases could √n+1 sampling be applied?

Where a validated procedure is established to justify reduced sampling, and scientific and statistical evidence is presented, √n+1 sampling may be justified as applicable.

2.2.6 Qualification and validation (Annex 15)

68. How do PIC/S recommendation documents like PI-006-3 Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation and PI-007-5 Recommendations on the Validation of Aseptic Processes relate to the Code?

These documents are for guidance only. The TGA encourages the use of these Recommendation documents as they expand on clauses 5.21, 5.22, 5.23, 5.24 and Annexes 1 and 15 of the Code.

69. Is it necessary to revalidate an already established and previously validated process?

Validation is required to ensure that therapeutic goods consistently meet product specifications and this principle is to be applied for all products (including complementary medicines). There are some critical processes that must be validated and risk assessment would not justify exemption from validation (e.g. mixing for tablets/capsule/powder dosage forms). For herbal products grouping can be considered and justification included in the VMP. Markers can be used for herbal process validation.

Clause 45 of Annex 15 is quite specific on the issue of revalidation, ie. 'Facilities systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation'.

The frequency of periodic revalidation is intentionally not defined (except for example, sterile media trials under Annex 1, clause 44) because this will vary according to a large range of factors. Manufacturers need to determine and justify their own revalidation frequency based on a risk assessment and other relevant factors.

If the process has not been previously validated, then it should be validated retrospectively according to items 31-35 of Annex 15. When retrospective validation is inadequate, then validation according to Annex 15 is required. The scope and extent of validation should be based on risk assessment and should be conducted according to a validation master plan.

70. Should batches made for process validation be the same size as the intended industrial scale batches?

The process must be validated for the smallest and the largest batch sizes. Process validation is not required for intermediate batch sizes if it could be demonstrated, based on risk assessment, that process consistency can be achieved for any intermediate batch size.

71. Should the scope and extent of validation be based on risk?

Yes, the scope and extent of validation should be based on risk according to the manufacturer's quality risk management procedures. Qualification and validation work is required to control the critical aspects of the particular operation and a common sense approach should be applied.

72. Is performance qualification (PQ) required to be carried out for each item of critical process equipment, if process validation is performed on the same equipment?

PQ is required to be preceded by IQ and OQ.

For significant changes to equipment (eg. for new or modified items of equipment), the PQ is separate from and precedes process validation. For minor changes not impacting on already qualified equipment (eg. to processing parameters only), process validation could be integrated in PQ and a repeated IQ and OQ may not be necessary.

73. What are the TGA's expectations for process validation for complementary medicines manufacture?

A separate guidance document for this is available: Technical guidance on the interpretation of manufacturing standards: Process validation for Listed complementary medicines

3. GMP for APIs

Complex manufacturing processes is intended to cover situations where the actual manufacture of the finished product involves a process which includes one or more processing steps that may give rise to scale-up difficulties. These will be considered on a case by case basis.
Where relevant, if a change is submitted as a type IB variation, it is up to the applicant to provide adequate justification for not considering a manufacturing process as a 'complex' one, in terms of scale-up. However, under the safeguard clause, it should be noted that if the supplied justification is not accepted, it is possible for the competent authority to upgrade the submission to a type II variation during the validation phase.
If unsure, applicants should consult the relevant competent authority before submitting the variation.

3.1 EU GMP (EMA)

EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances - UPDATED

1. How can GMP compliance for active-substance manufacturers be demonstrated? H+V April 2011
Directive 2001/83/EC as amended (Directive 2001/82/EC for veterinary medicinal products) states that manufacturing-authorisation holders are obliged to use, as starting materials, only active substances that have been manufactured in accordance with the detailed guidelines on GMP for starting materials. Thus the legislation puts the responsibility on the manufacturing-authorisation holders using the active substance and does not foresee mandatory routine inspections of active-substance manufacturers.
To provide guidance on how GMP compliance of active-substance manufacturers should be established, guidance documents have been published on this website, including the 'guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials' as part of the Community procedures.
This document states that it is expected that manufacturing-authorisation holders will normally gain assurance that the active substances it uses are manufactured in accordance with GMP through audit of the active-substance suppliers.
In addition, a number of questions and answers on audits of active-substance manufacturers on this page provide further guidance.

2. Do I need to perform an audit of an active substance supplier if it has been inspected by an inspectorate from a European Economic Area (EEA) Member State and a valid GMP certificate is available? H+V July 2006
Manufacturing-authorisation holders sometimes confuse the role of inspectorates with their own obligations but nevertheless, when inspection reports or GMP certificates issued by European Economic Area (EEA) mutual-recognition-agreement (MRA) partners or other recognised authorities are available, these can provide useful information to manufacturing-authorisation holders.
However, these alone cannot fulfil the statutory obligations of the manufacturing-authorisation holder or the requirements of section 5.25 of the GMP guideline, but the results of inspections may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active-substance suppliers.

3. Is it acceptable to perform a remote assessment based on, for example, questionnaires, review of documents, Internation Organization for Standardization 9000 certification, results of analytical testing and historical experience with the supplier? H+V July 2006
The EEA inspectorates are not generally in favour of 'paper-based audits' *per se* as they do not provide the same level of assurance as on-site assessments, but do accept that they have a part to play in a risk-based strategy.
They may be particularly applicable when recent positive inspection information is available and where satisfactory audits have been concluded in the past. They cannot replace on-site audits of active-substance suppliers but can be a useful interim and temporary measure within the manufacturer's audit programme.

4. How do the new requirements affect importers of medicinal products? H+V July 2006
Importers are manufacturing-authorisation holders and so the obligations under Article 46f/50f of Directive 2001/83(2) apply to them. For importers, the possibility of a second-party audit performed by the third-country manufacturer that uses the active substance as a starting material may be a further option.
Importers are already obliged to ensure that the third-country manufacturer complies with standards of GMP equivalent to those of the European Community and should have established arrangements in line with chapter 7 of the GMP guideline. They should therefore be fully satisfied that the third-country manufacturer has adequately demonstrated that the active substances it uses for products destined for the European Community have been manufactured in accordance with GMP.
Importers may of course choose to verify the standards of GMP at the active-substance suppliers themselves or through a third party. Whichever option is chosen, the questions and answers above are also relevant.

5. Is it possible to ask for a voluntary inspection of an active-substance manufacturer? H+V July 2006
European legislation does not require mandatory routine GMP inspections for active-substance manufacturers. Responsibility for only using active substances that have been manufactured in accordance with GMP is placed on the holders of a manufacturing authorisation.
Article 111 of Directive 2001/83/EC (Article 80 of Directive 2001/82/EC for veterinary medicinal products) however makes provision for GMP inspections of active-substance manufacturing sites to be carried out at the request of the manufacturer itself. The request for the inspection should be made to the EEA competent authority where the site is located or, in case of sites located in third countries, to a competent authority where the active substance is used as a starting material in the manufacture of medicinal products. If this is not the case, any EEA authority can be approached.
There is no guarantee that such a request will be fulfilled, as the competent authorities need to balance such requests with other priorities. It should also be borne in mind that an inspection does not replace the responsibility of the manufacturing-authorisation holder using the active substance in question as a starting material and will not be accepted alone as adequate assurance that the manufacturing authorisation holder has fulfilled its responsibilities.

6. The notice to applicants requires the submission of a declaration signed by the qualified person (QP) that the active substance used is manufactured in accordance with GMP. The active substance in my product is widely used, but not normally as a pharmaceutical active substance, and I am having some difficulty in confirming compliance. What should I do to furnish the required declaration? H+V September 2008
Full compliance with GMP for finished products and active substances is a legal obligation for manufacturing-authorisation holders. It is recognised that for a small number of medicinal products, the primary use of the active substance is not in a medicinal product and the producer may therefore not be aiming to meet the specific requirements of pharmaceutical customers that represent an insignificant volume of business.
Alternative sources should normally be sought, but in exceptional circumstances the manufacturing-authorisation holder should assess and document to which extent GMP is complied with and provide a risk-based justification for the acceptance of any derogation.
The declaration provided by the QP should set out in detail the basis for declaring that the standards applied provide the same level of assurance as GMP. The European Medicines Agency will collect experience with this approach, which can be used as a basis for discussion on related amendments to guidelines in the future.

7. What kind of GMP documentation is needed for an active-substance manufacturer that performs sterilisation of an active substance? July 2010
The GMP basic requirements for active substances used as starting materials (EU GMP guideline part II) only applies to the manufacture of sterile active substances up to the point immediately prior to the active substance being rendered sterile. The sterilisation and aseptic processing of sterile active substances are not covered by this guideline and should be performed in accordance with GMP for medicinal products (Commission Directive 2003/94/EC as interpreted in the basic requirements for medicinal products including annex 1 of the EU GMP guideline part I). This implies that for any active-substance manufacturer that performs sterilisation and subsequent aseptic handling of the active substance, a valid manufacturing authorisation or GMP certificate from an EEA authority or from an authority of countries where MRA or other Community arrangements apply has to be submitted.

The active-substance manufacturer also has to submit data on the sterilisation process of the active substance (including validation data) to the marketing-authorisation applicant or holder for inclusion in the dossier submitted for the finished product and approval by the licensing authorities.

8. During inspections, why do inspectors sometimes ask to see reports of audits of active substance manufacturers carried out by the medicinal product manufacturer? H+V May 2013
Inspectors may need to see audit reports during inspections as part of the assessment of the manufacturing-authorisation holder's systems for confirming GMP compliance of active substance manufacturers or suppliers. Inspectors will expect to see the full details of these reports upon request, including responses received from the audited site, indication of closure of deficiencies raised or commitments made.

9. What expectations do inspectors have for the content of reports of audits of active substance manufacturers carried out by the medicinal-product manufacturer? H+V May 2013
As a minimum, the following is expected to be included in the report:

- The full postal address of the site. The auditors must be identified by full name and their employer recorded. If the audit is conducted on behalf of other parties this should be clear in the report. Where an audit report is obtained through a third party, the manufacturing-authorisation holder is responsible for ensuring the validity and impartiality of the audit report. The identity of key staff participating in the audit should be recorded along with their roles.The full contact details of the person through which the audit was arranged should be recorded including contact details (e-mail address, telephone number). The dates of the audit should be recorded, with the full-day equivalents clarified if full days were not spent on site. A justification should be recorded for the duration of the audit. If, in exceptional circumstances, the audit had to be restricted to fewer days on site than required by the scope of the audit, the reasons should be explained and the conclusions with respect to the GMP status of the site should be justified.ackground information on the active substance manufacturer should be recorded; this should include the company ownership, the age of the site, the number of staff employed in total and for the specific products being audited. The role of the site in manufacture of the active substances being audited should also be clarified for each of the active substances being audited, e.g. if the site performs the full manufacture or only part of the manufacture.
- The scope of the audit should be clearly stated e.g. what activities (against European Union GMP part II / International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q7 chapters) were covered. The activities which were not covered by the audit should also be clearly recorded. Auditors should identify the high risk areas for audit specific to the site or products being audited. For example, these could include but not be limited to:
    - process, cleaning or validation;
    - risk of cross-contamination with other active substances or other substances;
    - potential for generation of unknown impurities;
    - risk of mix-up of materials and products through materials handling or packing;
    - change control;
    - deviation recording or management;
    - security sealing of active substance containers and security or temperature control of shipments.
- Subsequent audits conducted as part of the ongoing supplier audit program may have a reduced scope focusing on the highest risk areas. In such cases the highest risk areas should be identified and justified.
- A list should be recorded of all active substances directly included in the audit scope plus other active substances or intermediates (or other products) manufactured at the site.

There should be a clear record of the products, the stages of manufacture and the buildings audited. If access was denied to any relevant areas of the site this should be recorded and explained. The list should clarify which of the active substances in the scope of the audit are manufactured in multi-purpose equipment or buildings as either final product or any of the intermediate stages.

- Dates of any previous audit conducted by or on behalf of the same manufacturing-authorisation holder should be recorded. If any of the audits did not conclude with a positive GMP compliance status, a brief summary of the reasons for this should be recorded.
- Each of the applicable sections of EU GMP part II should form sections of the report with a summary of what was examined, the key findings and compliance with the requirements of

each section. The report should clearly state findings against each activity audited with particular focus on the high risk areas. Any GMP deficiency identified during the audit must be clearly recorded with its criticality defined. An explanation should be given, in the report or in a supporting standard operating procedure, of the categorisation system used to classify deficiencies, e.g. critical, major or minor.

- Responses to the audit by the active-substance manufacturer should be reviewed by the auditors. Corrective and preventative actions and timescales for completion should be assessed by the auditors to establish whether these are appropriate to the findings. Further clarification or evidence of completion should be requested, commensurate to the risk.
- A summary assessment of the status of corrective and preventive actions should be recorded by the auditors once these have been received and assessed. An overall recommendation should be made in the final report. The summary should include whether the auditor regards the actions as satisfactory. The responsible QP should ensure that he or she, or someone to whom it is delegated, is in agreement with the overall recommendation of the final report. The QP must not release the relevant medicinal products without knowledge of a positive recommendation from the auditors. This recommendation should include the GMP compliance status of the site and whether any reduced controls on materials receipt at the finished product manufacturing site are supported by the auditors.
- A proposed re-assessment period should be recommended.
- The final report should be signed and dated by, at least, the lead auditor.

10. How should active substance auditors be qualified? H + V May 2013

Auditors should have sufficient scientific, technical and other experience to enable them to perform an adequate and thorough audit of the active substance manufacturer, as related to the planned scope of the audit. Where a proposed auditor lacks an appropriate level of direct experience in the field of active substance manufacture, he or she should undergo a documented training and assessment programme in the areas that are relevant to the audit, taking into account the auditor's anticipated role in the audit and the technologies that are likely to be encountered during the audit. Auditors must also be trained and assessed in their knowledge and understanding of EU GMP part II and in auditing techniques in general. The training and assessment should be fully documented.
The qualification and experience of contracted auditors are the same as the requirements for the manufacturing-authorisation holder's own auditors.

Active Substance – Active substance master file procedure

1. Can a mixture of an active substance with an excipient be submitted through an active-substance-master-file (ASMF) procedure? H+V August 2007

No. A mixture of an active substance with an excipient cannot be submitted through an ASMF procedure.
The blending of an active substance and an excipient is considered as the first step in the manufacture of the medicinal product, and therefore does not fall under the definition of an active substance.
The only exceptions can be made where the active substance cannot exist on its own, for example, due to insufficient stability without a stabilising agent, or in the case of herbal dry extracts if it is not possible to produce a solid extract without excipients.

Active substance - Declaration by the qualified person on the good-manufacturing-practice status of the active substance manufacturer

1. The notice to applicants requires the submission of a declaration signed by the qualified person that the active substance used is manufactured in accordance with good manufacturing practice. The active substance in my product is widely used, but not normally as a pharmaceutical active substance, and I am having some difficulty in confirming compliance. What should I do to furnish the required declaration? H+V September 2008

Full compliance with good manufacturing practice (GMP) for finished products and active substances is a legal obligation for manufacturing-authorisation holders. It is recognised that for a small number of medicinal products the primary use of the active substance is not in a medicinal product and the producer may therefore not be aiming to meet the specific requirements of pharmaceutical customers that represent an insignificant volume of business. Alternative sources should normally be sought but in exceptional circumstances the manufacturing-authorisation holder should assess and document to which extent GMP is complied with and provide a risk-based justification for the acceptance of any

derogation. The declaration provided by the qualified person should set out in detail the basis for declaring that the standards applied provide the same level of assurance as GMP. The European Medicines Agency will collect experience with this approach which can be used as a basis for discussion on related amendments to guidelines in the future.

Active Substance - Good-manufacturing-practice compliance for sterilisation of an active substance

1. What kind of good-manufacturing-practice documentation is needed for an active substance manufacturer who performs sterilisation of an active substance? H+V July 2010

The good-manufacturing-practice (GMP) basic requirements for active substances used as starting materials (European Union (EU) GMP guide part II) only applies to the manufacture of sterile active substances up to the point immediately prior to the active substance being rendered sterile. The sterilisation and aseptic processing of sterile active substances are not covered by this guideline and shall be performed in accordance with GMP for medicinal products (Commission Directive 2003/94/EC; as interpreted in the basic requirements for medicinal products including annex 1 of the EU GMP Guide part I). This implies that for any active-substance manufacturer who performs sterilisation and subsequent aseptic handling of the active substance, a valid manufacturing authorisation or GMP certificate from an EEA authority or from an authority of countries where mutual recognition or other Community arrangements apply has to be submitted.

Also, the active-substance manufacturer has to submit data on the sterilisation process of the active substance (including validation data) to the marketing-authorisation applicant or holder for inclusion in the dossier submitted for the finished product and approval by the licensing authority or authorities.

Active Substance - Starting materials of herbal origin

1. How should the quality of a starting material of herbal origin be controlled when it is used to manufacture a semi-synthetic active substance? H+V February 2012

Definition of 'active substance' in relation to mixtures

1. In case more than one active substance produced at different manufacturing sites is mixed together at a different manufacturing site, is it possible to consider the mixing as active substance manufacture? H+V June 2011

No. The mixing of active substances that can exist and are produced on their own should be considered as the first step of the manufacture of the finished product.

It should be noted that the definition of active substance given in part II of the European Union (EU) good-manufacturing-practice (GMP) guide (active substances) states that an active substance is a substance or a 'mixture of substances', but this definition takes into account cases when active substances are not single chemically defined substances (e.g. herbal extracts) and it is not meant to allow a mixture of chemically defined active substances to be considered as a single active substance. As a consequence of what is stated above, the mixing of active substances is subject to compliance with part I of the EU GMP Guide (finished products) and it is not possible to present a single active substance master file for the mixture.

3.2 EU GMP (MHRA/UK)

1. If an API manufacturer is already supplying a number of APIs to a company and they have been audited previously to confirm compliance with GMP, is it necessary to perform another audit if a new API is to be sourced from them?
It may not be necessary to re-audit but this will depend upon the exact circumstances. There should be a documented review and risk assessment to justify receiving the new API from the current manufacturer. The company's ongoing audit programme should ensure the new API is covered during the next audit.

2. Do API audits have to be product specific if a number of APIs from one manufacturer are used in the same dosage forms?
API audits do not have to be product specific. You need to consider what dosage forms the APIs are being used in. The focus should be on GMP compliance. Changeovers, cleaning and cleaning validation should also be reviewed. Ensure that APIs are coming from facilities that you have actually audited.

3. Are there any plans to inspect all API manufacturers by European Union (EU) Regulatory Authorities?
The EC proposals to combat counterfeits mentions API manufacturers, this is currently awaiting consultation feedback. Some EU Regulatory Authorities and the European Directorate for the Quality of Medicines & HealthCare (EDQM) perform audits of API manufacturers which are recorded on the European Union Drug Regulatory Authorities (EUDRA) database. There is currently a pilot programme between the EU, the Food and Drug Administration (FDA) and the Therapeutic Goods Administration (TGA) to share inspection outcomes, focusing on API manufacturers. ICHQ7 is the internationally recognised standard used. Inspection findings and reports are shared and some joint inspections are being performed. See European Medicines Agency (EMA_ website for more details. There is the possibility this programme will include manufacturing sites in the future.

4. What can a company do if an API manufacturer refuses to sign a technical agreement?
Technical agreements are important to ensure each party understands its responsibilities, particularly surrounding management of changes. If an API manufacturer refuses to sign an agreement, then an alternate supplier should be found.

5a. A company has an established product which requires a variation to be submitted for a particular change. As part of the change the company has to submit a QP declaration for compliance of the API manufacturer with GMP, however the API manufacturer is not meeting GMP standards. What should the company do?

If the API is an atypical active (eg honey or glycerine and pharmaceutical business is small volume of sales) then the expectations are that there should be a clear specification, the site should have been audited, changes should be controlled, appropriate checks should be made on incoming goods. Each atypical active scenario should be assessed on a case by case basis.

5b. If the scenario in part a of the question was not for an atypical active but an established API which was not found to be in compliance with ICHQ7A, does this mean the QP cannot certify batches made with API from this site?
The deficiencies are known at the API site and there are plans to address the issues.

The QP should establish exactly what is being done to address the issues and build up a case to justify what they are doing. Work with the manufacturer to improve compliance. Document the situation; assess the risks and the action plan with the company. Conventional API manufacturers should be more willing to comply than atypical active manufacturers as the pharmaceutical industry is their main business. If serious deficiencies are found consider public health implications. The MHRA should be informed in these circumstances and a 'for cause' inspection of the manufacturer may be initiated. Ultimately if a site is not compliant with GMP then it should not be used and a QP should not certify it as such.

6. For natural and semi-synthetic APIs, how far back should you audit for compliance with GMP?
Guidance on establishing the point at which production of the API begins is outlined in 1.2 and Table 1 of Part II of the Guide. A risk assessment should be performed to identify potential problems eg supplier history, process control, variation in starting materials, how difficult these are to control and to identify how far back in the past there is the potential for problems that are unlikely to be removed or detected during later processes. Consideration should also be given to the revisions of Annex 2 of the Guide and the learning points from the recent Heparin contamination issue, where a low molecular weight Heparin used widely in Europe contained low levels of contaminant.

7. Some excipients are coming under the same expectations for GMP compliance as APIs. What are the timescales for guidelines?
The EC in consultation with industry representatives developed a questionnaire and regulatory impact assessment. This was circulated to excipient manufacturers and users and the output has been analysed and recommendations have been put forward. We await further developments. The list of 'certain' excipients is still to be confirmed by the EC. The MHRA considers guidance such as that published by the Pharmaceutical Quality Group (PQG) and The International Pharmaceutical Excipients Council Europe (IPEC) provides a useful contribution to supply chain management.

8. Can a GMP certificate issued by an EEA Competent Authority, MRA partners or other recognised authority be used in lieu of an audit by a manufacturing authorisation holder to confirm GMP Compliance of an active substance manufacturer / supplier?
Article 46(f) of Directive 2001/83/EC as amended requires the holder of a manufacturing authorisation to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials. Compliance with this obligation should be gained through audits of the active substance suppliers by the manufacturing authorisation holder themselves or a third party acting on their behalf. GMP certificates issued by EEA, MRA partners or other recognised authorities cannot fulfill this statutory obligation or the requirements of section 5.25 of the GMP Guide.

GMP certificates can however provide useful information to manufacturing authorisation holders and may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active substance suppliers.

4. GMP for IMPs

4.1. EU GMP (EMA)

EU GMP guide annexes: Supplementary requirements: Annex 13

1. At what point of processing or incorporation would an active substance be considered a product intermediate and therefore an IMP? H June 2007
Commission Directive 2001/20/EC defines an IMP as 'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.'
An active substance would be considered an IMP if presented in a packaged form for use in a clinical trial. Any such packaging operation could only be carried out by a site holding an IMP manufacturing authorisation.
Any form of mixing or processing the active substance with other substances would also result in the need for a manufacturing authorisation for IMPs if the resulting product is to be used in a clinical trial. Physical processing such as milling of an active pharmaceutical ingredient would not constitute IMP manufacturing.
The above does not refer to reconstitution. Separate guidance on this subject is under development.

2. How can the QP of a site assure compliance with the requirements of the clinical-trial application in situations where a QP may be required to certify a batch before the application is submitted to, or accepted by, the competent authority? H June 2007
The QP of a site that is manufacturing a drug product intermediate should assure that the product is produced and controlled in compliance with the EU GMP guideline, in particular the requirements of annex 13.
A product specification file should be developed with contributions from the QPs and other technical personnel of the sites involved with the other manufacturing activities of the IMP. The sponsor of the clinical trial should also be involved in this process. While this may be in a rudimentary form and contain little detail, it should be developed as knowledge of the product evolves and include specifications for critical parameters and controls. The product specification file should be updated and evolve in line with the product development as envisaged in annex 13.
The development of the product specification file should be managed under a technical agreement or a number of technical agreements between the various manufacturing sites. These should include the QP responsible for the final certification of the product and the sponsor, if the sponsor has already been appointed. In any event, final release of the product to trial sites should take place only when the sponsor has established that the product has been manufactured in compliance with the terms of the approved clinical-trial application (as required by annex 13.44). This is defined in annexes 13.40 and 13.44: 'The sponsor should ensure that the elements taken into account by the QP when certifying are consistent with the information notified pursuant to Article 9(2) of Directive 2001/20/EC.'

3. Is it possible to perform packaging or labelling at the investigator site? H September 2007
This is normally possible only if a manufacturing authorisation has been granted to the site by the national competent authority.
According to Article 9(1) of Directive 2005/28/EC, the "authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall be required for both total and partial manufacture of IMPs, and for the various processes of dividing up, packaging or presentation."
However, an exemption to this obligation is foreseen in Article 9(2) of Directive 2005/28/EC:
'Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the IMPs are intended to be used exclusively in those institutions.' In addition, reference should be made to section 33 of annex 13 in respect of any re-labelling to extend shelf life.

4. Who is responsible for the packaging or labelling activities carried out at the investigator site? H September 2007
The sponsor has the ultimate responsibility for all trial activities performed at the investigator site, but should seek the advice of the QP of the IMP manufacturer, if possible, or the clinical-trials pharmacist at the investigator site regarding:

- adequacy of premises and equipment (storage conditions etc.);
- adequacy of written standard operating procedures;
- training of personnel involved, both on GMP requirements and any protocol specific requirements for the IMPs;
- written instructions to perform activities;
- forms to document the activities carried out;
- checks to be done;
- the keeping of retention samples;
- record-keeping.

5. Who is responsible for the transport and storage conditions when an IMP is transported from the manufacturer to the distributor or investigator sites? H May 2009
The sponsor should exercise control over the entire chain of distribution of IMPs, from manufacture or importation into the EEA, through to supply to the investigator sites, so as to guarantee that IMPs are stored, transported, and handled in a suitable manner.
When an IMP originates from a third country, the importer is responsible for verifying that the transportation and storage conditions for the product are suitable. For products originating within the EEA, the manufacturer is responsible for transportation and storage conditions. The respective responsibilities of the sponsor, manufacturer, importer and, where used, distributor should be defined in a technical agreement.

6. What measures should be taken to ensure that the IMPs are kept under suitable conditions during transportation between the manufacturer or distributor and the investigator sites? H May 2009
Storage conditions during transportation should be validated or monitored using a suitable temperature-measuring device that is capable of showing fluctuations in temperature e.g. Temperature Logger. The choice of method of transport should be influenced by the nature and sensitivity of the product and should ensure timely delivery of IMPs to the investigator sites.
The outer packaging should be labelled showing the final destination, the name of manufacturer or sponsor and the storage conditions required.

7. What measures should be taken to ensure that IMPs are kept under suitable conditions during storage at the investigator sites? H May 2009
IMPs should be packaged to prevent contamination and unacceptable deterioration during storage. The sponsor should determine acceptable storage temperatures and any other required storage conditions for the IMPs (e.g. protection from light).
The sponsor should ensure that all involved parties (e.g. monitors, investigators, pharmacists, storage managers) are aware of these conditions and the actions to be taken in the event that the conditions are not met.
Where appropriate, there should be a restricted area for the storage of IMPs. The temperature of the areas and equipment used for the storage should be monitored using suitable means, such as a temperature recorder or, as a minimum, a record of the maximum and minimum temperatures, at a suitable frequency (for example, daily).

8. What written procedures should be in place at the investigator site regarding IMPs? H May 2009
The sponsor should ensure that written procedures include instructions that the investigator or institution should follow for the handling and storage of IMPs. The procedures should address adequate and safe receipt, handling, storage, where relevant any reconstitution process to be carried out before administration, retrieval of unused product from subjects, and return of unused IMPs to the sponsor (or alternative disposal, if authorised by the sponsor and in compliance with the applicable regulatory requirements).
Procedures should also give instructions on the actions to be taken when defined conditions are not met.

9. What records must be kept at the investigator site regarding the abovementioned procedures? H May 2009

EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances in investigational medicinal products (IMPs)

1. Are active substances used as starting materials in the production of IMPs subject to GMP? H July 2006

Specific types of product - Quality of investigational medicinal products

1. Setting specifications for impurities (2.2.1.S.4.1, 2.2.1.S.4.5, 2.2.1.P.5.1 and 2.2.1.P.5.6): On which basis should specifications for related impurities be set? H January 2011

Reference to relevant paragraphs of the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004) is given for each question.

Safety considerations should be taken into account. The limits should be supported by the impurity profiles of batches of active substance used in non-clinical and clinical studies. Results between batches should be consistent (or the clinical batches should show better purity results than non-clinical and previous clinical batches).

Compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) requirements is not required, if proper justification is provided.

Where specifications are set for potential genotoxic impurities, the guidance given in questions and answers on the guideline on limits of genotoxic impurities (EMEA/CHMP/SWP/431994/2007) should be taken into consideration (question 6: staged threshold-of-toxicological-concern approach).

2. Substantial amendments (chapter 8): How should industry notify amendments? January 2011 (corrected November 2011)

Reference to relevant paragraphs of the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004) is given for each question.

The table in the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004) gives examples of what should be notified as substantial amendments and of changes where a notification will not be necessary. The list is not exhaustive, and the sponsor should decide on a case-by-case basis if an amendment is to be classified as substantial or not.

For non-substantial amendments documentation should not be proactively submitted, but the relevant internal and study documentation supporting the change should be recorded within the company and if appropriate, at the investigator site. At the time of an overall investigational medicinal product dossier update or submission of a substantial amendment the non-substantial changes can be incorporated into the updated documentation. There is no need to use the notification of amendment form for these changes.

3. Shelf-life extensions (2.2.1.P.8 and chapter 8): What information should be included in the file in order to make shelf-life extensions without notification of a substantial amendment? H January 2009

Reference to relevant paragraphs of the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004) is given for each question.

The criteria based on which it is intended to extend shelf life during an ongoing study should be given. The information should include extension protocol limiting the maximum time period for extrapolation. In the case of any significant negative trend for stability data observed during long-term and accelerated testing, the sponsor should commit to notify any shelf-life extension as a substantial amendment.

4. Batch data (2.2.1.S.4.4 and 2.2.1.P.5.4): Are certificates of analysis needed? H January 2009

Reference to relevant paragraphs of the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004) is given for each question.

No, tabulated batch results are sufficient. Data for representative batches should be included in the batch analysis table of the investigational medicinal product dossier. Results for batches controlled

according to previous, wider specifications are acceptable if the results comply with the specification for the planned clinical trial. The results should cover the relevant strengths, but the batches do not need to be the same that will be used in the clinical trial.

5. Drug substance and drug product batch data for proposed manufacturing sites: Are drug substance and drug product batch data for all proposed manufacturing sites listed in S.2.1/P.3.1 required to be submitted in the investigational medicinal product dossier, or provided as a substantial amendment prior to use in a study? H January 2011 (corrected November 2011)
Reference to relevant paragraphs of the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004) is given for each question.
Data from representative batches should be provided. This implies that data should be provided for each proposed site. However, where one legal entity has multiple sites (in the same country), then batch data from one site only would be sufficient.
For non-substantial amendments documentation should not be proactively submitted, but the relevant internal and study documentation supporting the change should be recorded within the company and if appropriate, at the investigator site. At the time of an overall investigational medicinal product dossier update or submission of a substantial amendment the non-substantial changes can be incorporated into the updated documentation. There is no need to use the notification of amendment form for these changes.

4.2 EU GMP (MHRA/UK)

1. My investigational medicinal product (IMP) unit is engaged upon reconstituting sterile injections and then giving them to the clinical trial subjects. What licence, if any, do I need?
A simple reconstitution or dilution (including serial dilution) of an IMP including a sterile injection for the purpose of administration falls outside the definition of manufacture and so no manufacturer authorisation for investigational medicinal products (MIA(IMP)) would be needed. It is also permissible without an MIA(IMP) to label them after reconstitution with an identifier to ensure that the dose goes to the correct subject. See also Q22 for further information.

1a. The reconstitution we are carrying out involves the addition of another material as well as the diluent. Does this still fall outside the definition of manufacture?
No. This would fall within the scope of manufacture. Any operation such as weighing out, adding other materials, or combining IMPs is not considered to be for the purposes of administration and so would require appropriate authorisation under a MIA(IMP). This situation is potentially complicated and should be considered on a case by case basis by the MHRA.

2. I know that small quantities of medicinal products can be manufactured and labelled by my local hospital with no licence at all as long as it is done by a pharmacist. Why is a hospital required to hold an MIA(IMP) authorisation to conduct a similar activity for IMPs?
The Human Medicines Regulations 2012 applies to therapeutic doses. In this legislation there are some exemptions from the need for a manufacturing licence such as the 'Section 10' exemption which can be invoked here. There is no such exemption for the manufacture of IMPs. So, the manufacture of even one dose for immediate use requires an MIA(IMP) authorisation and Qualified Person (QP) certification.

2a. Does this mean that all such manufactured IMPs need to be analytically tested before they can be certified, even if the quantity is very small?
Yes. The analytical requirements should be agreed with the Clinical Trials Unit (CTU) via the clinical trials application (CTA). If an activity defined as manufacture takes place (see above) then the resultant IMPs should be tested to confirm that the specification submitted in the CTA is met.

3. We have a contract to supply the local hospital with 'Specials' and IMPs. We are even located within a hospital site. We need to employ a QP at great expense just to certify the IMPs. We have never needed one for the specials. Why?
'Specials' are unlicensed medicines which are manufactured under a manufacturer's specials licence (MS) for a special clinical need and are under the responsibility of the prescribing doctor. There is no requirement for QP certification. IMPs are governed by different legislation (The medicines for Human Use (Clinical Trials) Regulation 2004 as amended [SI 2004 1031]). IMPs are not 'Specials'. A clinical trial authorisation application including a description of the IMPs has to have been submitted to the MHRA. When granted a QP certification against that clinical trial authorisation is required.

4. I work in a clinical trials unit situated in my local hospital. We have a MIA(IMP) and carry out assembly of IMPs for immediate use within the unit. However, the hospital production unit itself assembles IMPs and doesn't have a MIA(IMP). Is this permissible?
Section 37 of the clinical trials legislation contains a specific exemption which is relevant here. This exemption provides an exemption from the need for a hospital or health centre to hold a MIA(IMP) authorisation to assemble an IMP in a hospital or health centre, when the 'assembly' is carried out by a doctor or pharmacist, or under the supervision of a pharmacist. 'Assembly' is related to packaging and labelling, and not to the preparation of medicines from their ingredients. The exemption applies only if the product is to be used exclusively in that hospital or health centre or any other that is a trial site for the clinical trial in which the product is to be used. This exemption does not apply to anyone else such as separate organisations which happen to be situated within a hospital or to companies which have a contract to supply hospitals or health centres.

5. We perform over encapsulation of tablets in order to blind them. Capsules are containers so this counts as packaging doesn't it?
No. Capsules are specifically excluded from the definition of a container in the Clinical Trials Regulations SI 2004 1031. A MIA(IMP) with 'capsule manufacture' authorised would be necessary in this case.

6. We are a firm of respected pharmaceutical consultants some of whom are QPs. We do a lot of contract regulatory and auditing work for companies involved in clinical trials and the manufacture of IMPs. Can we have a MIA(IMP) so that we can perform IMP certification for our clients?
No. An organisation cannot act as a contract batch certification site only. The sponsors of a clinical trial may wish to keep the final QP certification step of IMP manufacture in house as they carry ultimate responsibility for the trial. Otherwise, any contract organisation such as yours must be involved with some manufacturing or importation of an IMP if they wish to carry out batch certification.

7. We wish to enter the business of storing and distributing IMPs. What licences do we need if any?
There is no requirement within the legislation for any MHRA licence to carry out storage and distribution of IMPs. In this respect, the legislation differs from that for medicinal products. However, you will need to be named within the appropriate annex of your client's MIA(IMP) as a site of storage and distribution. Therefore any clients who wish to make use of your services will need to vary their MIA(IMP) accordingly.

Note that the storage and distribution of a licensed medicinal product must remain in the licensed distribution chain until it is supplied to the Sponsor for use in a trial.

8. We need to import some IMPs from a manufacturing site in the USA. The site has had a voluntary IMP inspection by the MHRA a few months ago. Does this mean that I don't need to go out there to do another audit myself before I sign the QP declaration of GMP compliance?
No. The starting point for a QP declaration of EU GMP should be an audit conducted by or on behalf of the importing company. Any departure from this should be justified and documented and will be subject to scrutiny during an MHRA inspection. It may be possible to use the fact of an MHRA voluntary inspection as part of this justification but these are general inspections which may not

address the specific technical or GMP issues associated with your product. It may not even have covered the same factory or part of the factory. A regulatory inspection cannot be used unconditionally to remove the need for your own audit. The audit does not need to be done by the QP himself but the QP needs to be satisfied that it has been done correctly by an appropriately trained individual as the QP will be taking final responsibility.

9. We import an IMP for a clinical trial which has just been halted for ethical reasons. We need to continue to supply the IMP as a therapy to patients who were on the trial. What is the regulatory situation here?

Once a trial has stopped, the product ceases to be an IMP and becomes a medicinal product. If it is a licenced medicinal product then it can be purchased and supplied as normal. However, more often than not, the ex-IMP will not be licenced. Material already existing as an IMP can be supplied after the trial but any fresh material must be imported as an unlicensed medicinal product. A manufacturer's 'specials' licence must be held. Also, the requirements of SI 2005/2789 must be complied with. Essentially, the MHRA must be notified of this importation beforehand to ensure that it can be justified. It is likely that such a need as described above would justify continued importation.

10. We prepare radio-imaging pharmaceuticals from licenced kits and Technetium generators for use in clinical trials. Do we need a MIA(IMP)?

The preparation of such radiopharmaceuticals using Technetium generators is considered to be manufacture and so a MIA(IMP) would be required if they were to be used as IMPs. Note that the Clinical Trial Regulations define an investigational medicinal product (including a licenced medicinal product) as being:

(a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation
(b) used for an indication not included in the summary of product characteristics under the authorization for that product
(c) used to gain further information about the form of that product as authorised under the authorization (Article 2).

However, it may be that the radiopharmaceutical used in a clinical trial may not be an IMP. There are classes of products used in clinical trials which are 'not IMPs' (NIMPs) and details of the definitions can be found in Eudralex Volume 10 on Clinical Trials. NIMPs include challenge agents, rescue medication, agents used to assess end points and others. Clinical trial legislation does not apply to these. and as long as a), b), and c) don't apply.

11. We manufacture tablets used for IMPs and some of these contain penicillins or other beta-lactams. There doesn't seem to be a specific box for these on the licence application. Does the MHRA not need to know about such manufacture?

The latest version of the MIA(IMP) application form is aligned with a pan-European design and there is no obvious space to include such information. The MHRA does need to know about such manufacture which brings with it special GMP considerations (the manufacture of doses containing potent Active Pharmaceutical Ingredients (APIs) would be another example). Please include a sentence describing such manufacture in each individual dosage form heading as appropriate.

12. We have got some more stability information on our IMP and wish to extend the shelf life. What do we do?

Firstly, the Clinical Trials Unit (CTU) at the MHRA would need to be informed via a variation to the CTA. Extension of shelf life represents a substantial amendment, unless you have previous agreement to extend the shelf life when more stability information becomes available.

Secondly, the Product Specification File (PSF) would need to undergo a controlled change such that manufacturing sites and the QPs can take appropriate action such as updating labelling instructions, certification criteria etc.

Thirdly, if advantage of the longer shelf life is to be taken for IMPs already manufactured, these IMPs will need to be relabelled. This relabeling will need to be conducted, checked and documented as per Annex 13 (see also the following question).

13. Some of our stock has already gone out. Do we need to bring it back to the site with the MIA(IMP) to be relabelled with the new shelf life?
No. Although this would be preferable, it is recognised that this shipping backwards and forwards could cause more GMP problems than it solves. It is permissible in these circumstances for the relabeling to be done at the clinical site. The certifying QP should certainly be aware of this and be involved in setting up the required GMP systems. The relabeling should be done by knowledgeable staff, documented, and the records stored in the original trial file.

Note that Paragraph 33 of Annex 13 of the Orange Guide deals specifically with this issue. It states:

'If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.'

14. What happens if there is an adverse event during a clinical trial and the possibility of a recall of IMPs?
You should inform the Defective Medicines Report Centre (DMRC) at the MHRA as you would for a medicinal product. It will also be necessary to inform the Clinical Trials Unit (CTU) at the MHRA. The Clinical Trial Regulations makes provision for notification of adverse events and notification of suspected unexpected serious adverse reactions.

15. We manufacture IMPs purely for export to countries outside the EEA. Do we need a MIA(IMP)?
Yes. A MIA(IMP) licence is required for the manufacture on an IMP regardless of whether the IMP is for use in the UK another EEA Member State or a non-EEA Member State (Third Country).

16. What is the regulatory situation with respect to veterinary clinical trials and IMPs?
The Veterinary Medicines Directorate is responsible for such regulatory issues and can be contacted on 01932 336911.

17. What sites should appear on the QP declarations relating to IMP manufacture in third countries which accompany CT applications?
All sites involved in manufacturing steps starting with the conversion of the API into the dosage form and including primary and secondary packing and also any contract laboratories involved with release or stability testing.

18. If an IMP has a shelf life extension after QP certification and is consequently relabelled with a revised expiry date, is a further QP certification required?
A new certification after relabeling is required for stock which has not been shipped to an investigator site. For product held at the investigation site, QP certification is not required if the relabeling activity is carried out by, or under the supervision of a pharmacist, or other healthcare professional, with appropriate documented evidence in accordance with Paragraphs 33 and 42 of Annex 13.

19. Please clarify reference sample requirements for IMPs
Paragraph 8 in Part 2, Schedule 7 of the Clinical Trial Regulations requires the manufacturing authorisation holder to keep samples of each batch of formulated products readily available for examination. There should be enough finished packs for testing in duplicate. As IMPs are often small packing runs from one bulk batch, Annex 19 accepts a justification for retaining the required sample

quantity of the bulk batch and separate samples of packaging components used on each packing run. The sample of the bulk batch should be in the final primary pack in order to be representative of the materials going on to be used. The requirements have been clarified in the revised Annex 13 – paragraphs 36 and 37. In addition, the EMA has published a Q&A concerning testing of sterile products (external link).

20. Are QP statements required for APIs used in IMPs?
There is no requirement for APIs used in IMPs to comply with EU GMP Part II but there remains a responsibility for IMP manufacturers to assure themselves that the API is of an appropriate quality. The EMA has published a Q&A concerning the GMP status of APIs used in IMPs (external link).

21. Do the MHRA issue certificates of eligibility for transitional IMP QPs?
Certificates for transitional IMP QPs are not currently issued. Confirmation that a transitional IMP QPs has been assessed as being suitable and eligible to act as a QP at a given site can be verified by referring to list of authorised personnel within the appropriate MIA(IMP) licence.

22. Paragraphs 33 and 42 of Annex 13 of the Orange Guide allow for some packaging and labelling to take place after QP certification. Under what circumstances is this permissible and what are the GMP expectations?
This 'post certification labelling' can be used for the following and is usually performed prior to despatch in the distribution area or immediately prior to administration to a subject or patient:

- application of an identifier to ensure that a reconstituted IMP in its final container is administered to the correct subject
- application of expiry date labelling (or revised expiry date labelling)
- application of an investigator name
- application of a protocol number.

It should, in the first instance, be done at a site with an MIA(IMP) unless the risk to the quality of the product is unacceptably elevated by any required transportation back to this site. The level of assurance of product quality should not be less than if this labelling were performed prior to QP certification.

NOTE: Such labelling should not effectively incorporate allocation of doses against a randomisation code. It is important that allocation takes place before this to ensure adequate QA scrutiny and QP confirmation and to ensure that staff applying such post certification labels are not accidentally unblinded.

GMP expectations for 'post certification labelling' are:

- finished IMP doses, certified by a QP, should exist prior to the labelling
- the activity should be planned and described in the CT protocol
- relative responsibilities should be described in a technical agreement where appropriate
- the process should be described in an SOP
- personnel doing the labelling should be appropriately trained and retrained at intervals
- labels should be stored securely with arrangements in place to ensure that records for removal and usage are kept. Labels should be transported in a secure way from the label store to the location for use
- the activity should be carried out in an area which is partitioned or separated from other activities. It should also preferably be done in a quieter environment
- a line clearance at the start and end of the activity should be carried out and label reconciliation performed to 100%. An investigation should be carried out if this is not the case. This should be verified by a second person
- the activity should be recorded in a batch record or equivalent document which is subject to independent review
- the certifying QP should be aware of the post certification process and be satisfied that the elements described above are in place. Although further QP certification is not necessary, some oversight is expected and some assurance should be gained (e.g. by sampling of

records) to confirm that the process is being carried out correctly. If conducted at an investigator site the sponsor is responsible for ensuring that the activity is carried out in accordance with GMP, and the advice of the QP should be sought in this regard
- the process should be covered by normal quality system elements such as change control and non-conformance management.

23. What is the MHRA view on medication pooling?
A Medication pooling is the production of IMPs which may be used in a number of clinical trials and which are left in a "generic" state until after QP certification. This would usually be by leaving a space for the protocol number to be added at the point of dispensing, or where multiple protocol numbers are on the label with the others being deleted at the point of dispensing. Only after certification is it decided which protocol the particular IMPs are destined for, this is when it is being dispensed to the patient. This is acceptable as long as the QP certification is against all of the possible clinical trials which may use the IMPs, the protocol number is added to the IMP doses prior to release to the trial, and the GMP points outlined in Q22 (above) are considered.

24. What is the expectation for QPs in relation to non-investigational medicinal products?
Non investigational medicinal products (NIMPs) are not IMPs and so the legislative requirements of Directive 2001/20/EC and SI 2004/1031 as amended do not apply to such products. There is therefore no requirement to source such products from a site holding an MIA(IMP) or for QP certification of the product. There is an expectation for the Sponsor to ensure that NIMPs are of the necessary quality for human use. Further guidance on sourcing NIMPs is included in Volume 10 Clinical Trials Notice to applicants.

Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials (external link)

25. What is the regulatory situation for the importation of NIMPs into the UK?
As such products are not IMPs, then the general requirements relating to medicinal products come into force, in particular the need for a Marketing Authorisation in Regulation 3(1) of the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994. Where a medicinal product is not the subject of a valid Marketing Authorisation, there are limited options for it's supply in the UK and as a consequence the regime for the supply of an unlicensed product provides a means of actually getting the NIMP into the UK for use in a clinical trial. The framework described in Guidance Note 14 is seen as an appropriate means of giving the legal vires for the sponsor to actually obtain the NIMP, otherwise there would be no legal basis for supply. Further information on the importation of unlicensed medicines is available on the MHRA website using the following link: Importing unlicensed medicines

26. Provided it is considered that the safety, quality and efficacy of a batch of IMP have not been compromised, does a QP have any discretion to certify that batch as suitable for release even if it does not meet the specification in the Clinical Trials Authorisation?
There is no such discretion available to a certifying QP. However, if a batch is manufactured and does not meet the authorised specification then a substantial amendment to alter the specification may be submitted to the Clinical Trials Unit (CTU) provided it is deemed that safety, quality and efficacy are not compromised. CTU has a target turn-around time of 30 days for such substantial amendments. If required an expedited review may be requested via the Clinical Trials Helpline.

4.3 TGA Australia

65. How does Annex 13 distinguish between earlier and late phase clinical trials in requirements for drug product stability and characterisation studies (including level of assay validation required)?

The manufacture of Phase 1 clinical trial medicines is not subject to inspection and licensing by the TGA (specified in Item 1, Schedule 7, Therapeutic Goods Regulations). However, the manufacture of Phase 2 and 3 clinical trial products is subject to inspection (including Annex 13) and licensing by the TGA.

66. Would a dedicated pilot facility for the development of dosage forms and new products, which is not used for the manufacture of saleable product, be subject to TGA inspecting and licensing?

If the dedicated pilot facility is used to manufacture investigational medicinal products for clinical trials in Phase 2 or later (or for commercial supply) the facility is subject to inspecting and a TGA licence or clearance is required.

67. What is meant by 'certain characteristics' in clause 32 of Annex 13?

The 'certain characteristics' in clause 32 refers to non-commercial clinical trials performed by researchers without the participation of the pharmaceutical industry. These trials are usually performed with registered (or listed) products that are obtained from the market for use in a clinical trial. The requirements in this clause relate to the way these products are to be labelled.