Guidance on the interpretation and implementation of European Good Distribution Practice

Chapter 5 – Operations
Preface

It is of key importance that medicinal products are not only made to a high quality in accordance with Good Manufacturing Practice, but that the quality and integrity of these products are maintained through the entire supply chain to the patient. This is where Good Distribution Practice (GDP) comes into play.

The distribution network for medicinal products is often complex, involving many different parties. In addition to the challenges associated with this complexity, there is also a growing threat from criminal activities seeking to introduce falsified medicines into the legal supply chain. The European regulators recognised several years ago that there was a need to update the content of the 1994 GDP guideline to take into account advancements in practices and changes in legislation since it was issued. A consultation draft was issued in mid 2011 and, following the receipt of many comments from interested parties, a final revised version was issued in March 2013 with an effective date of 8 September 2013. A corrected version dated 5 November 2013 was published in the Official Journal on 23 November 2013 to be effective immediately. This version corrects factual mistakes identified in subchapters 5.5 and 6.3 of the March 2013 version and also gives more explanations on the rationale for the revision.

The new guideline has a much stronger focus on the quality system with clear responsibilities and processes and the application of risk management principles. More detailed guidance is given on most elements. New chapters relating to transportation and specific provisions for brokers have been added.

The Pharmaceutical Quality Group issued a monograph on Pharmaceutical Distribution in 1997 and initiated planning to revise this in line with the new regulatory guideline. Whilst undertaking this planning it was identified that the European Compliance Academy were also planning to produce some guidance in response to requests from members. The two organisations therefore decided to join forces and set up a joint steering committee led by Afshin Hosseiny with Philip Butson, Ashley McCraight and Oliver Schmidt.

An early decision was that we would initially target key chapters and issue each as it became available rather than wait until a complete guide had been prepared. This has enabled us to shorten the time to the provision of some guidance and also provides an opportunity for us to collect feedback and enhance the material before issuing a complete guide. The first versions of the chapters will have different formats and styles due to the different volunteer teams involved in their preparation which we have chosen not to edit into a common format for the time being. We would appreciate feedback on what works best for you, the user.

In this document, text from the EMA guideline is given in italic Calibri font, followed by guidance from the team in normal Times New Roman font.

Please provide any feedback and suggestions for improvement using the email address monographs@pqg.org or info@gmp-compliance.org.

For this particular chapter on Operations, we would like to thank the hard work of the authoring team Mike Taras, Kane Edgeworth, Neil Raven and Mike Regan. Additional authoring and editing was undertaken by Philip Butson, Afshin Hosseiny and Ashley McCraight.
5.1. Principle

All actions taken by wholesale distributors should ensure that the identity of the medicinal product is not lost and that the wholesale distribution of medicinal products is performed according to the information on the outer packaging. The wholesale distributor should use all means available to minimise the risk of falsified medicinal products entering the legal supply chain.

All medicinal products distributed in the EU by a wholesale distributor must be covered by a marketing authorisation granted by the EU or by a Member State (1).

Any distributor, other than the marketing authorisation holder, who imports a medicinal product from another Member State must notify the marketing authorisation holder and the competent authority in the Member State to which the medicinal product will be imported of their intention to import that product (2). All key operations described below should be fully described in the quality system in appropriate documentation.

(1) Article 76(1) and (2) of Directive 2001/83/EC.
(2) Article 76(3) of Directive 2001/83/EC.

5.2. Qualification of suppliers

Wholesale distributors must obtain their supplies of medicinal products only from persons who are themselves in possession of a wholesale distribution authorisation, or who are in possession of a manufacturing authorisation which covers the product in question (3).

(3) Article 80(b) of Directive 2001/83/EC.

Wholesale distributors receiving medicinal products from third countries for the purpose of importation, i.e. for the purpose of placing these products on the EU market, must hold a manufacturing authorisation (4).

(4) Article 40, third paragraph of Directive 2001/83/EC.

Where medicinal products are obtained from another wholesale distributor, the receiving wholesale distributor must verify that the supplier complies with the principles and guidelines of good distribution practices and that they hold an authorisation for example by using the Union database. If the medicinal product is obtained through brokering, the wholesale distributor must verify that the broker is registered and complies with the requirements in Chapter 10 (5).

(5) Article 80, fourth paragraph of Directive 2001/83/EC.

Appropriate qualification and approval of suppliers, should be performed prior to any procurement of medicinal products. This should be controlled by a procedure and the results documented and periodically rechecked.

When entering into a new contract with new suppliers, the wholesale distributor should carry out ‘due diligence’ checks in order to assess the suitability, competence and reliability of the other party. Attention should be paid to:

(i) the reputation or reliability of the supplier;
(ii) offers of medicinal products more likely to be falsified;
(iii) large offers of medicinal products which are generally only available in limited quantities; and
(iv) out-of-range prices.
What is the rationale for this point in the guidance?

These points are largely reminders of legislative requirements.

Wholesale distributors have a key role in safeguarding the supply chain of medicinal products and a fundamental part of this is to ensure that products are obtained from legitimate sources – the manufacturer or another authorised wholesale distributor.

Where products are sourced from outside the European Union (EU), there is a requirement for a Qualified Person (QP) to certify that they have been manufactured and checked in accordance with EU Good Manufacturing Practice (GMP) legislation and so a manufacturing authorisation (on which the QP is named) must be held.

The Falsified Medicines Directive (FMD, 2011/62/EU) introduced new requirements around the brokering of medicinal products – the negotiation around sale or purchase of products without physically handling them – including the registration of brokers. The GDP Guideline has subsequently provided specific provisions relevant to brokers in Chapter 10.

To ensure that suppliers are authorised and appropriate to act as suppliers it is important that an initial ‘due diligence’ and further ongoing qualification and approval of the selected suppliers is performed by the wholesalers. To ensure that these activities happen, and evidence is documented and maintained the process of selection, and approval should be controlled by a written procedure.

What are the risks and benefits associated with this aspect of the guidance?

The requirements to ensure that products are only obtained from authorised suppliers are intended to minimise the risks of:

- Falsified medicines entering the supply chain
- Products not being maintained (stored and transported) to appropriate GDP standards, thus impacting quality

Complying with these requirements will also safeguard against risks that might be associated with receipt of goods:

- Without appropriate documentation
- Prior to QP certification
- With incomplete audit trail
- Not having the requisite marketing authorisation
- Labelled in the wrong language for the intended customer
- Subject to recall
- With inadequate shelf life remaining to enable onward supply to customers

Issues with a supplier can impact your business efficiency and reputation.

Periodic re-evaluation helps to ensure on-going compliance and safeguards against the use of a supplier who has been found to have significant GDP deficiencies or is no longer authorised.

The additional requirements relating to products sourced from outside the EU are to address the risk of products not having been manufactured to standards equivalent to EU GMP.

The primary benefit is the minimisation of these risks and thus assurance of patient safety. In addition, authorisation of wholesale distributors enables the movement of products between distributors to occur with the minimum delay and checking, thus helping to maintain supply of products to patients.

How might this be implemented/ what does it mean?

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If products are to be sourced from outside the EU, then the appropriate manufacturing authorisation must be obtained and requirements followed (these are outside the scope of this GDP guidance). A Qualified Person (QP) will need to be employed and named on the authorization. The QP for a company sourcing products from outside the EU should have a good understanding of the GMP and GDP requirements in the source country and how these compare with EU requirements.

The primary requirement is to have a procedure for the appropriate qualification and approval of suppliers. It must be ensured that this procedure is followed for all suppliers, including brokers, and the resultant documents kept. You will need to be able to provide these documents to regulatory inspectors and third party auditors.

The initial supplier approval should include appropriate ‘due diligence’ checks. These will look not only at GDP-specifics, such as appropriate legal authorisations (as per member state procedures), quality system, and capability and competence relevant to the products being supplied, but also at matters such as financial strength and searches for any legal action.

Subsequent periodic re-evaluations and approvals should ensure as a minimum that the legal authorisation has been maintained and service has been in line with agreements. The re-evaluation period should be defined based on risk assessment; an annual re-evaluation is recommended initially.

Use of the EudraGMDP database is recommended. Over time, this will hold details of current Wholesale Distributor Authorisations (WDA) and both GDP certificates and non-compliance reports (it is currently being compiled, not all certificates are available yet). The database may be accessed via the url http://eudragmdp.ema.europa.eu/inspections/displayHome.do

Registers of brokers are maintained by the national competent authorities. Not all member states currently publish such a list, but it is intended that this should be the case in the near future.

For the UK, the list of registered brokers may be found on the page giving advice to brokers at: http://www.mhra.gov.uk/Howweregulate/Medicines/Overviewofmedicineslegislationandguidance/TheFalsifiedMedicinesDirective/Brokersoffinishedmedicinalproducts/index.htm

In addition to using the EudraGMDP database, the supplier should be asked to provide you with a copy of their authorisation (as per local procedures).

A mechanism should be in place to promptly detect any loss of authorisation by suppliers. Availability of this information will depend on national competent authority processes. In the UK, MHRA issue an updated list monthly, which is available from their website and it is possible to sign up for email notifications of updates:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/ManufacturersandWholesalerslicences/index.htm

In addition to assessing the suitability of suppliers in terms of their compliance, appropriate technical/quality agreements should be put in place before using them. Agreements should include:

- Arrangements to allow for audits
- The communication of outcomes of regulatory inspections
- Arrangements for the communication and handling of complaints and recalls
- Any quality critical aspects specific to the products to be supplied
- Suitable Key Performance Indicators (KPIs) to enable performance to be monitored

Procurement procedures and training of relevant staff should include points (ii) to (iv) of the EU Guideline as part of the ongoing vigilance against the introduction of falsified products into the supply chain. Remember the old adage about an offer that seems too good to be true! Prices may vary from time-to-time and market-to-market, but products which are offered at below market prices should be viewed as suspect.
5.3 Qualification of Customers

Wholesale distributors must ensure they supply medicinal products only to persons who are themselves in possession of a wholesale distribution authorisation or who are authorised or entitled to supply medicinal products to the public.

Checks and periodic rechecks may include: requesting copies of customer’s authorisations according to national law, verifying status on an authority website, requesting evidence of qualifications or entitlement according to national legislation.

Wholesale distributors should monitor their transactions and investigate any irregularity in the sales patterns of narcotics, psychotropic substances or other dangerous substances. Unusual sales patterns that may constitute diversion or misuse of medicinal product should be investigated and reported to competent authorities where necessary. Steps should be taken to ensure fulfilment of any public service obligation imposed upon them.

- **What is the rationale for this point in the guidance?**

As with the steps taken to qualify suppliers, these requirements to qualify customers are part of the wholesale distributor’s role in safeguarding the supply chain of medicinal products. By ensuring that they only supply to appropriately authorised persons, wholesale dealers help to maintain a reliable ‘chain of custody’ to the patient and reduce the risk of products being misdirected and/or misused.

It is important that there are periodic rechecks because authorisations may change over time.

Wholesalers may be in a position to detect unusual sales patterns that might indicate illegal activities which would not otherwise be identified.

- **What are the risks and benefits associated with this aspect of the guidance?**

If products are provided to customers other than those authorised to receive them, then patients may be put at risk because of the risks that:

- Product stability will be affected by incorrect storage or transportation, thus affecting suitability for use
- Traceability will be lost, affecting the ability to recall a product if required
- Products may be tampered with, making them unsafe
- Products may be sold without the safeguards of a prescription from a medical practitioner or supervision from a pharmacist
- Products may be sold for purposes other than those legally permitted

- **How might this be implemented/what does it mean?**

Local procedure(s) should be put in place to address these requirements defining:

- How *bona fides* of customers are established before they can be accepted as customers. This would include not only the submission of documentary evidence from the customer, but also independent checks on competent authority or professional regulator databases (with the exception of the EudraGDMP database for EU WDA holders, these are likely to be national and vary from country to country). Contact your local Competent Authority to seek advice.
- Additional checks that may be appropriate to customers of controlled substances
- How to ensure any limitations on products that may be supplied to a customer are identified and complied with
- Triggers for periodic re-evaluations and the process for conducting these (this could be by time, number of orders or even on each order, depending on customer history and/or product)
- What might constitute an ‘unusual sales pattern’ and how sales will be monitored for these
- How potential issues should be flagged first of all to company management and then to competent authorities as appropriate
### 5.4 Receipt of medicinal products

The purpose of the receiving function is to ensure that the arriving consignment is correct, that the medicinal products originate from approved suppliers and that they have not been visibly damaged during transport.

Medicinal products requiring special storage or security measures should be prioritised and once appropriate checks have been conducted they should be immediately transferred to appropriate storage facilities.

Batches of medicinal products intended for the EU and EEA countries should not be transferred to saleable stock before assurance has been obtained in accordance with written procedures, that they are authorised for sale. For batches coming from another Member State, prior to their transfer to saleable stock, the control report referred to in Article 51(6) of Directive 2001/83/EC or another proof of release to the market in question based on an equivalent system should be carefully checked by appropriately trained personnel.

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<td>Receipt checks are an important part of maintaining a reliable ‘chain of custody’ to the patient, providing assurance that:</td>
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<td>- The supplier is authorised</td>
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<td>- The product is as ordered and is authorised for sale</td>
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<td>- The product has not been tampered with or visibly damaged</td>
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<td>- The product has been, and is, maintained under the correct storage conditions as defined on the label; see Chapter 9 for guidance on the management of excursions</td>
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<th>What are the risks and benefits associated with this aspect of the guidance?</th>
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<td>Risks associated with inadequate receipt processes include:</td>
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<td>- Products coming from unauthorised sources, which as well as being a compliance issue increases the risk that they might be falsified</td>
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<tr>
<td>- Products not being transported under appropriate storage conditions or not being promptly transferred into appropriate storage following receipt, thus impacting product stability</td>
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There may be additional risks associated with particular products, requiring ‘special arrangements’ to be in place to handle them, for example cold chain products or controlled drugs (e.g., narcotics). Whenever ‘special arrangements’ are required, there are added risks that these arrangements will not be followed due to lack of resource, training or human error.

Large volume receipts, or multiple receipts in a short time period, can stress resources available to handle receipts and consideration should also be given to the risk of storage capacity being exceeded.

Benefits of a good receipt process include:
- Assurance of the ‘chain of custody’, providing confidence to customers and enabling recall if required
- Prompt detection of any issues with the received material, such as tampering, physical damage or incorrect storage
- Confidence that materials invoiced have actually been received
- Confidence during regulatory inspections
**How might this be implemented/ what does it mean?**

Whilst appropriate checks on arriving consignments are essential, certain elements of receipt are actually best dealt with as part of the ordering process and/or agreements with suppliers. For example, it should be ensured that there is ready access to certificates of analysis and/or certificates of compliance (conformance) either through documentation to be sent with each shipment or through provision in other ways, such as via the supplier’s website. Furthermore, arrangements such as the provision of an Advance Shipping Notice (ASN) with details of lot number, expiry date and SSCC (Serial Shipper Container Code*) number can facilitate quick and easy receipt checking.

*A SSCC is an 18 digit code in a GS1 barcode format or radio frequency identification (RFID) tag which identifies the manufacturer/supplier and packaging unit.

A receipt procedure should be in place which includes the following:

- Confirmation that the supplier is approved
- Confirmation that the receipt is as ordered (Invoice check against Purchase Order)
- Confirmation that the receipt is as stated (check physical stock identification, quantities, batch numbers and expiry dates against Invoice)
- Confirmation of territories for which the product is authorised for sale
- Confirmation that the received material has not been damaged or tampered with
- Confirmation that the received material has been transported under appropriate storage conditions
- Arrangements for booking the received material into inventory
- Arrangements for ensuring the material is promptly transferred to appropriate storage
- Any particular national arrangements, e.g., for samples to be taken and retained
- Any special arrangements for certain types of product*

*Note that whilst all medicinal products must be stored under appropriate conditions to avoid deterioration, some require tighter controls and may therefore require special arrangements, e.g., vaccines may have very limited stability outside 2 - 8°C. Some products may have very short shelf life (e.g., ‘Specials’ ordered for specific patients). Certain classes of product (typically those of high value) may be more susceptible to falsification and others may be subject to additional legal restrictions and controls. All of these may require arrangements over and above those for more ‘standard’ products.

As with other elements of GDP, staff training and assessment of competence is important.

Careful facility and capacity planning is required to ensure adequate volumes of the required types of storage. Have systems in place that check storage capacity prior to ordering. Stage deliveries to smooth out the workload.

A specific cold store, or segregated area within a cold store, for incoming materials will enable appropriate storage conditions to be maintained whilst receipts are processed.

Make arrangements with suppliers to ensure that the specific storage requirements for each product are readily identifiable on the delivery documents.

Aim to separate product flows according to storage requirements and do not allow products with different storage requirements to occupy space intended for products with specific requirements (e.g., avoid ‘room temperature’ products being placed in cold stores).

The ‘control report’ referred to in Article 51(1) of Directive 2001/83/EC is the document signed by the Qualified Person at the manufacturing site which declares the marketing authorisation against which the batch has been certified. Agreements with suppliers should ensure that a copy of this document is provided with each batch.
The receipt procedure should ensure that documents, including temperature records, are readily available to allow rapid review by the Responsible Person or other appropriately trained staff.

A procedure should also describe how it is assured that batches of product are not transferred into saleable stock (made available for picking to fulfil customer orders) until relevant associated documents have been reviewed and deemed satisfactory.

Ensure freight documents are archived promptly so that they can be accessed at a later date if required.

5.5 Storage

*Medicinal products and, if necessary, healthcare products should be stored separately from other products likely to alter them and should be protected from the harmful effects of light, temperature, moisture and other external factors. Particular attention should be paid to products requiring specific storage conditions.*

- **What is the rationale for this point in the guidance?**

To safeguard products from environmental factors that might impact their stability or other quality parameters that would render them unsuitable for use, e.g., packs with faded text or carrying an odour.

- **What are the risks and benefits associated with this aspect of the guidance?**

Environmental factors can create a number of risks if not adequately controlled:

- **Light:** Light can cause physical discolouration of product or printed components and certain products may be susceptible to light-catalysed chemical degradation. Product development activities should include packaging providing appropriate light protection, but issues can still be caused by exposure to strong artificial light sources or sunshine.

- **Temperature:** Chemical degradation increases as temperature increases and some products, such as suppositories (which can melt), creams (which can separate) and suspensions (which can flocculate), may have their physical stability impacted by either high or cycling temperatures. Most product packaging has minimal thermal insulation relying on control of the environment to prevent products being exposed to adverse temperatures. Liquid products may also be susceptible to freezing.

- **Moisture:** If products are exposed to excess water vapour then they can be susceptible to hydrolytic degradation or physical deterioration. As with light, product development activities should result in appropriate packaging systems, possibly including a desiccant, to protect from humidity, but these can be overloaded if high humidity is maintained over a long period of time. Cartons and labels may also be susceptible to damage by prolonged high humidity.

- **Other external factors:** These could include strong odours or spilled chemicals which could have direct impact on products or their packaging rendering them unsuitable for use.

In some cases degradation of product or packaging will be readily apparent to the recipient resulting in complaints. In other cases, the fact that the product is not suitable for use may not be apparent to the end user and could result in adverse effects on their health.

Good environmental control will assure product suitability for use throughout the stated shelf life.
How might this be implemented/ what does it mean?

Storage facilities should be designed, validated, maintained and operated in order to provide appropriate product protection:

- Products should not be stored in areas exposed to strong artificial or sun light – sky lights should be avoided and artificial lights should be ‘low energy’; if strong artificial lights are needed, then additional protection may be required for products stored nearby.
- The facility should have sufficient capacity of temperature-controlled storage areas appropriate to the label storage conditions of the different products handled.
- Receipt procedures should ensure that products are promptly located to the correct storage areas based on their label storage conditions.
- Storage facilities should be temperature mapped to identify any hot or cold spots (and thereafter avoiding storage of thermally sensitive products in such zones).
- Storage facilities should be subject to ‘continuous’ temperature monitoring with temperatures being captured from calibrated probes in representative and ‘worst case’ (hot and cold spot) locations. It is recommended that data are captured at least every 15 minutes.
- Alarms should be set at appropriate temperature limits and procedures should cover actions to be taken promptly in the event of an alarm being triggered.
- The storage facility should prevent the entry of rain and should be well ventilated to prevent humidity build up. Humidity control may be required in certain local climates.
- Procedures should be in place to rapidly deal with any spillages to prevent contamination of stored products.
- If possible, the storage area should be dedicated to medicinal products. If other chemicals or food products are stored in the same facility, then consideration should be given to the potential for odour contamination. Strong-smelling items should be segregated from medicinal products.
- In the event that fumigation is required to deal with an infestation, product must be removed prior to the procedure to prevent chemical contamination and very carefully inspected prior to return to avoid reintroducing the infestation.

5.5 Storage

Incoming containers of medicinal products should be cleaned, if necessary, before storage.

- What is the rationale for this point in the guidance?

The purpose is to reduce the risk of contaminating the warehouse and products stored with dust, debris or insects.

- What are the risks and benefits associated with this aspect of the guidance?

Any dust/debris which is not removed could subsequently be transferred to the patient pack during picking, which would undermine recipient confidence in the medicine, resulting in additional returns and thus increased workload.

Additional work is created if the warehouse becomes infested by insect or other pests.
### How might this be implemented/ what does it mean?

- Include expectations for delivery which help to ensure minimal contamination, e.g., shrink/stretch wrapping of pallets, in Technical/Quality Agreements with suppliers together with the right to refuse delivery or to charge for cleaning if these expectations are not met.
- The receipt procedure should include checks for cleanliness and light wiping of dusty boxes prior to placement in store.
- Any received materials requiring more than a light wiping away of dust should be referred to relevant management to determine if agreed terms and conditions have been broken.
- To help avoid potential disputes, capturing photographic evidence is recommended.

### 5.5 Storage

*Warehousing operations must ensure appropriate storage conditions are maintained and allow for appropriate security of stocks.*

#### What is the rationale for this point in the guidance?

- To ensure that the products are stored according to labelled storage conditions, thus maintaining their stability over full shelf life;
- To safeguard products from pest, vermin, insects and birds;
- To reduce the risk of stock being damaged, tampered with or pilfered.

#### What are the risks and benefits associated with this aspect of the guidance?

- Incorrect storage can result in degradation of medicinal products, reducing their effectiveness or even causing them to be harmful.
- Pests can result in products being damaged, especially where packaging is not robust, rendering them unfit for purpose.
- Poor security could make products vulnerable to illicit activity. There are historical cases of malicious product tampering resulting in patient harm. Theft of stock impacts business operations and can be a starting point for falsification activities.
- Note: In UK, MHRA has stated (2014) that any depot, freight consolidator or freight forwarder which holds stock in either ambient or cold room conditions for more than 36 hours must be licenced. Consult your local competent authority to clarify the requirements in your country [http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/News/CON447997](http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/News/CON447997)
• How might this be implemented/ what does it mean?

• See previous comments around the design, validation, maintenance and operation of facilities in order to assure product stability
• Storage areas should be well-built and secure with access restricted to appropriate company personnel
• Procedures and staff training should ensure that entry points are securely closed at all times when not in active use
• Security cameras should be located to cover entrances; internal cameras should also be considered, especially for areas used for high value products or controlled drugs.
• A ‘right of search’ should be established and periodic random searches should be conducted of staff leaving the premises
• A comprehensive pest control programme should be in place and maintained. This would typically include:
  o A procedure
  o A risk assessment of entry points for different types of pest
  o Appropriate arrangements to address these risks, which might include:
    • Insect killing devices
    • Rodent bait traps
    • Mesh over windows
    • Air blankets or curtains at large entry points to prevent access by birds
    • The location of all the above measures should be included on the site plan
  o Regular checks on pest activities
  o Expert review and recommendations

5.5 Storage

Stock should be rotated according to the ‘first expiry, first out’ (FEFO) principle. Exceptions should be documented.

• What is the rationale for this point in the guidance?

This is to ensure that product is supplied in a controlled manner and that shortest expiry dated product is placed into the market first. This reduces wastage of valuable stock and therefore helps to maintain efficient supply of product to patients.

Exceptions are necessary for customers who request a specific batch size/quantity to be supplied. Other exceptions might occur where the supplied product is intended to be used as a starting material for a manufacture, such as might be the case when preparing blinded investigational medicinal products, and the customer therefore requests supply with product carrying the longest possible expiry date.

• What are the risks and benefits associated with this aspect of the guidance?

The primary benefit is that inventory is not lost due to stock going out of date, thus reducing additional work and cost associated with returns.
• **How might this be implemented/ what does it mean?**

Use of a validated computerised inventory system with FEFO rules forming part of the picking module is probably the best way to ensure compliance with this guidance. It should be possible to override the automatic selection to enable exceptional circumstances to be met.

Smaller organisations using manual inventory control systems will need to put a process in place to review the batches of product held and ensure that the batch with lowest shelf life is picked first to meet an order.

Inventory checks carried out for accounting purposes and/or self inspections should be used to confirm that the FEFO process is operating effectively.

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**5.5 Storage**

*Medicinal products should be handled and stored in such a manner as to prevent spillage, breakage, contamination and mix-ups. Medicinal products should not be stored directly on the floor unless the package is designed to allow such storage (such as for some medicinal gas cylinders).*

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• **What is the rationale for this point in the guidance?**

Products stored on the floor are more likely to become damaged or contaminated by spillages, water and or pests.

Mix ups in storage can result in incorrect products being picked and supplied to customers.

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• **What are the risks and benefits associated with this aspect of the guidance?**

The principal risk is that any damage or contamination which occurs is likely to render the packs unfit for purpose.

Damage can also lead to product exposure creating a potential health and safety risk to staff.

If incorrect products are supplied to customers, then this will result in complaints and damage to reputation.

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• **How might this be implemented/ what does it mean?**

Have a procedure and racking/pallet system which requires/enables products not being stored on the floor. This can be reinforced by clear signage and staff training.

Computerised inventory systems should not include the floor as a location.

Regular self inspections of areas to confirm that products are stored appropriately is also recommended.

Assigning specific locations for the storage of any highly toxic products might be beneficial. A similar approach is recommended for large volume bottled liquids.
### 5.5 Storage

Medicinal products that are nearing their expiry date/shelf life should be withdrawn immediately from saleable stock either physically or through other equivalent electronic segregation.

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<td>To ensure that products reaching end users have sufficient remaining shelf life.</td>
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<td>The remaining shelf life is likely to be checked by customers on receipt and if they deem this to be too short, a complaint/return for replacement is likely. This is inefficient for both supplier and customer and could result in patients experiencing delays in receipt of the medicines they need.</td>
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| Agree and implement a policy on the minimum acceptable remaining shelf life (for each product) for both received and issued stock. Include these limits into both the receiving and issuing stock control systems, regardless of whether they are computerised or manual. A procedure should be in place to describe the process used to maintain the minimum shelf life acceptable for each product, and how to update the inventory system.  

Note: In defining this limit, consider product stability, availability and utilisation. Products such as antibiotics, which are prescribed frequently and normally only used for a short period of time, will be acceptable with shorter remaining shelf than products that might be held by patients for long periods of time for use ‘as needed’, e.g., rescue/reliever inhalers for asthmatics. |

### 5.5 Storage

Stock inventories should be performed regularly taking into account national legislation requirements. Stock irregularities should be investigated and documented.

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| Regular inventory checks provide assurance that product has not been lost or unaccountably gained.  

This provides confidence in warehouse systems and the ability to meet orders. |

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| Incorrect inventory figures result in the risk of company being unable to fulfil customer orders, which could have knock-on effects on the patient.  

In addition to the financial impact, criminal activity carries with it the risk of falsified medicines entering the supply chain (there have been cases of stolen products being tampered with and later re-introduced illegally into the supply chain). |
### How might this be implemented/ what does it mean?
- Define acceptable tolerances, based on quantity and not on value
- Introduce a regular programme of stock checks
- Ensure that stock checks happen as planned
- Ensure that significant stock irregularities are documented and communicated to management for review and further action as appropriate
- A validated IT system can help to provide controls that reduce the risk of inventory errors

### 5.6 Destruction of obsolete goods

**Medicinal products intended for destruction should be appropriately identified, held separately and handled in accordance with a written procedure.**

**Destruction of medicinal products should be in accordance with national or international requirements for handling, transport and disposal of such products.**

**Records of all destroyed medicinal products should be retained for a defined period.**

### What is the rationale for this point in the guidance?

This guidance ensures that:
- Such products do not inadvertently enter the supply chain for patient use or become diverted.
- Destruction takes place in a suitable, controlled, manner that minimises the environment, health and safety risks
- A full audit trail exists in the event that there is a need to investigate a batch history

### What are the risks and benefits associated with this aspect of the guidance?

If medicinal products intended for destruction are not appropriately controlled, then there is a risk that they will not be destroyed but will enter the supply chain – either through being picked to meet an order or through criminal diversion. In either case, patient health may be impacted by product not fit for use.

Improper destruction processes can result in waste or emissions which adversely affect either people or the environment. This could additionally incur a public liability.

If records are well kept, then they can be used as evidence in the event of any questions over practice.
• How might this be implemented/ what does it mean?

• Have a written procedure for handling products intended for destruction and train staff
• Inventory systems, whether manual or computerised, should clearly indicate when stock is assigned to be destroyed and record the actual destruction
• Computerised systems should be validated to prevent stock assigned for destruction being allocated to orders
• With manual systems, ‘stock cards’ should be flagged and ideally moved so that they are not visible to staff allocating stock to orders
• Physical labelling of boxes or pallets of material for destruction and moving them to a dedicated and designated area will provide additional assurance against inadvertent picking
• Having locks on this designated area provides an additional barrier to both inadvertent picking and theft
• Certificates of destruction should be reconciled with records of materials sent for destruction
• Establish an understanding of your country’s national and international requirements for handling, transport and disposal of medicinal products
• Be aware of and appropriately communicate the hazards associated with each product handled
• Be aware of and follow special requirements for controlled drugs (narcotics) and high value products
• Use only certified contractors for destruction
• Audit contractors used for destruction prior to appointment and periodically thereafter (every 2-3 years would be typical) to ensure that the appropriate facilities, equipment and processes are in place and maintained
• Have written agreements in place with contractors used for destruction clearly stipulating their responsibilities for secure and safe operations and the provision of appropriate documentation
• Certificates of destruction should detail product, batch number and quantity and should be promptly archived for a defined period of time

5.7 Picking

Controls should be in place to ensure the correct product is picked. The product should have an appropriate remaining shelf life when it is picked.

• What is the rationale for this point in the guidance?

The picking and checking process determines the product that is sent to the customer. If the process is not robustly controlled, then complaints will result from customers not receiving what they have ordered.

Likewise, complaints will be received if the customer is not satisfied that there is sufficient remaining shelf life on the products received.

Note: There are rigorous checks on supply of the correct product to patients by the dispensing pharmacist.

• What are the risks and benefits associated with this aspect of the guidance?

A robustly controlled picking process will prevent complaints arising from errors.

The main risk associated with picking is a failure to check all elements of the product’s identity, e.g., just looking at the name and selecting a different strength, dosage form or pack size.
How might this be implemented/ what does it mean?

- Ensure that staff are aware of all elements of a product’s identity relevant to delivering what the customer has ordered, e.g.:
  - Trade name
  - Dosage form (tablet, capsule, suspension, etc.)
  - Strength (dose)
  - Quantity per pack / pack Volume / size
  - Pack language / intended market
- As detailed in 5.5, agree and implement a policy on the minimum acceptable remaining shelf life (for each product) for issued stock and build a check for compliance into the process; follow FEFO principles unless an exception is agreed.
- Where possible, make use of validated electronic systems to allocate materials and facilitate their picking. Use the system to allocate the stock to be picked according to FEFO principles with validation of remaining shelf life and scanning of the barcode on each container picked to make up the consignment checks that what has been picked matches the allocation and flags an error message if this is not the case.

5.8 Supply

For all supplies, a document (e.g. delivery note) must be enclosed stating the date; name and pharmaceutical form of the medicinal product, batch number at least for products bearing the safety features; quantity supplied; name and address of the supplier, name and delivery address of the consignee (actual physical storage premises, if different) and applicable transport and storage conditions. Records should be kept so that the actual location of the product can be known.

(7) Article 82 of Directive 2001/83/EC.

What is the rationale for this point in the guidance?

- To ensure that the driver knows where to deliver the ordered product(s) & to whom
- So that the recipient can check the delivery against the order
- So that the recipient is aware of and able to confirm the transport and storage conditions
- To provide a ‘chain of custody’ in the event of a recall or other issue.

What are the risks and benefits associated with this aspect of the guidance?

Without a delivery note, there are risks that

- Delivery will be to the wrong address
- It is not possible to link the delivery to an order
- Inappropriate transportation conditions may not be identified
- Stock may be stored under the wrong storage conditions
- It is not clear where stock is located or what its pedigree has been in the event of a recall or query about potential falsification.

How might this be implemented/ what does it mean?

- A standard delivery note template with all the required information fields should be used
- The delivery note should be used by the recipient to check:
  - That the goods received are those that have been ordered
  - That products have been transported under appropriate conditions
5.9 Export to Third Countries

The export of medicinal products falls within the definition of ‘wholesale distribution’\(^{(8)}\). A person exporting medicinal products must hold a wholesale distribution authorisation or a manufacturing authorisation. This is also the case if the exporting wholesale distributor is operating from a free zone. The rules for wholesale distribution apply in their entirety in the case of export of medicinal products. However, where medicinal products are exported, they do not need to be covered by a marketing authorisation of the Union or a Member State\(^{(9)}\). Wholesalers should take the appropriate measures in order to prevent these medicinal products reaching the Union market. Where wholesale distributors supply medicinal products to persons in third countries, they shall ensure that such supplies are only made to persons who are authorised or entitled to receive medicinal products for wholesale distribution or supply to the public in accordance with the applicable legal and administrative provisions of the country concerned.

\(^{(8)}\) Article 1(17) of Directive 2001/83/EC.
\(^{(9)}\) Article 85a of Directive 2001/83/EC.

- **What is the rationale for this point in the guidance?**

  These points are largely reminders of legislative requirements.

  The guidance is intended to ensure that all products passing through EU-based wholesale distributors are protected by EU GDP standards irrespective of their intended market. This helps to safeguard global supply chains.

  It also ensures that only products with an EU marketing authorisation reach the EU market, thus ensuring that EU patients only receive products meeting EU regulatory standards.

- **What are the risks and benefits associated with this aspect of the guidance?**

  The benefit of these arrangements is that products may pass through EU wholesale distributors even if they are not licensed for marketing in the EU and that they are protected by EU GDP standards as they do so. This contributes to safeguarding patients globally by ensuring safe chain of custody.

  Failure to apply GDP to all products through all supply chains can introduce risks to product quality or enable entry of falsified medicines.

- **How might this be implemented/ what does it mean?**

  EU based wholesale dealers should work to a single standard of GDP which meets EU requirements, irrespective of where products are going to be supplied.

  A robust process should be in place to ensure that products are only supplied to markets where they are authorised, or to other wholesale dealers. Include market details within the inventory description.

  Apply the guidance in 5.3 to the qualification of customers wherever they are based.