Guide to Pharmaceutical Drug Product Sampling

Understanding the Regulatory Expectations
Introduction

Today’s supply chains are complex in nature. Business competitiveness and achieving profitable sales often translates into getting your drug product to the end user or target market on a global scale.

Your drug product may cross multiple borders, be subjected to numerous modes of transport and have interactions with a large number of supply chain actors. Of course the more complex the supply chain becomes, the greater the potential risks to the safety, efficacy and quality of your finished drug product and ultimately your brand.

We are all aware that the EU pharmaceutical regulators (Competent Authorities) require risk management and quality control of drug products entering their jurisdictions. Quality Control testing is an established methodology for assuring the quality, identity, safety and efficacy of drug products that started their supply lifecycle journey very far from their point of use.

But how do we ensure that we get accurate test results on which to base the decision that the consignment we have received is fit for purpose? Accurate quality control testing relies intrinsically on representative sampling. On the 15th April 2016 the new and revised Eudralex Volume 4 Part 1 Annex 16 will come into effect. Within the revised Annex its fair to say the regulators have clarified and reinforced their expectations. Its also fair to say that in some cases the expectations have not radically changed from where they were before but rather that the text of the Annex now aims to makes it clear and more prescriptive as to what is accepted practise. Sampling of drug product arriving from third countries into the EU is a practise we see our clients engaging in as a matter of course in the conduct of their daily business. And often we work with clients who are realising compliance with the expectations Annex 16 as amended will bring, involves re-thinking the way they sample drug product. Is your organisation ready?

Through this guide Pharma Quality Partners aims to summarise the current EU and WHO requirements with respect to sampling of finished drug product and provide you with the information you need to assure your pharmaceutical quality management system is designed to achieve representative samples on which to base accurate quality decisions.
Annex 16 - What Does it Say?

For many medicinal finished drug product manufacturers operating in the EU member states today, it's not uncommon for at least some stages of the drug products manufacturing and supply lifecycle to occur in another member state or in a third country. The EU regulators have clarified their expectations around importation of drug product from third countries in the now published revision of Eudralex Volume 4 Part 1 Annex 16 which will come fully into effect by 15th April 2016.

With regard to importation of finished drug product from third countries the EU Competent Authorities have made the following stipulations in the revised Annex:

• Sampling of imported product should be fully representative of the batch. Samples may either be taken after arrival in the EU, or be taken at the manufacturing site in the third country in accordance with a technically justified approach which is documented within the company’s quality system.

• Responsibilities in relation to the sampling should be defined in a written agreement between the sites. Any samples taken outside the EU should be shipped under equivalent transport conditions as the batch that they represent.

• Where sampling is performed at a third country manufacturing site, the technical justification should include a formal Quality Risk Management process to identify and manage any risks associated with this approach. This should be fully documented and include at least the following elements:
  
  • Audit of the manufacturing activity including any sampling activity at the third country site and evaluation of subsequent transportation steps of both the batch and samples to ensure that the samples are representative of the imported batch.
  
  • A comprehensive scientific study, including data to support any conclusions that samples taken in the third country are representative of the batch after importation. This study should at least include:
    
    1. Description of the sampling process in the third country.
    
    2. Description of the transported conditions of the sample and the imported batch. Any differences should be justified.
3. Comparative analysis of samples taken in the third country and samples taken after importation.

4. Consideration of the time interval between sampling and importation of the batch and generation of data to support appropriate defined limits.

- Provision for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in a third country.

- A review of any unexpected result or confirmed out of specification result. These may have implications for reliance on sampling performed at the third country manufacturing site and should be notified to the Supervisory Authority for the site where certification is performed. Such an occurrence should be regarded as a potential quality defect and investigated in line with the guidance in Chapter 8 of EudraLex, Volume 4, Part I.

- Different imported finished product batches may originate from the same bulk product batch. The QPs certifying the different finished product batches may base their decision on the quality control testing of the first imported finished batch provided that a justification has been documented based on Quality Risk Management principles. This should take into account the provisions of paragraph 1.5.6(of the Annex) in relation to reliance on any samples taken in third countries. Evidence should be available to ensure that the integrity and identity of the imported finished product batch has been established through documented verification of at least the following:

  - Relevant requirements for storage of the bulk product prior to packaging have been satisfied;
  - The finished product batch has been stored and transported under the required conditions;
  - The consignment has remained secure and there is no evidence of tampering during storage or transportation;
  - Correct identification of the product has been established;
  - The sample(s) tested are representative of all finished product batches derived from the bulk batch.
Overall View

Based on a reading of the revised text of Annex 16 its easy to conclude the overall aim at an EU Competent Authority level is to make it prohibitive to consider sampling in third countries in place of sampling in the EU after importation. Though the Annex concedes that sampling can occur in the third country, it goes on to set a list of criteria by which sampling in third countries will be accepted. Fulfilling these criteria is likely to make this route somewhat cumbersome, though arguably not impossible.

Included in the specified criteria is a clear requirement for periodic comparative testing which is likely to offset any financial/operational gain achieved through relying on samples taken in the third country. This requirement enforces an expectation that the importer will have to periodically prove the validity of the sampling process and the samples themselves. But most importantly a scientific study is required to justify this approach in the importers quality management system. The level of resource and work that this may require really makes sampling in the EU country a more palatable option.

On this basis the remainder of this guide will focus on requirements relating to sampling in the EU after importation as opposed to sampling in third country.*

*However should you require expertise or support with developing robust processes in your quality management system to assure compliance with Annex 16 requirements to conduct sampling in third country Pharma Quality Partners Ltd can help. You can contact us through our website at www.pharmaqpltd.com or see the contact section of this guidance document for further contact information)
Sampling Guidance in the EU

Apart from the afore-mentioned references in EU GMP Volume 4 Part 1 Annex 16 as amended, there are several texts published by the EU Commission (EU) and the World Health Organisation (WHO) which provide guidance in relation to sampling. The main texts of interest are:

- EU GMP Volume 4 Part 1 Chapter 6
- EU GMP Volume 4 Part 1 Annex 8
- EU GMP Volume 4 Part 1 Annex 19

EU GMP Volume 4 Part 1 Chapter 6

The content of EU GMP Guide Chapter 6 relates to the topic of Quality Control. Within the text of this chapter and with reference to general requirements for good QC laboratory practises it is stipulated that:

- Sampling should be done and recorded in accordance with approved written procedures that describe:
  
  - The method of sampling;
  
  - The equipment to be used;
  
  - The amount of the sample to be taken;
  
  - Instructions for any required sub-division of the sample;
  
  - The type and condition of the sample container to be used;
  
  - The identification of containers sampled;
  
  - Any special precautions to be observed, especially with regard to sampling of sterile or noxious materials;
  
  - The storage conditions;
  
  - Instructions for the cleaning and storage of sampling equipment.
Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach.

Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimise the risk of mix-up and to protect the samples from adverse storage conditions.

Further guidance on reference and retention samples is given in Annex 19.

EU GMP Volume 4 Part 1 Annex 8

The content of EU GMP Guide Annex 8 relates to the topic of sampling of raw materials and packaging materials used for finished drug product manufacture. Within the text of this Annex there is a note that states that “Sampling is dealt with in Chapter 6 of the Guide, items 6.11. to 6.14. This annex gives additional guidance on the sampling of starting and packaging materials.” As the main content of the Annex is not concerned with finished drug product it is not summarised here. However it does specify general requirements with regard to sampling and personnel which have relevance as guiding principles when considering sampling of finished drug product. Those general requirements are stipulated as:

- Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on non-representative samples. Correct sampling is thus an essential part of a system of Quality Assurance.

- Personnel who take samples should receive initial and on-going regular training in the disciplines relevant to correct sampling. This training should include:
  
  - sampling plans,
  - written sampling procedures,
  - the techniques and equipment for sampling,
  - the risks of cross-contamination,
  - the precautions to be taken with regard to unstable and/or sterile substances,
• the importance of considering the visual appearance of materials, containers and labels,

• the importance of recording any unexpected or unusual circumstances.

EU GMP Volume 4 Part 1 Annex 19

The content of EU GMP Guide Annex 19 relates to the topic of reference and retention samples of finished drug product. Within the text of this Annex there is guidance as to the taking and holding of reference and retention samples for starting materials, packaging materials and finished drug product. The requirements are stipulated as:

• It is necessary for the manufacturer, importer or site of batch release, as specified under section 7 and 8, to keep reference and/or retention samples from each batch of finished product.

• Records of traceability of samples should be maintained and be available for review by competent authorities.

• Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed.

• The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the Marketing Authorisation File which has been assessed and approved by the relevant Competent Authority / Authorities. Where it is necessary to do so, unopened packs should be used when carrying out each set of analytical controls. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.

• Where applicable, national requirements relating to the size of reference samples and, if necessary, retention samples, should be followed.
• Reference samples should be representative of the batch of starting material, intermediate product or finished product from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). Where a batch is packaged in two, or more, distinct packaging operations, at least one retention sample should be taken from each individual packaging operation. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.

• Storage of reference samples of finished products and active substances should be in accordance with the current version of the Note for Guidance on Declaration of Storage Conditions for Medicinal Products and Active Substances.

• Storage conditions should be in accordance with the marketing authorisation (e.g. refrigerated storage where relevant).

• Where the marketing authorisation holder is not the same legal entity as the site(s) responsible for batch release within the EEA, the responsibility for taking and storage of reference/retention samples should be defined in a written agreement between the two parties in accordance with Chapter 7 of the EC Guide to Good Manufacturing Practice. This applies also where any manufacturing or batch release activity is carried out at a site other than that with overall responsibility for the batch on the EEA market and the arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement.

• The Qualified Person who certifies a batch for sale should ensure that all relevant reference and retention samples are accessible at all reasonable times. Where necessary, the arrangements for such access should be defined in a written agreement.

• Where more than one site is involved in the manufacture of a finished product, the availability of written agreements is key to controlling the taking and location of reference and retention samples.

• Reference samples are for the purpose of analysis and, therefore, should be conveniently available to a laboratory with validated methodology. For starting materials used for medicinal products manufactured within the EEA, this is the original site of manufacture of the finished product. For finished products manufactured within the EEA, this is the original site of manufacture.

• For finished products manufactured by a manufacturer in a country outside the EEA;
• where an operational Mutual Recognition Agreement (MRA) is in place, the reference samples may be taken and stored at the site of manufacture. This should be covered in a written agreement (as referred to in section 6 above) between the importer/site of batch release and the manufacturer located outside the EEA.

• where an operational MRA is not in place, reference samples of the finished medicinal product should be taken and stored at an authorised manufacturer located within the EEA. These samples should be taken in accordance with written agreement(s) between all of the parties concerned. The samples should, preferably, be stored at the location where testing on importation has been performed.

• reference samples of starting materials and packaging materials should be kept at the original site at which they were used in the manufacture of the medicinal product.

• A retention sample should represent a batch of finished products as distributed in the EEA and may need to be examined in order to confirm non-technical attributes for compliance with the marketing authorisation or EU legislation. **Therefore, retention samples should in all cases be located within the EEA.** These should preferably be stored at the site where the Qualified Person (QP) certifying the finished product batch is located.

• In accordance with 8.1 above, where an operational MRA is in place and reference samples are retained at a manufacturer located in a country outside the EEA (section 7.2.2 above), separate retention samples should be kept within the EEA.

• Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the Competent Authority.

• Where more than one manufacturing site within the EEA is involved in the manufacture importation/packaging/testing/batch release, as appropriate of a product, the responsibility for taking and storage of retention samples should be defined in a written agreement(s) between the parties concerned.

The content of WHO Technical Report Series No. 929, 2005 Annex 4 presents a set of guidelines primarily intended for use by governmental organisations, drug regulatory authorities, quality control laboratories, customs and police authorities but it does state that some of its principles may be appropriate for application by manufacturers.

It highlights that choice of sampling plan should always take into consideration the specific objectives of sampling and the risks and consequences associated with inherent decision errors. It provides a bibliography of sampling standards and highlights that this should be consulted when justifying a sampling plan for a given purpose.

It provides the following guidance:

- Sampling is a set of operations designed to select a portion of a pharmaceutical product for a given purpose. The sampling procedure must be appropriate to that purpose, to the type of controls intended to be applied and the procedure must be described in writing.

- All operations related to sampling must be done with care, using proper tools and equipment. Contamination of a sample will jeopardise its validity as a sample.

- A material is regarded as homogenous if it is all of the same origin i.e. from the same batch.

- Sampling facilities should be designed to:
  - Prevent contamination of opened containers, the material and the operator
  - Prevent cross contamination by other materials, products or the environment
  - Protect the sampler.

- Samplers need to be adequately trained and this training should be documented.

- Sampling records should include:
  - Date of sampling
  - The sampled container
The sampler.

- The sampler should remain alert to signs of contamination, deterioration or tampering. Any suspicious signs should be recorded in detail on sampling records.

- The sampler should have available suitable tools for sampling.

- Sampling tools should be adequately controlled, cleaned and stored and their cleaning procedures should be documented and recorded. An Annex is provided with examples of typical sampling tools for different applications.

- There should be a written procedure describing the sampling operation that ensures representative samples are taken in sufficient quantities for testing.

- Sampling procedures should be such that non-uniformity in material can be easily detected. During sampling special attention should be given to signs of non-conformity. Non-conforming portions should be sampled and tested separate to normal material.

- Samples should be labelled with sufficient information:
  
  - Sample type
  - Name of material
  - Identification code
  - Batch/Lot number
  - Code
  - Quantity
  - Date of Sampling
  - Storage Conditions
  - Handling precautions
  - Container number

- For finished drug products sampling should consider both official tests and non-officials tests. Non-official tests might be testing for counterfeits.

- The sampling procedure should also take into account past experience with the
Containers used to store samples should not interact or contaminate the sample. It should protect the sample from light, moisture and air and should be tamper evident.

Security and storage conditions for where samples are stored should be given consideration.

An appendix is supplied with examples of sample storage containers.

Finished product quality needs to be verified at the time of their importation or purchase. Sampling in this regard needs to be by a suitable method and with regard to expected uniformity. As single batch from a single supplier in a single consignment may be considered uniform.

The size of the sample must be enough for the required testing. Sampling units may be defined in terms of individual packs (each) or bundles (collation of packs) or shipper units as appropriate. Sampling may be adjusted dependant on previous experience with the product and/or supplier.

Choice of sampling plan should always take into account the specific objective of the sampling and the risks associated with the inherent decision errors.

Each sampling unit should be inspected to ensure it is intact and free from obvious damage.

The guide recommends statistically based sampling plans for the sampling of finished drugs products. Statistical sampling plans referenced in the guide are:

- BS600-1
- ISO 2859
- ANSI/ASQCZ 1.4-1993

An example of a sampling regime, based on ISO 2859, to apply to finished drug product is illustrated in an appendix. It cautions that single whole packs should be used as sampling units.
Contact Us:
Hi I’m Justin Ahern, Managing Director of Pharma Quality Partners Ltd. We are a pharmaceutical quality consultancy and training service provider with a guiding business objective of “Quality Excellence Through Partnership”. We aim to achieve quality excellence for our clients by partnering our expertise in Qualified Person, GMP, Quality Assurance and Clinical Drug Development (Pharmaceutical Medicine) services with their business needs.

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- GMP/GDP/GCP Compliance, Advice and Consultancy Services
- Pharmaceutical Quality Auditing Services
- ADME (Absorption, Distribution, Metabolism and Excretion) Services & Training
- Pharmacokinetics Services & Training
- Pharmacogenomics and Personalised Medicine Services & Training
- Clinical Pharmacology Training

We hope this guidance document will be useful to you and that you find it beneficial in gaining knowledge with respect to sampling of drug product in the EU. This guide is of course free for you to use within the terms of the copyright. If you would like any further information on the topic in this guide, require any of our services or indeed would like to see further guides developed on topics of interest to you, we’d love to hear from you. We can be contacted as follows:

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