EBE Position Paper

A Risk-Based Approach to Identity Sampling of Biological Drug Substances

15 October 2019

Executive Summary

Good Manufacturing Practices require that the identity of materials received for use in the manufacturing of drug products is confirmed. However, the direct sampling of primary containers of biological drug (active) substances at the biological drug product manufacturing site, after thaw can expose the biological drug substance to risks. The use of a representative sample taken at the biological drug substance manufacturing site to confirm identity avoids these risks.

There are basically two major international guidance documents for identity sampling of “starting materials” or “components”:

- Annex 8 of EudraLex Vol 4 GMP Guidelines - Sampling of Starting and Packaging Materials
- 21 CFR 211.84- Control of Components and Drug Product Containers and Closures: Testing and approval or rejection of components, drug product containers, and closures; with the explanatory Questions and Answers (Q&A) on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Control of Components and Drug Product Containers and Closures.

Due to imprecise terminology, Annex 8 is subject to variable interpretation. Since “starting materials” are not defined in Annex 8, it is questionable whether Annex 8 is applicable to biological drug substance. However, with a literal interpretation of Annex 8, this guidance requires identity verification of ALL containers in a batch as soon as a parenteral application of the end product is intended.

The purpose of this position paper is to provide a framework for the Identity testing of biological drug substance without thawing, sampling and testing of each incoming main Biological Drug Substance container, because the risk of degradation and microbial contamination in case of 100% container-wise sampling may jeopardize the quality of the final biological drug product.

The position paper also provides recommendations for the adaptation of the current main international guidelines, to take account of the specificities of biological substances.

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Abbreviations

API	Active Pharmaceutical Ingredient
BDS	Biological Drug (Active) Substance
CFR	Code of Federal Regulations
CMO	Contract Manufacturing Organisation
CQA	Critical Quality Attribute
DP	Drug Product
DS	Drug Substance
EBE	European Biopharmaceutical Enterprises
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
ID	Identity
Q&A	Questions & Answers
WHO	World Health Organisation

1. Introduction and problem statement

Good Manufacturing Practices (GMP) require that the identity (ID) of materials received for use in the manufacturing of drug products (DP) is confirmed. However, the direct sampling of primary containers of biological drug (active) substances (BDS), after thaw can expose the biological drug substance to risks. The use of a representative sample to confirm identity avoids these risks.

There are basically two major guidance documents published, which regulate the matter:

- Annex 8 of EudraLex Vol 4 GMP Guidelines - Sampling of Starting and Packaging Materials
- 21 CFR 211.84- Control of Components and Drug Product Containers and Closures: Testing and approval or rejection of components, drug product containers, and closures; with the explanatory Questions and Answers (Q&A) on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Control of Components and Drug Product Containers and Closures.

Relevant extracts of these guidance documents are provided in Appendix 1.

Annex 8 of EudraLex Vol 4 GMP Guidelines permits to reduce the amount of testing in presence of a "*validated procedure*". On the other hand, it states that "*it is improbable that a procedure* [exempting identity testing of each incoming container of starting material] *could be satisfactorily validated for starting materials for use in parenteral products*".

Due to imprecise terminology, Annex 8 is subject to variable interpretation. Indeed, since "starting materials" are not defined in Annex 8, it is questionable whether Annex 8 is applicable to BDS. In other words, it is unclear, if BDS falls into the category of "starting material".

The EBE concept paper on "Management and Control of Raw Materials Used in the Manufacture of Biological Medicinal Products" (see reference), gives an appropriate definition for starting materials. In this EBE concept paper, starting materials are defined as the recombinant cell line, tissue, body fluid or primary cells from which the desired molecule with the requisite therapeutic activity (i.e. the Drug Substance, sometimes also called the active substance or active pharmaceutical ingredient (API)) is expressed and/or purified. WHO Annex 4 "WHO guidelines for sampling of pharmaceutical products and related materials" (http://apps.who.int/medicinedocs/en/d/Js21440en/) also makes the distinction between starting materials and active substances. Finally, Part II of the EU GMP Guide: Basic Requirements for Active Substances used as Starting Materials delivers the definition of an "Active Substance Starting Material"[1]. Implicitly this differentiates between a mere starting material and an active substance as a consequence of a series of process steps with the input of a series of starting materials.

Single use, small volume containers (e.g. 1 to 50 L bags or bottles) are commonly filled for storage and shipping of biopharmaceutical drug substances[2] (BDS), typically under frozen conditions (these containers will be referred later in this document as the "main BDS containers"). The amount of low volume main BDS containers can be large, e.g. 30 up to 100 for a 300 L BDS batch. Identity testing conducted on each main BDS container received at the DP manufacturing site can result in numerous identity samples required for a single DP lot.

1 An "Active Substance Starting Material" is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance.

2 BDS, Biopharmaceutical Drug Substance, refers predominantly to monoclonal antibodies and therapeutic proteins.

A survey of EBE (European Biopharmaceutical Enterprises) member companies shows that industry interpretations and quality system requirements vary, driven in part by perceived inspectorate interpretation of Annex 8. The interpretation of Annex 8 of EudraLex Vol 4 GMP "*Sampling of Starting and Packaging Materials"* requirements causes debate. Companies adopting a literal interpretation of Annex 8 require 100% container-wise sampling and identity testing[3] of thawed BDS. Other approaches involve using representative "travel sample(s)"[4] for ID testing. The identity of the "travel" sample, sampled as part of the BDS manufacturing and sampling process, confirms the identity of the entire batch. This approach for ID testing allows release of the BDS batch for DP manufacture without requiring thaw of all primary BDS containers.

The purpose of this position paper is to provide a framework for the ID testing of BDS without thawing, sampling and testing of each incoming main BDS container, because of the risk of degradation and microbial contamination in case of 100% container-wise sampling, which jeopardizes the quality of the biological DP.

2. Survey of current industry practices

EBE member companies have a wide range of experiences with regional GMP inspections, regarding the interpretation of how to obtain the samples of biopharmaceutical products required for confirmatory ID testing of bulk DS units upon receipt. While some GMP inspectors of biopharmaceutical products historically and currently accept travel samples to confirm the identity of the bulk DS units in a shipment, the EBE survey shows increasing instances where EU GMP inspectors are not accepting travel samples for confirmation ID testing. 100% container-wise identity testing has been required, i.e. thawing, opening, sampling every – even small – bulk DS unit in each shipment to obtain samples subjected to identity testing, despite some attempts to validate alternative procedures. This practice of thawing, opening, and sampling aseptic biological solutions presents several risks to product quality, as described in section 5.

The questions raised from the results of the EBE survey are:

- What, from the regulatory side, has caused a change in this EU inspectional interpretation?
- Has a new risk emerged from the historically-accepted testing of travel samples that outweighs the risk to product quality from opening each bulk container?

The answer may be further complicated by variability in industry practices for bulk DS identity testing. The EBE survey also revealed that the biopharmaceutical industry has applied various operational interpretations of the sampling required for cGMP ID testing of bulk DS shipments. The implemented practices vary from company to company, sometimes even from site to site within a company, and between sponsors and contract organizations.

Some of the variations include:

- 100% container-wise sampling of individual units of the received bulk DS shipment at DP site after thawing.
    - Results available at time of DP release (not prior to further «use», i.e. manufacture at risk)
    - Results available before DP filling (where extended hold times are possible)

[3] **"100% container-wise"** samples will be used in this paper to mean obtaining a test sample directly from every unit in a bulk DS shipment (i.e. from every main BDS container)

[4] Terms for these samples vary; "travel samples" or "piggy-back samples" or "satellite samples" or "side samples" have been used in different regions. In this paper, the term **"travel samples"** will be used for simplicity reasons. Based on the purpose of these representative BDS test samples, they must travel with the bulk DS shipment or any partial DS shipment, and are representative of the DS batch and not of individual containers.

- Testing the received bulk DS shipment travel sample(s) prepared during DS fill at DS manufacturing site
  - One travel sample shipped with each DS container (taken during DS fill and aliquoted), one representative travel sample tested per batch or shipment or each travel sample tested
  - Travel samples shipped with a bundle of containers, and representative travel sample(s) tested per batch or shipment
- Sampling of individual containers using a reduced sampling plan at DP site, e.g. square root of (N) + 1 sampling plan

Hence, there is no common industry practice which causes frequent debates e.g. when dealing with Contract Manufacturing Organisations (CMOs) or when interacting between different sites of the same company. The authors of the paper also identified a certain inspection risk if interpretations are varying that much.

3. The regulatory dilemma

For biopharmaceutical products, in most cases, it is not possible to have procedures compliant with all requirements in the current relevant international guidance and, at the same time, acceptable from a quality standpoint:

Either travel samples taken during the DS fill at the DS site are used for ID testing and the results are available **prior** to further "use", i.e. DP filling,
or, the DS containers are sampled at the DP site, when containers are thawed with the consequence that **DP manufacture is progressed without ID results being available** due to the limited hold-time of BDS after thaw.

Less than 100% sampling, i.e. a reduced sampling plan or travel samples, is not acceptable if Annex 8 is followed, since with only few exceptions, biologicals molecules are applied via the parenteral route. Therefore, EBE would recommend that the current international guidelines, especially Annex 8, are revised (see Appendix 2 for recommendations) to match the needs of BDS and to allow a risk-based approach as described in section 7 of this paper.

4. Scope of this position paper

The manufacture of medicinal products containing biopharmaceutical drugs begins with the thawing of vials of the Master Cell Bank, followed by inoculation, expansion in various bioreactors or continuous fermentation in a perfusion process, separation of the cells, purification, virus inactivation and formulation. In most cases, this formulated DS bulk is stored and transported to decouple DS and DP manufacture sites, as regards to timing and location.

At the DP manufacturing site, the DS is thawed, homogenised, in some cases finally formulated and filtered. Finally, the bulk for fill is sterile filtered and simultaneously or subsequently dispensed into the final DP containers for the market.

The identity test, which we are discussing here, occurs before the conversion of DS to DP (see figure 1, process steps considered in this paper are highlighted in the green box).

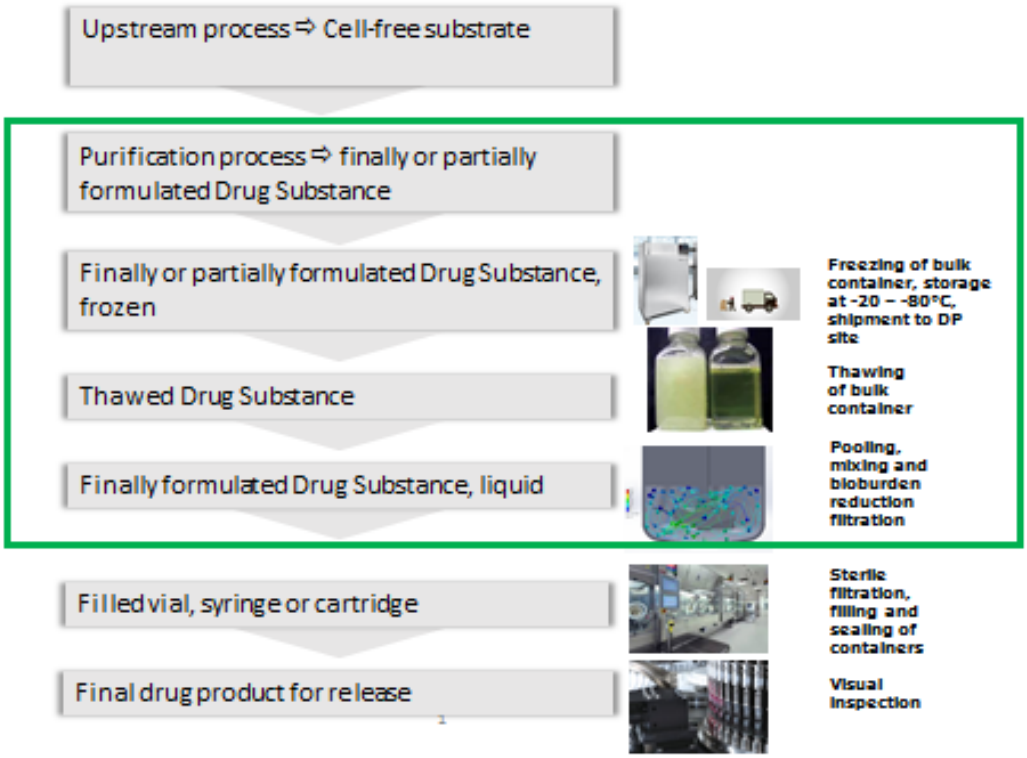

Figure 1: End-to-end process, typical for biological molecules such as monoclonal antibodies

5. Unique risks for biological drug substances

Whilst the practice to sample all of the containers may be suitable for use with chemical product parenterals, when applied to biologically-derived parenterals, 100% sampling of containers of biological products introduces two significant risks to product quality and safety:

1) Thawing and re-freezing every bulk DS container (given the limited hold time of BDS) would introduce more physical stress on the product and could have an impact on critical quality attributes (CQA) such as increase of aggregates and particulates in the DS solution. Even though freeze/thaw cycle studies are normally done for cold-chained biologics due to the risk of increased aggregation or demixing during freezing and thawing, this remains a risk and an additional (unnecessary) significant stress for the therapeutic protein.

2) Sampling every aseptically-filled bulk DS container increases the risk of microbial contamination from the sampling operation. Although suitable aseptic techniques (such as sampling under laminar flow, use of single-use sterilized sampling components, use of BDS containers with built-in aseptic connectors to enable as closed access) may reduce the risk of contamination, they cannot exclude the risk and may introduce other risks such as failing container-closure integrity of assembled tubes during frozen transportation and storage.

   Due to the structural complexity of many biological drugs such as IgG1s, methods for ID testing of biological DS may involve more complex protein-specific analytical procedures which take time - not comparable to small molecules and their identification with easy stand-by analytics like NIR.

In addition, many *chemical* drug products can be sterilised with heat and pressure treatments to mitigate the risk of microbial contamination due to sampling. In contrast, *biological* products are denatured by such treatments. Therefore, biological products are handled aseptically and sterilised by filtration, which can remove viable organisms, but does not remove endotoxins or other microbial by-products which are biologically active. Furthermore, a dry chemical DS does not constitute a good environment for microbial growth leading to such microbial by-products - as opposed to biological DS.

6. Role of procedural controls: drug substance fill, labelling, shipping and receipt

EBE agrees with the text of Annex 8 that describes the improbability of satisfactorily validating a procedure if starting materials (drug substance) is "*supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited*". Biological drug substance is manufactured under the control of the pharmaceutical company owning the product license, and is being transferred to a fill and finish site under 'control' of the company (i.e. sister site or CMO under a Quality agreement).

Where biological drug substance suppliers are unable to establish procedural controls to ensure that no single container of starting material has been incorrectly labelled, the identity of every container must be verified prior to using material for drug product manufacturing. As Annex 8 describes, 100% container-wise sampling would be required in the unlikely event that drug substances are supplied by a manufacturer that does not understand GMP requirements of the pharmaceutical industry, or if drug substances do not come directly from a manufacturing site or in the manufacturer sealed containers.

Biological drug products must be manufactured according to Good Manufacturing Practices whether administered in clinical trials or prescribed after commercial approval. Current GMPs require production and procedural controls that prevent mix-up and mislabeling of drug substance containers: procedural controls utilised during fill and labelling, tamper evident technology used for transport and reconciliation at incoming inspection prevents mix-up described by Annex 8. This applies also to Biological drug substance manufactured under the control of the pharmaceutical company owning the product license, and transferred to a fill and finish site under 'control' of the company (i.e. sister site or CMO under a Quality agreement).

7. Recommendations for identity testing of biopharmaceutical parenterals

Suitability of the BDS manufacturer quality system must be verified and continued compliance to defined quality system procedures must be ensured. Representative samples that accompany BDS shipments can be used for identity confirmation of an entire incoming BDS batch, when it can be demonstrated processes are under control.

While the current Annex 8 requires "validation" of processes, EBE recommends continuous adherence to procedural controls during drug substance production, use of tamper evident technology (Figure 2) during transport, and receiving inspection and reconciliation to ensure drug substances are appropriately identified.

The identity testing could be conducted only on a portion of the main BDS containers or on representative (travel) sample(s):

- Representative samples may be collected at the time of DS fill ('travel' samples) and can be acceptable where procedural and quality requirements are defined.
- A program for travel samples must be procedurally defined at both BDS and DP sites.
- Sample(s) collected during fill of main BDS containers must be representative of the entire BDS batch
- Travel samples must be shipped with the main BDS containers as a unit (i.e. not as pre-shipment samples).
- Appropriate controls must be in place for:
  - Labeling, identification and reconciliation
  - Secure shipping and transport
  - Appropriate monitoring of transport and documented chain of custody

Figure 2: Examples to assure integrity of travel sample and BDS storage container

A process flow as depicted in figure 3 reveals that biological parenteral products can have a safe supply chain with controlled and robust procedures when using travel samples for DS receipt ID testing. Many years of successful practices for using controlled, traceable travel samples for bulk DS shipments of biological products have demonstrated that it is possible to assure the accurate identity of the whole batch without sampling individual bulk DS containers. Furthermore, data collected from various companies and facilities reveal that the established measures and controls to avoid mix-ups are highly efficient. Over 3000 ID tests generated by sampling 100% container-wise were evaluated for this position paper, zero test results were not conforming.

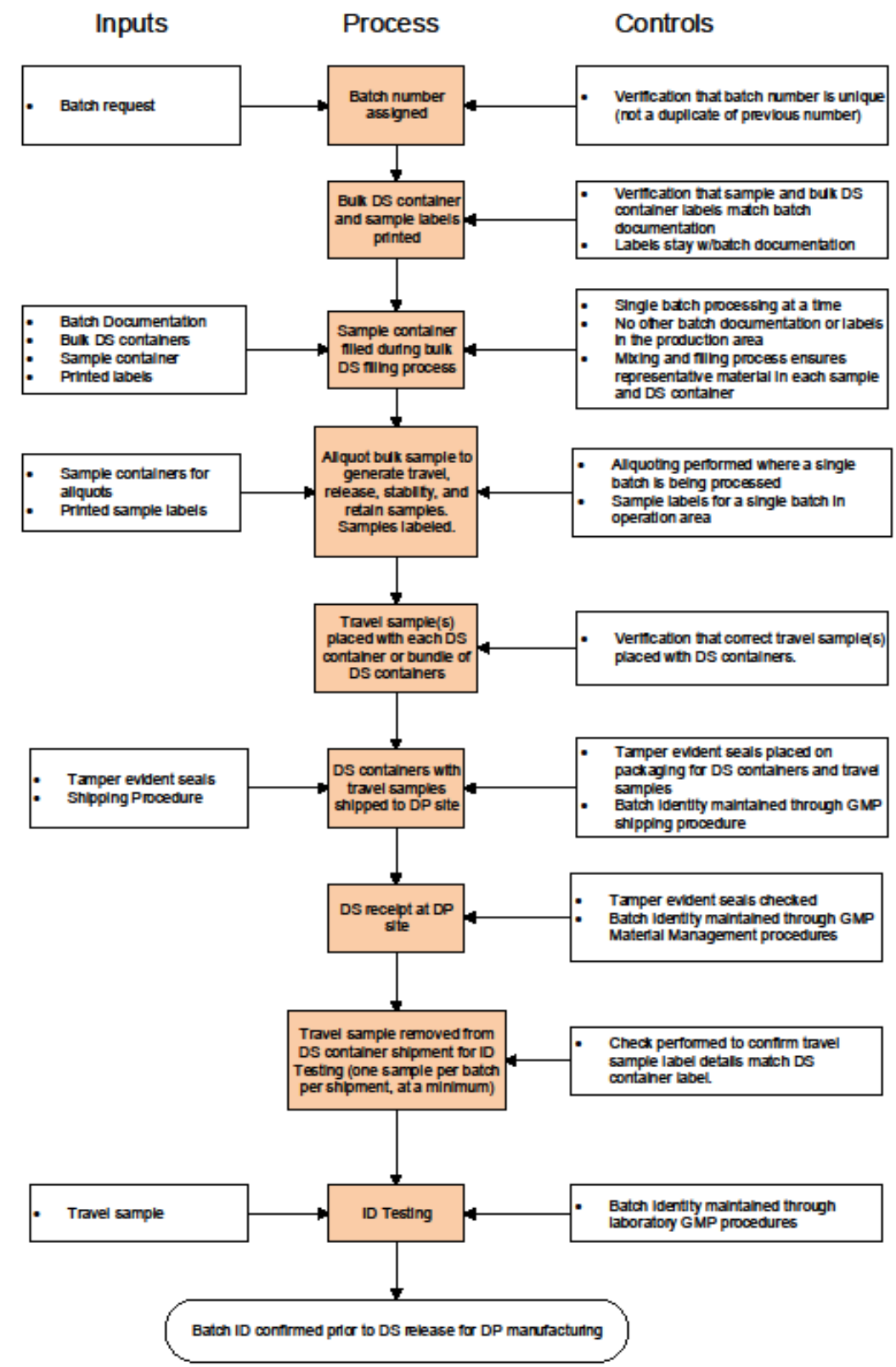

Figure 3: Example of a process flow ensuring uncompromised identity of the DS bulk containers

8. Conclusions

EBE recommends to (continue to) use a scientifically sound, controlled, risk-based approach for ID verification, without mandating 100% container-wise sampling and testing of thawed BDS upon receipt by DP manufacturing site. Alternative procedures such as travel samples taken at the BDS manufacturing site and shipped together (inseparably) with the BDS should be acceptable to local inspectors, if the company can provide appropriate measures and quality systems (i.e. thorough FMEA / risk assessment of the defined process, considering the cross-contamination risk based on the procedures applied at BDS manufacturing site, mitigation by the audit program and by appropriate documentation like photos taken or labels printed etc.). This is in line with the philosophy of ICH Q9-12, which also present risk-based approaches.

9. References

- Annex 8 to EU GMP Guide, Sampling of Starting and Packaging Materials
- CFR 21, §211.84 Testing and approval or rejection of components, drug product containers, and closures
- Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Control of Components and Drug Product Containers and Closures
- EBE concept paper on "Management and Control of Raw Materials Used in the Manufacture of Biological Medicinal Products", published on 29 November 2017
- EU GMP Guide, Part II: Basic Requirements for Active Substances used as Starting Materials, 2014

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Appendix 1: Extracts of Annex 8 of EudraLex Volume 4 (EU) and of 21 CFR 211.84 and Q&A (FDA)

❖ Annex 8 of EudraLex Vol 4 GMP: SAMPLING OF STARTING AND PACKAGING MATERIALS

"Principle

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.

….

Starting materials

1. 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 labelled.*

2. This validation should take account of at least the following aspects:
   - the nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
   - the Quality Assurance system of the manufacturer of the starting material;
   - the manufacturing conditions under which the starting material is produced and controlled;
   - the nature of the starting material and the medicinal products in which it will be used.

   Under such a system, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:
   - starting materials coming from a single product manufacturer or plant;
   - starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

   It is improbable that a procedure could be satisfactorily validated for:

   - starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
   - *starting materials for use in parenteral products.*

3. The quality of a batch of starting materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample should also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

…"

❖ **CODE OF FEDERAL REGULATIONS**

CFR 21, PART 211, Subpart E—Control of Components and Drug Product Containers and Closures

§ 211.84 Testing and approval or rejection of components, drug product containers, and closures

"…

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past
quality history of the supplier, and the quantity needed for analysis and reserve where required by §211.170.

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

…."

❖ **FDA "Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Control of Components and Drug Product Containers and Closures"**
(https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124780.htm)

"… ***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 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.

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, nondestructive 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 (http://www.fda.gov/cder/dmpq/preamble.txt), 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.

...”

Appendix 2: recommendations for a change of guidance

Current Guidance Text	Guidance Reference	Proposed Change	Scientific Rationale
It is improbable that a procedure could be satisfactorily validated for: — starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited; — *starting materials for use in parenteral products.*	EudraLex Vol 4 GMP Annex 8: SAMPLING OF STARTING AND PACKAGING MATERIALS	Delete "starting materials for use in parenteral products"	Validation approaches mentioned in Annex 8 are applicable for bulk DS of a biological product. See section 7, Figures 2 and 3, as an appropriate example.
• 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).	21 CFR 211.84 with the explanatory Q&A on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Control of Components and Drug Product Containers and Closures	Travel samples that accompany BDS shipments should be acceptable for bulk DS receipt ID testing	If travel samples are representative of the batch, are controlled and shipped with the batch, they should be considered acceptable for ID testing.

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