

Guidance 080 Reduced Testing Program

For any approach, documentation of the review of data and the decision made, using Quality Risk Management principles must be prepared and approved using local or regional procedures prior to the elimination of any testing.

Special attention must be given to materials intended for use in sterile applications based on global regulatory requirements, as some countries/regions may not allow reduced testing of materials used in sterile products.

Consideration must also be given if the material is used in more than one product. In this case, the more conservative approach needs to be adopted unless the material is shown to be non-critical to the quality of all affected products.

A. Elimination of Analytical Tests Performed Only at the User Site (see Figure 1)

- (1) Determine if the test is necessary from a scientific perspective (*e.g., is the data obtained required in order to provide confidence of a satisfactory process and/or product(s).*)
 - i. If the test is scientifically necessary, continue testing.
 - ii. If the test is not needed, determine if it is required in any regulatory application.
- (2) If the test is confirmed to be a **regulatory** requirement, evaluate if the effort (resources, variation fees, etc.) required to make the regulatory change results in an overall benefit.
 - iii. If a regulatory change will provide significant benefits, initiate internal and external change control procedures to eliminate the test with supporting documentation justifying the change.
 - iv. If there is no significant benefit, continue testing.
- (3) If the test is a **non-regulatory** requirement and is considered not to be scientifically necessary, initiate change control procedures to eliminate the test, with supporting documentation justifying the change.

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- a. A minimum of 3 consecutive lots tested by user site must be used for evaluation.
 - b. If the user site results met the specifications for all lots and nothing else was observed that calls into question the reliability of the vendor's results, user site testing may be eliminated and materials received based on ID testing and vendor COA.
 - c. If there was a confirmed failure of any lot tested by user site in the past year or the prior 3 lots fully tested (whichever is the higher number of lots), then the supplier cannot be deemed reliable. Verification that appropriate corrective actions have been taken by the vendor to address the failure must be performed. Testing by user site must be continued until at least 3 consecutive lots received meet user site specifications.
 - d. No statistical comparison of user site results versus supplier results is necessary as long as the user site specification is the same as *or wider than the vendor specification*. If the user site specification is tighter or different than the vendor's specification, a statistical comparison of user site results and vendor results will be necessary.
 - e. If sufficient data has been generated regarding the material and vendor under review (as outlined above), it is not necessary to have information whether or not the vendor performs skip lot testing in order to make a decision on the supplier's reliability.
 - f. In rare instances, there may be regulatory commitments that indicate that user site will perform certain testing on incoming goods from vendors. If it is confirmed that a regulatory commitment was made:
 1. Evaluate if the effort (resources, variation fees, etc. required to make the regulatory change results in an overall benefit
 2. If the regulatory change has a significant benefit, initiate internal change control procedures to eliminate the test with supporting documentation justifying the change.
- iii. Once all requirements have been satisfied, reduce testing to COA review, ID testing and visual inspection unless additional testing is warranted for business purposes.
 - iv. One (1) lot of the material must undergo full testing annually.
 - v. For materials used for products intended for the EU market, it may be acceptable to perform ID testing from only one (1) container of each material receipt, provided that the requirements of Annex 8 are met and the assessment properly documented. As outlined in Annex 8, the

Example of Quality Risk Management Process Application

(Note that other alternative approaches are equally acceptable)

A Quality Risk Management approach is illustrated in this guidance to help evaluate the feasibility of reducing or eliminating incoming release testing of individual lots of starting materials, intermediates, APIs, excipients and packaging components. The approach identifies the different risk factors to consider when performing the evaluation and how to group potential risks into low, medium, or high categories.

For the purpose of this evaluation, three risk components, severity, probability and detection, will be examined for each material identified. From this evaluation, a list of potential materials (starting materials, intermediates, APIs, excipients and packaging components) for reduced testing will be developed. Each material will be considered a risk.

Through application of a simple tool coupled with requisite background knowledge, it is expected that this assessment will serve as a model for GMP sites to standardize the evaluation process for reduction of release testing of starting materials, intermediates, APIs, excipients and packaging components.

Organization of Information

The assessment will consider the following data with respect to a specific starting material, intermediate, API, excipient or packaging component:

- Criticality of the material to the overall performance/quality of the finished product
- Regulatory commitments/expectations
- Supply history of a vendor for a specific material
- Quality History for a specific material
- Audit history of vendor
- Process monitoring/product release strategy

Risk Question

In this case, the desire for implementation of a reduced testing schedule or reduced testing program results in the following risk questions:

- *“What are the analytical tests that can be eliminated or reduced for incoming material receipts with the least impact to product quality or regulatory compliance?”*
- *“What are the product quality and regulatory compliance risks associated with accepting incoming materials using a vendor’s CoA?”*
- *“What are the starting materials, intermediates, APIs, excipients and packaging components that can be transitioned to a reduced testing schedule with the least impact to product quality?”*

Risk Assessment Tool

Based on the data to be used for the assessment, an enhanced Risk Ranking and Filtering

Table 1. *Probability, Severity and Detection Ranking Scales*

Severity	Description	Probability	Description ¹	Detection	Description
1 (MINOR)	Unregistered Raw materials, Non-critical excipients (e.g. filler) or Tertiary packaging components	1 (PROBABLE)	≥10 consecutive lots sourced without issue and Vendor has received an Acceptable rating as a result of most recent audit. Quality Agreement in place.	1 (ALWAYS DETECTABLE)	Multiple in-process and/or finished product tests exist that would identify nonconforming material or the process equipment tolerances are such that nonconforming components would not be machinable.
2 (MAJOR)	Registered starting materials & intermediates, Major excipients (e.g. plasticizer) or Secondary packaging components	5 (OCCASIONAL)	≥3 consecutive lots sourced without issue and/or Vendor has received a Conditionally Acceptable rating as a result of most recent audit. No Quality Agreement, however, cGMP commitment document in place.	2 (SOMETIMES DETECTABLE)	In-process or finished product tests exist that would identify nonconforming material or the process equipment tolerances are such that only components diverging widely from specifications would not be machinable.
3 (SEVERE)	API and critical excipients (e.g. antimicrobial agent) or Primary packaging container and labeling/inserts	10 (FREQUENT)	Sourcing change (new vendor, facility or process) or history of periodic rejects of material based on receipt testing and/or Vendor has received an Unacceptable rating as a result of most recent audit. No Quality Agreement or cGMP commitment document in place.	3 (NOT DETECTABLE)	No in-process or finished product tests exist that would identify nonconforming material or the process equipment tolerances are not such that would prevent nonconforming components to enter the finished product stream.

¹ Represents performance history after material vendor approval process has been completed.

The tool is applied to the risks identified and a Risk Score is calculated using the values assigned for severity, probability and detection.

$$\text{Probability} \times \text{Severity} \times \text{Detection} = \text{Risk Score}$$

Risk Acceptance

After the Risk Score has been calculated for the individual potential risks it must be assessed versus an evaluation matrix to determine the acceptability of the existing risk or conversely, identify the need for reduction of the risk through implementation of controls, where possible. The evaluation matrix is to be devised based on a site's willingness to accept different levels of risk (determined prior to conducting ranking of the various risks). Examples of the risk score evaluation matrices are shown in Tables 2a and 2b. Table 2a exhibits preliminary scoring based only on the two components of risk: severity and probability. The interpretation of the risk associated with a particular material should be based on Table 2b which incorporates the scoring indicated for all three risk components: severity, probability and detection.

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This document can be applied to site-manufactured intermediates, APIs, bulk and/or finished drug products. This document does not apply to materials sourced and manufactured by other companies regardless of their approval status.

RATIONALE

Current Good Manufacturing Practices (cGMPs) require that the identity of components¹ (starting materials²) such as intermediates, active pharmaceutical ingredients (APIs), bulk and finished drug products must be verified prior to use.

21 CFR 211.84(d)(1) states that *“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.”* Per 21 CFR 211.84(b), the regulations allow representative sampling of each shipment of each lot for testing or examination.

Chapter 5, section 5.30 of the European GMPs requires the availability of *“...procedures or measures to assure the identity of each container of starting material.”*

Per Annex 8 of the EU GMPs, it is permissible to sample only a proportion of the containers *“...where a validated procedure has been established to ensure no single container of starting material has been incorrectly labeled.”* Annex 8 further stipulates that: *“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:*

¹ From 21 CFR 210.3(b)(3) as “any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.” ² From EU GMP Glossary as “any substance used in the production of a medicinal product, but excluding packaging materials.”

- *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 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.” ... ³*

Based on the FDA and EU regulation sections cited above, only one (1) container of each shipment of a component (starting material), API, bulk and finished goods lot received by a GMP site, manufactured and shipped from other sister plants/sites, will be used for identity testing (ID).