Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion
This document defines a science and risk-based approach for the evaluation and implementation of a reduced testing program for the release of starting materials, intermediates, APIs, excipients and packaging components at a GMP user site upon receipt from vendors (manufacturer/supplier). The guidance also provides an example of the application of Quality Risk Management principles in the implementation of a reduced testing program.

There is limited value in testing starting materials, intermediates, APIs, excipients and packaging components previously released from vendors or other sites whose operations are in a state of compliance with cGMPs and where the materials have reliably supported the production/supply of goods that meet the site's in-house specifications.

The chief benefits of reduction of in-house testing of starting materials, intermediates, APIs, excipients and packaging components upon receipt are reduced lead times for production and significant reduction in resource utilization (test reagents, equipment, analysts, reviewers, etc.). Therefore, each site should assess opportunities to eliminate in-house release testing of raw materials and packaging components on a case by case basis. A review of organizational directives (constraints), in regards to sourcing of materials, should be reviewed prior to initiation of any assessment.

For reducing analytical testing, there are two (2) categories for consideration:

(1) Analytical tests performed only at a user site and
(2) Duplicate analytical testing performed by both user site and the vendor.

To address these categories, the following are the recommended approaches for reduced testing of each category:

(1) Eliminate unnecessary testing at the user site
(*see section A*)
(2) Accept an approved vendor's test results in lieu of testing by the user site when both user and vendor perform testing (*see section B*)

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.

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

method (which considers detection in addition to severity and probability) is adopted to aid in determining those starting materials, intermediates, APIs, excipients and packaging components that can be transitioned to a reduced testing schedule without assumption of detrimental levels of risk (*third risk question*).

Risk Ranking and Filtering (RRF) typically focuses on two separate risk components, severity and probability, associated with each potential risk relevant to an issue. However, in this instance, the ability to detect (detection) nonconforming materials within the existing operation prior to release of the finished product (API, DP or Medical Devices) will also assessed.

Risk Assessment -*Identification, analyses, and evaluation of potential risks*
The following risk factors were identified as having an impact related to a reduction or elimination of release testing for starting materials, intermediates, APIs, excipients and packaging components:

> ***Impact on Product Quality/Performance* –** the criticality of the material to the overall quality and performance of the finished product. The failure of a material to conform to specifications could result in the finished product not achieving the desired therapeutic effect or meeting specifications throughout shelf life.
>
> ***Regulatory Compliance*** -it is suggested that the expectations for the most stringent market served be used for the assessment when multiple markets are involved, since requirements vary from one market to another. Furthermore, efforts should be made to identify any specific commitments related to release testing that may have been made to a particular regulatory agency either through correspondence or within an approved filing.
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> ***Business Risks*** – any impact to the overall business may be assessed. Decisions on reducing or elimination of release testing for incoming materials may require considerable resources to perform proper risk assessment or pose business risks, e.g. product rejection or missed production schedule due to investigations or failures obtained during finished goods testing when a required test was not performed, etc.
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> The stated risk factors related to a change in the release testing of starting materials, intermediates, APIs, excipients and packaging components must be considered during the risk assessment. As identified previously each potential risk (i.e. material) has an associated severity, probability and detection. Table 1 below represents the suggested scale (differentiations) for each of the three risk components to be used in the assessment to answer the third risk question:
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> - "*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?*"
>
> To address the remaining risk questions, a variation to the descriptions of the suggested scale can be made.
> In this scenario, it is assumed that the acceptance of goods based on vendor COA is an accepted practice. As a result regulatory and business risks will not be evaluated. The

For this example, an acceptance threshold value of 30 was selected. This means that any material evaluated that receives a score greater than 30 represents a high risk to implement a reduced testing schedule based on the current conditions. This value was derived based on the willingness to accept reduced testing for API, critical excipients and primary packaging and labeling resulting in a severity value of 3. A value of 5 was deemed the minimal acceptable level of probability, meaning we would expect that a vendor would have at least a Conditionally Acceptable status and have demonstrated acceptable performance through the supply of at least three consecutive conforming lots of the material. When viewing detection it was determined that having at least one IPC or finished product test to assess the material's performance in the finished product was desired, rendering a detection value of 2. When the values for each of the three risk components were multiplied together (3 x 5 x 2 = 30), a total risk score of 30 was obtained. Additionally, any total risk scores derived using a probability value of 10 would represent an unacceptable level of risk. Vendors are given a probability score of 10 when they have been shown to be unacceptable through audit and/or supply performance or have undertaken recent change in their production process rendering past performance data meaningless.

Table 2a. ***Preliminary Risk Score Evaluation Matrix***

↑ Increasing Probability				
	10	10	20	30
	5	5	10	15
	1	1	2	3
		1	2	3
		Increasing Severity →		

Table 2b. Total Risk Score Evaluation Matrix

↑ Increasing Preliminary Risk Score (Severity x Probability)				
	30*	30	60	90
	20*	20	40	60
	15	15	30	45
	10*	10	20	30
	10	10	20	30
	5	5	10	15
	3	3	6	9
	2	2	4	6
	1	1	2	3
		1	2	3
		Decreasing Detection →		

*Derived using probability score of 10.

Interpretation:

Scores 1-30 represent acceptable risk

Scores 45 and all scores (10-90) derived using a probability value of 10 represent unacceptable risk

