Pharmaceutica
Analytica Acta

Mallu et al., Pharm Anal Acta 2014, 5:2
http://dx.doi.org/10.4172/2153-2435.1000283

Review Article Open Access

Periodic or Skip Testing in Pharmaceutical Industry: Us and Europe Perspective

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Abstract

Periodic Testing (PT) or Skip Testing (ST) is an important and widely discussed concept for the purpose of cost saving in the generic pharmaceutical industry where widespread expenditure is a necessity. As there is no particular/appropriate/apropos guideline recommending the implementation of the PT or ST concept so pharmaceutical companies implement it depends on their vendor qualification procedure and other aspects. All pharmaceutical industries have their internal Standard Operating Procedure (SOP) for the implementation of periodic or skip testing. These tests can be implemented for Active Pharmaceutical Ingredients (APIs), excipients, packing materials and in-process testing of finished products analysis. Implementation of PT or ST for API, excipient and packaging material can be approached according to SOPs which would be available for an audit by the regulatory agencies. However, the implementation of PT for in-process testing of finished product can be undertaken only after seeking concurrence from the agency either during the review of a marketing authorization application or after approval of the application. A suitable supplement or variation needs to be submitted to the agency for its review if PT is to be implemented for in-process testing. This article explains the periodic testing/skip testing approach for in-process samples, APIs, excipients and packing materials.

Keywords: Periodic testing or skip testing; SUPAC (Scale Up and Post Approval Changes); Pre-approval supplement; Variations; Filing documentation; Routine analysis

Introduction

NPharmaceutical industry and regulatory agencies have acquired significant knowledge about drug product development by utilizing scientific approaches and automation. In the past drug product quality was ensured by testing but now a new concept is being considered which believes in building quality in the product by design. The critical quality attributes for the drug product are controlled by building a control space within a design space by implementing the scientific and statistical approaches such as Quality by Design (QbD) and Process Analytical Technology (PAT). Before the implementation of PT/ST approaches for the testing of commercial products, the applicant should have sufficient data on the control strategy which has been built in the manufacturing process of the product to ensure product quality [1-3].

Periodic Testing (PT) or Skip Testing (ST)

As per WHO, "Performance of specified tests at release on pre-selected batches and/or at predetermined intervals, rather than on a batch-by-batch basis, with the understanding that those batches not being tested still meet all acceptance criteria established for that product. This presents a less than full schedule of testing should therefore be justified and presented to and approved by the regulatory authority prior to implementation".

PT or ST frequency, criteria, stage and material on which it has to be implemented are usually defined by the company's written procedure after taking in to consideration vendor qualification information and other available data. The frequency for the implementation of Periodic testing (PT) or Skip testing (ST) may be one batch per twenty batches or the first batch manufactured every year (whichever is earlier) and it may vary from one company to another. PT or ST can be implemented for the testing of Active Pharmaceutical Ingredients, Excipients Packaging material and in-process samples. PT/ST cannot be implemented for finished product testing.

Where We Can Apply

Periodic testing or skip testing should be implemented after performing sufficient risk evaluation and assessment of product quality during drug product development. It should be implemented at commercial level only after gaining sufficient confidence. Periodic or skip testing approach and stages are represented in the Figure 1.

Periodic (Pt) or Skip Testing (St) Selection Considerations

PT or ST can be selected and implemented for the testing of regular commercial batches. For selecting the periodic or skip tests, the following points should be considered,

1. Whether materials are received from the approved supplier.

2. A documented history of satisfactory results for material supplied and performance of supplier is available.

3. A documented history of satisfactory performance for the process and product is available.

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Received December 16, 2013; **Accepted** January 17, 2014; **Published** January 23, 2014

Citation: Mallu UR, Raman NVVSS, Sachin RD, Anand K (2014) Periodic or Skip Testing in Pharmaceutical Industry: Us and Europe Perspective. Pharm Anal Acta 5: 283. doi: 10.4172/2153-2435.1000283

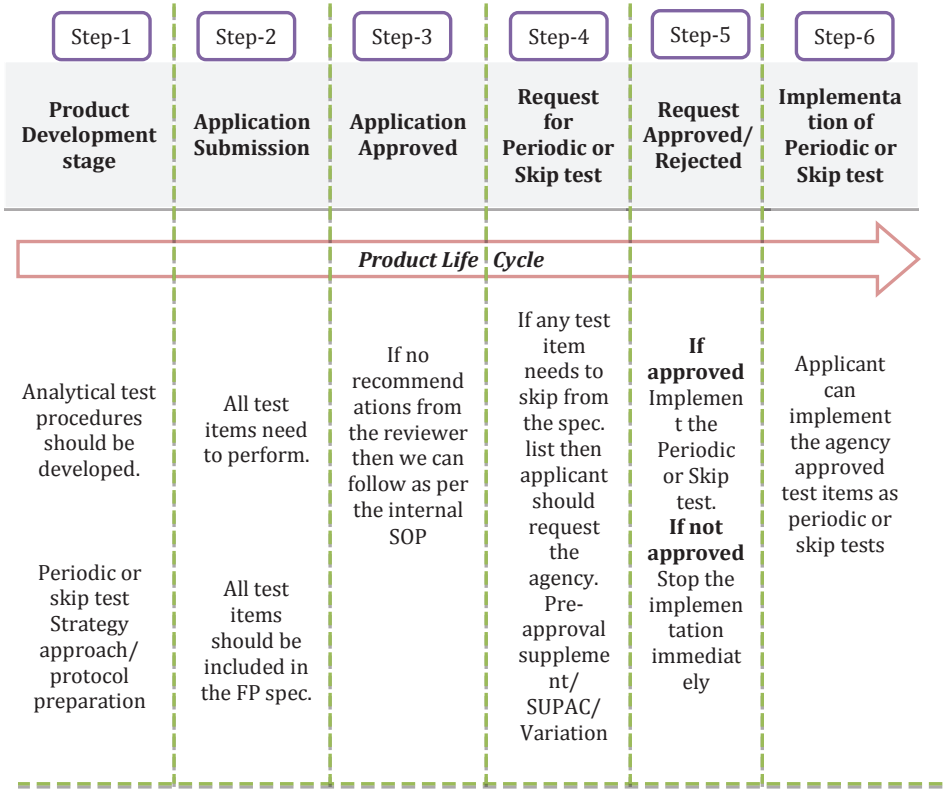

Figure 1: Periodic or Skip test life cycle.

4. Compliance with specific regulatory requirements of testing is ensured.

5. Sufficient development data for the specified tests is available.

6. Scientific justification can be provided.

7. To be implemented for tests which are not critical to assess the product quality.

8. Batch to batch retesting to be stored in the event of failure and it should be properly investigated and closed.

9. An impact assessment of the PT or ST should be undertaken.

10. Does the specification or method provide information about the purity or potency of the finished product? If not, the specification or method should be reconsidered.

11. Analytical method should predict or prevent the compliance issue.

12. What would be the regulatory impact of eliminating or reducing the test?

Risk assessment must be carried out for all suppliers of the material being assessed. Where there is more than one supplier for a particular material, then each supplier must be assessed individually. A periodic review must be conducted to ensure that the risk assessment and PT or ST schemes remain valid. Where an assessment has identified a significant risk it must be appropriately mitigated.

Implementation of the PT or ST concept for the important test

API	Description (DS), Identification (ID), Loss on Drying (LOD), water content, particle size, bulk density, assay, purity test and microbial test.
Excipients	DS, ID, particle size, bulk density, powder fineness and microbial test
Packing materials	
Al foil paper back	DS, ID*, Total grammage and width
Al foils plain	DS, ID* and width
Al foils printed	DS, ID*, width, printing matter and shade
Ampoules	DS, dimensions and weight*
Closures	Type of closure, dimensions, heat seal and pulp lines
Cold formable foil	DS, ID*, width and shade
Laminated Al foil pouch	DS, ID*, dimensions and printing
Molecular sieves	DS and adsorption capacity
Plastic containers	DS and physical parameters
Poly Bag	DS and dimensions
Purified cotton/Rayon filter	DS, ID, water content
PVC and PVDC	DS, ID, width and shade*
PVC Aclar	DS, ID*, width, total grammage
Rubber stopper	DS, dimensions and absorbance
Silica gel bag	DS and weight
Silica gel canister	DS, dimension and adsorption capacity
Vials	DS, dimensions, weight*
Carton	DS, printing matter and shade
Leaflets	DS and printing
Self-adhesive label	DS, Text and Color

*If applicable this test can be recommended
Note: Key identification test only required.

Table 1: Mandatory test items for API, excipients and packing materials.

items such as description, loss on drying, purity test and microbial testing etc. The list of recommended test items are represented in the below table for active ingredients, excipients and packing materials (Table 1).

Periodic or Skip Testing for in-Process Samples

Skip testing approach can be implemented for in-process samples of all categories of finished drug products such as tablets, capsules, semi solids and liquids. This can be implemented after review of data for 20 to 30 consecutive batches which have been manufactured without any change in process, formula, equipment or specification. PT/ST can be implemented after approval from the respective regulatory agency. After implementation of PT or ST if the process, formula, equipment etc. is changed then the skip testing procedure should be reevaluated. If any OOS/incident is encountered due to process quality and the Root Cause Analysis indicates in-process testing or a change in the process, specification or test procedures, then complete testing needs to be performed on few consecutive batches without any change. The internal quality assurance team will be responsible to perform the risk assessment (Figure 2) [4-7].

Periodic or Skip Testing for Api, Excipients and Packing Materials

Generally, after analyzing 30 to 40 batches, periodic testing or skip testing may be implemented if data is found satisfactory and without much variation. If any OOS/incident is encountered then complete testing of few consecutive batches is to be performed and the quality assurance team needs to perform the risk assessment. Different companies may follow different PT or ST procedures (Figure 3).

Regulatory Authorization

PT or ST may be implemented for APIs, excipients and packaging material after a favorable review of sufficient batch data and by preparing SOPs which would be available for an audit by the regulatory agencies. However, for implementation of PT for in-process testing of finished product concurrence from the agency during the review of an application or after approval is necessary. A suitable supplement or variation needs to be submitted to the regulatory agency for its review if PT is to be implemented for in-process testing of finished product post approval.

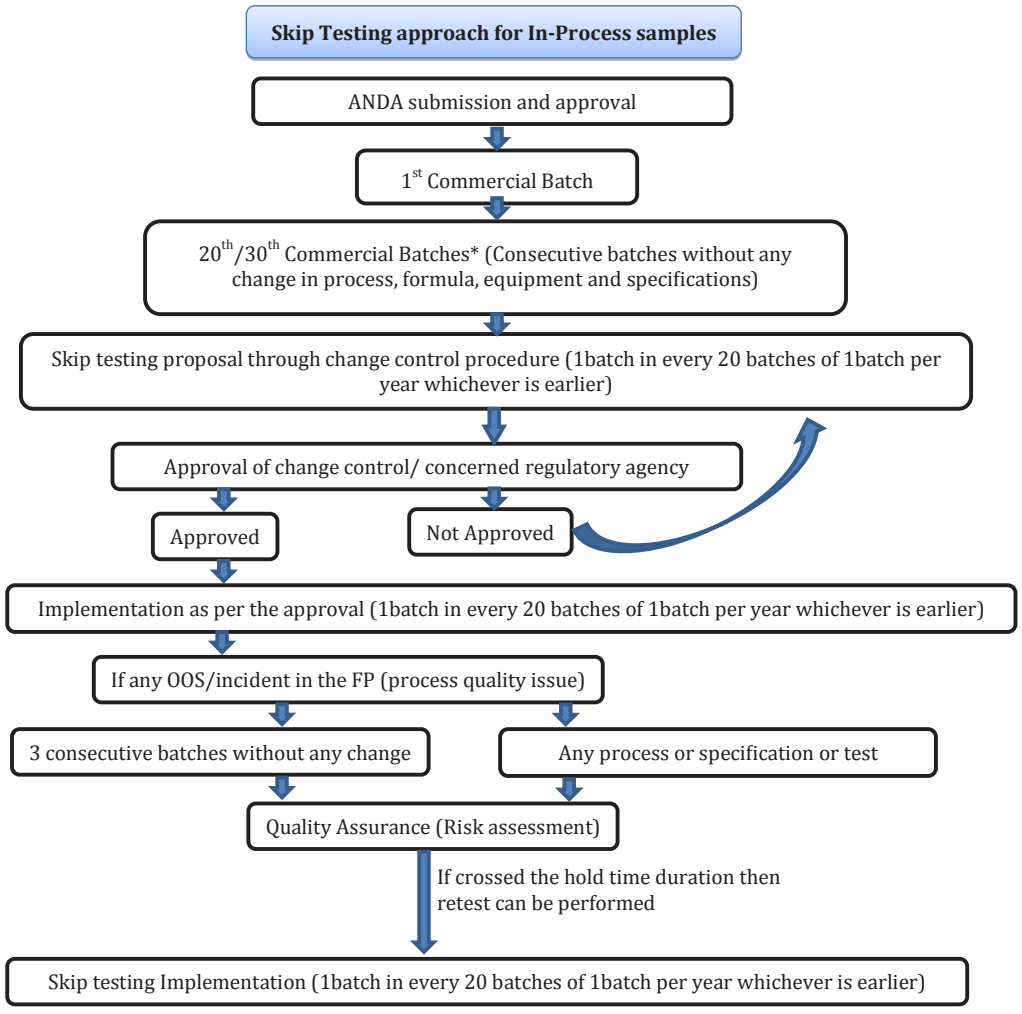

Figure 2: Periodic or Skip testing approach for In-process samples.

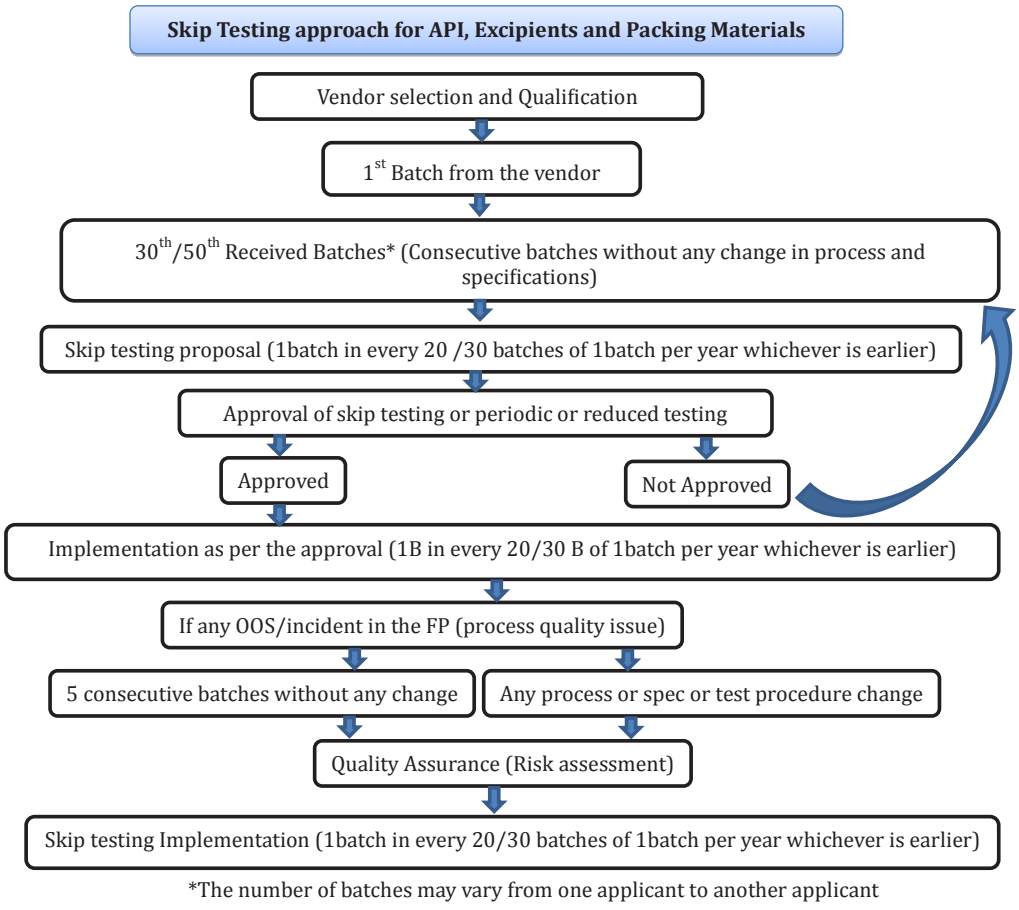

Figure 3: Periodic/Skip testing approach for API, Excipients and Packing materials.

USFDA Prospective [8]

As per the USFDA recommendations, PT or ST implementation has to be submitted as a supplement to an approved application,. Some changes may not require approval before implementation and some changes may require an approval before implementation. Figure 4 represents the PT or ST items classification as per the USFDA.

Major-Prior Approval Supplement (PAS)

PAS submission is required for implementation of PT or ST for in-process testing of the finished product. We cannot implement PT or ST for in-process testing of the drug product unless agency approves the supplement.

Moderate-Changes Being Effected 30 Days (CBE-30)

Relaxing an acceptance criterion or deleting a test for raw materials used in the manufacture of the drug substance, in-process materials prior to the final intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

CBE 30 days

The CBE (Changes being effected) 30 supplement serves as a notification to the FDA that a change will be implemented in the process, analytical techniques/technologies. The Agency has 30 days from the day of receipt to respond to the applicant. This is usually a minor change which does not impact final product quality. The FDA has 30 days to respond as to whether the changes are satisfactory. If the manufacturer does not receive any response within the 30-day period, it may be assumed that the change is acceptable.

Minor (Annual Report)

For DS/DP, the addition or revision of an alternative analytical procedure that provides the same or increased assurance of the quality being tested as the analytical procedure described in the approved product or deletion of an alternative analytical procedure.

Annual report: For the above change, applicant should provide the sufficient data in the annual report.

EU Variations (Type-IA) [9]

Implementation of PT or ST is categorized as a type-IA variation and the applicant can proceed with annual report submission. As per EMA recommendations, Type IA variations do not require approval by the authorities before their implementation by the holder. However, within 12 months from the date of implementation, the holder must submit simultaneously to all national competent authorities. It needs to be highlighted that if the variation is to be rejected by the competent

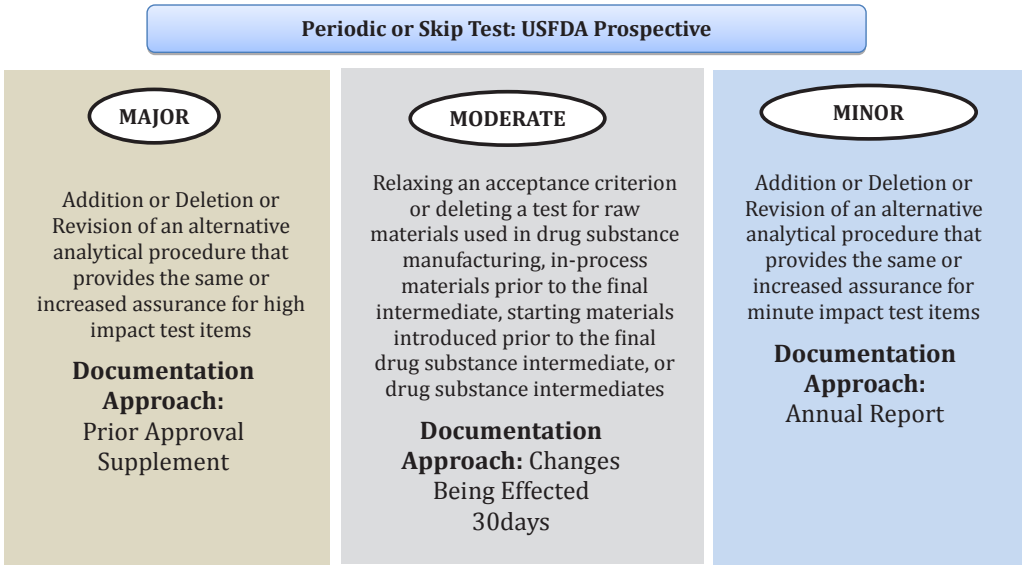

Figure 4: PT or ST classification as per USFDA.

authority then the holder would immediately stop to implement the concerned variations. Figure 4 represents the PT or ST implementation as per the EMA regulations.

The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.

The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the finished product) any critical physical characteristics (hardness or friability for uncoated tablets, dimensions…) a test that is required for the particular dosage form in accordance with the general notices of the Ph. Eur.; any request for skip testing.

Conclusion

Periodic Testing or Skip Testing can be implemented for testing of products which are intended for commercialization. Generally, the industry has to assess the possibility of acceptance of the parameters by the regulatory agency. Generally parameters are proposed for PT or ST for a minimum of 20 and 30 lots/batches of packaging material and excipient etc. If the change is accepted by the agency then the company should follow the internal SOP on PT/ST for the implementation of PT/ST. As per USFDA, these changes are addressed under PAS, CBE-30 or annual reportable category..As per EMA, these changes come under type-IA (annual reporting) variation. As per USFDA, if the change is major then the applicant should submit the prior approval supplement, if the change is moderate then the applicant should follow the CBE 30days procedure and if the change is minor then the applicant can include the change in the annual report. If the variation is accepted then PT/ST may be implemented. But if the variation is rejected by the agency then the sponsor should immediately stop the implementation.

References

1. EMEA_ICH topic Q6A specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.
2. ICH q6a Guideline Specifications: Test procedures and Acceptance criteria for New Drug Substances and New Drug Products. Comments for its application.
3. The Complete Stability Testing for a Successful Application Based on a (Strategies, Requirements, Basic Principles Performance, Documents) 2. Basic principles of stability testing.
4. Joint position paper from excipient manufacturers, drug product manufacturers and USP on pharmaceutical excipient testing and control strategies; Based on a PQRI survey and workshop.
5. Specifications and Control Tests on the Finished Product.
6. Lyon RC, Taylor JS, Porter DA, Prasanna HR, Hussain AS (2006) Stability Profiles of Drug Products Extended beyond labeled Expiration Dates. J Pharm Sci 95: 1549-1560.
7. USFDA Guidelines (2004) Changes to an Approved NDA or ANDA; Specifications-Use of Enforcement Discretion for Compendial Changes.
8. IRISH Medicines Board (2009) Quality Assessment and GMP Similarities and Differences, EMEA.
9. EDQM: Topic 7_Certificate of Pharmaceutical Substances.

Citation: Mallu UR, Raman NVVSS, Sachin RD, Anand K (2014) Periodic or Skip Testing in Pharmaceutical Industry: Us and Europe Perspective. Pharm Anal Acta 5: 283. doi: 10.4172/2153-2435.1000283