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A Review on Alternate Vendor Development

Pavani Duggi and V. Shanmugam
Department of Pharmaceutics, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupathi - 517503, India.

ABSTRACT
Vendor Development is an important strategy followed by Pharmaceutical industries in order to meet the continuous demand of materials for production of dosage forms. AVD is very important in pharmaceutical industry because of the changes occurred in the manufacturing of pharmaceutical product. The Scale Up and Post Approval Change Guidance (SUPAC) and the Changes to an Approved NDA or ANDA offer a significant amount of information. Similarly, for global changes various guidance provides requirements for various types of changes.

Keywords: AVD, Development, Vendor.

INTRODUCTION

Alternate Vendor Development (AVD)

Alternate Vendor Development is an important strategy followed by Pharmaceutical industries in order to meet the continuous demand of materials for production of dosage forms. AVD is very important in pharmaceutical industry because of the changes occurred in the manufacturing of pharmaceutical products. Changes can be major, moderate or minor[3].

A **major change** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product, such changes include reformulation, new test methods, new or relaxed specifications, packaging changes to a less protective package, new packages, new strengths outside of the approved range, new API synthesis, critical excipient changes, etc.

A **moderate change** is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product, changes in this category include a manufacturing site change to a new location, which uses the same procedures and equivalent equipment, more significant changes to raw material composition, testing site change etc.

A **minor change** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product, such changes include change in manufacturing location within the same facility, scale-up of batch size using equipment of the same operational principle, secondary packaging site changes, simple process changes, small changes in excipient composition, deletion of colorant or flavour etc.

The Scale Up and Post Approval Change Guidance (SUPAC) and the Changes to an Approved NDA or ANDA offer a significant amount of information. Similarly, for global changes various guidance available provides requirements for various types of changes. Type I (minor) and type II (major) variations guidance provide the requirements for the product changes in Europe. Similar guidance is provided by the Who using equivalent definitions for minor and major changes.

Reasons for the AVD[1, 2]

- ✓ To break the monopoly of the existing product.
- ✓ To reduce the cost of the product.

***Corrosponding author**

Pavani Duggi
Email id: pavanigeetha2@gmail.com

- ✓ To improve the Quality of the product
- ✓ To reach the continuous market demand of the product.
- ✓ To maintain the supply of the product for consumer in time.

A) Site changes

Site changes consist of changes in location of the site of manufacture, packaging operations, *labelling operations* and/or analytical *testing sites*. They do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. A typical site change includes a move to a different manufacturing site that involves other changes (e.g., process, equipment) and hence it should be evaluated as a multiple related change.

B) Process Changes

Manufacturing changes may involve the manufacturing process itself (critical manufacturing variable). For modified release solid oral dosage forms, consideration should be given as to whether or not the change in manufacturing process is critical to drug release (critical processing variable).

C) Equipment Changes

Manufacturing changes also involve the equipment used in the manufacturing process (critical manufacturing variable). For a change in manufacturing equipment that is not identical in every respect to the original manufacturing

D) Scale Changes

Changes in batch size beyond a factor of ten times the size of the pilot/bio-batch, where the equipment used to produce the test batch is of the same design and operating principles where the batch is manufactured in full compliance with cGMPs, Change in batch size, up to and including a factor of 10 times the size of the pilot/bio-batch, where the equipment used to produce the test batch is of the same design and operating principles. The batch is manufactured in full compliance with CGMP's Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by no more than 50% beyond the validated limits.

FORMULATION CHANGES

A) Product Reformulation

Reformulation of the drug product could lead to changes in the product stability. For example, the current formulation may contain an ingredient (inactive or another active) which is reacting with the API or causing the API to form a degradation product which increases over time. Therefore, a new formulation (with different excipients) is developed. An acceptable reformulation should have an improved degradation profile versus the original formulation. Changes in the qualitative or quantitative formulation, including inactive ingredients are considered as major changes and should be evaluated. A similar approach would likely be taken for a change in the critical excipient (rate-controlling) of an extended release or transdermal dosage form. In this case the potential event triggering the re-formulation may be a decrease in dissolution results on stability as the formulation ages causing out-of-specification (OOS) results and/or a shortening of the expiration date. Thus the successful re-formulation may yield several benefits from a compliance perspective as well as a supply standpoint, such as improved dissolution performance on stability, an extension of the expiration date, and a decrease in rejected batches at release, since the internal requirements for dissolution may be relaxed. The available guidance provides the information on excipient changes within certain ranges and also describes requirements for critical and non critical excipients.

B) Changes in Non-Critical / Non- Release Controlling Excipient

Major Changes

- ✓ Addition or deletion of excipient(s)
- ✓ Changes in the excipient(s), expressed as percentage (w/w) of total excipient(s) in the formulation, greater than 10% w/w of total excipient content in the solid oral dosage form.

Moderate Changes

- ✓ Change in the technical grade and/ or specifications of an excipient (non release controlling excipient).
- ✓ Changes in excipients expressed as percent (w/w) of total formulation, greater than those listed for a Minor change but less than or equal to the following percent ranges

Minor Changes

- ✓ Deletion or partial deletion of an ingredient intended to affect the color or flavour of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
- ✓ Changes in excipients (non-release controlling excipient in case of Modified Release dosage form), expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges in Table no.2.

C) Changes in Critical Excipient / Release Controlling Excipient

Major Changes

- ✓ Addition or deletion of release controlling excipient(s) (e.g., release controlling polymer/plasticizer).

Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed for a Moderate change (i.e., greater than 10% w/w of total release controlling excipient content in the modified release solid oral dosage form).

Moderate Changes

- ✓ Change in the technical grade and/or specifications of the release controlling excipient(s).

- ✓ Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, less than or equal to 10% w/w of total release controlling excipient content in the modified release solid oral dosage form.

Minor Changes

- ✓ Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation less than or equal to 5% w/w of total release controlling excipient content in the modified release solid oral dosage form.

PACKAGING CHANGES

The potential for adverse effect on the product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system and likelihood of interaction between the packaging component and the dosage form, changes to the primary packaging component (product contact materials) have the potential to affect the product stability. Changes to secondary packaging such as cartons or a change in the packaging site do not directly impact product stability. However, deletion of a secondary packaging component that provides additional protection (e.g. light, moisture, or oxygen) may affect the product stability.

Major Changes

For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments, dosage forms, a change to or in Polymeric materials (e.g., plastic, rubber) of primary packaging components or in permeable or semi-permeable container closure systems a change to an ink or an adhesive used on the permeable or semipermeable packaging component.

- ✓ A change in the primary packaging components for any product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered dose inhaler).
- ✓ For sterile products, any other change that may affect product sterility, such as:
- ✓ A change from a glass ampoule to a glass vial with an elastomeric closure
- ✓ Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels)
- ✓ Change in the size or shape of a container for a sterile drug product
- ✓ Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases)

Moderate Changes

- ✓ A change in or addition or deletion of a desiccant
- ✓ A change in the size or shape of a container for a non-sterile drug product, except for solid dosage forms

Minor Changes

- ✓ A change in the size or shape of a container containing the same number of dose units, for a non-sterile solid dosage form
- ✓ changes in packaging materials used to control odour (e.g.,charcoal packets), a change in or addition of a seal (e.g., heat induction seal), a change in an antioxidant, colorant or stabilizer for production of the container or closure etc
- ✓ Similarly for liquid and semisolid dosage forms: adding or changing a child-resistant closure, changing from a plastic to metal screw cap or vice versa, a change in or addition of a cap liner or seal etc

Table.1 Excipient and its Percentage

S. No	Excipient	Percent excipient (w/w) out of total dosage form weight
1	**Filler**	±10
2	**Disintegrant** Starch Other	 ±6 ±2
3	**Binder**	±1
4	**Lubricant** Ca or Mg stearate Other	 ±0.5 ±2
5	**Glidant** Talc Other	 ±2 ±0.2
6	**Film Coat**	±2

Table.2 Excipient and its Percentage

S. No	Excipient	Percent excipient (w/w) out of total dosage form weight
1	**Filler**	±5
2	**Disintegrant** Starch Other	 ±3 ±1
3	**Binder**	±0.5
4	**Lubricant** Ca or Mg stearate Other	 ±0.25 ±1
5	**Glidant** Talc Other	 ±1 ±0.1
6	**Film Coat**	±1

CHANGES TO ACTIVE PHARMACEUTICAL INGREDIENT (API)

Selection of API phase is one of the important decisions in the formulation development process. Subsequent to phase selection, the focus shifts to the API properties i.e., characterization of the chemical and physical properties of the drug substance. Chemical properties especially the identification of impurities is very important. In addition, the physical properties such as solubility, polymorphism, hygroscopicity, particle size, density, etc. must be addressed. In the recent years, there has been a steady increase in the number of low solubility compounds in drug development. It is estimated that up to 90% of new chemical entities would be categorized as BCS class II or IV compounds. However, with the increase in the number of compounds in development and the shortened timelines for formulation development, focus now mainly sifted to development of better formulations with the existing drug substances.

Major Changes

- ✓ Transfer of manufacturing of an aseptically processed sterile drug substance to a newly constructed or refurbished aseptic processing facility or area or an existing aseptic processing facility that does not manufacture similar products.
- ✓ Addition, deletion or substitution of sterilization steps etc
- ✓ Filtration to centrifugation, or vice versa change in the route of synthesis Any process change made after the final intermediate processing step
- ✓ Changes in the synthesis or manufacture if the drug substance that may affect its impurity profile or the physical, chemical or biological properties.

Moderate Changes

- ✓ A move to a different manufacturing site for the manufacture or processing of the final intermediate.
- ✓ In increase or decrease in production scale during finishing steps that involves new or different equipment
- ✓ Changes in the size or shape of a container for a sterile drug substance.
- ✓ An addition to a specification that provides increased assurance that the drug substance will have the characteristics of identity, strength, purity or potency that it purports to or is represented to possess.

Minor Changes

- ✓ A move to a different manufacturing site for the manufacture or processing of drug substance intermediates, other than the final intermediate.
- ✓ The addition, deletion or revision of an alternative analytical procedure that provides the same or greater level of assurance of identity, strength, purity or potency of the material being tested.

MISCELLANEOUS CHANGES

A) Specification changes

Specifications (i.e., tests, analytical procedures and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents and other components, including container and closure systems and in-process materials.

Major changes:

- ✓ Relaxing an acceptance criteria
- ✓ Deleting any part of specification
- ✓ A change in an analytical procedure used for Testing

Moderate changes

- ✓ Relaxing an in-process acceptance criterion associated with monitoring of the production environment, materials and components.

An addition to a specification that provides increased assurance that the drug product will have the characteristics of identity, strength, purity or potency that it purports to or is represented to possess; for example, adding a new test and associated analytical procedure and acceptance criterion.

Minor changes

- ✓ Any change in a specification made to comply with an official compendium.
- ✓ Tightening of acceptance criteria.

B) Labelling Changes

A drug product labelling change includes changes in the package insert, package labelling or container label.

Major changes

- ✓ Changes based on post marketing study results, including, but not limited to, labelling changes associated with new indications and usage.
- ✓ Claims of superiority to another product
- ✓ Change in the labelled storage conditions, unless exempted by regulation or guidance.

Moderate changes

- ✓ Addition of a precaution arising out of a post marketing study
- ✓ Addition of an adverse event

Minor changes

- ✓ Changes in the layout of the package or container label that is consistent with the regulations without a change in the content of the labelling.
- ✓ Labelling changes made to comply with an official compendium

CHANGE IN API SOURCE

Often changes to the API source are proposed and implemented after product approval. Equivalence of impurity profile, chemical and physical properties is shown by testing three batches according to the approved specifications and utilizing the appropriate testing (e.g., X-ray powder diffraction, solid state NMR) to establish that the polymorph and crystal habit are unchanged.

On the other hand, many changes do involve synthetic and/or process equipment changes by the approved source. Changes early in the synthesis may have less impact on the final drug substance as compared to changes later in the synthesis. A change in the synthesis after the final intermediate step is typically considered a major change.

Any change that may impact the physical properties of the API or the impurity profile needs to be evaluated from a stability perspective as well as the potential effect to the finished product. The safety of the drug may be based upon the type and level of impurities and different physical characteristics may affect dissolution or content uniformity. Consequently, changes to the manufacturing process for the drug substance may change the purity profile or physical characteristics and thus cause problems with the finished dosage form. Physical characteristics of raw materials can vary among manufacturers of drug substances and sometimes will vary from lot-to-lot from the same manufacturer. Chemical properties of the new drug substance lead to a chemical and/or physical stability decrease in the drug product, including an increase in the impurity levels. In the case of sterile drug products, increased endotoxins from the new drug substance will lead to increased endotoxins in the drug product.

Typically, a change from one drug substance source to another involves more than simply a site change. In most cases, there will be additional differences (e.g., route of synthesis, process, solvents, and equipment). Without extensive knowledge of the new and old sources (e.g., access to the drug master file), an applicant cannot adequately describe the differences between the sources or evaluate the multiple change.

Often during qualifying a new API source (new supplier), the synthesis procedure will be different from that of the approved source. This change would necessitate a complete evaluation of the API from a release and stability testing perspective.

Need for Changing API Source

- ✓ Following are some of the intentions behind changing source for any material:
- ✓ To improve the quality of the drug product.
- ✓ To get the cost effective material. This would ultimately reduce the input material cost and subsequently the finished product.
- ✓ To get the material with superior quality (applicable in case of product specific requirements).
- ✓ To find a source (vendor) having better regulatory compliance.
- ✓ To ensure timely material availability with minimum lead times.
- ✓ To break the monopoly of the existing approved source.
- ✓ To ensure material availability for production even if the existing approved supplier stops supplying.

GENERAL PROCEDURE FOR EVALUATING CHANGES[3, 6]

After the product approval, we may make changes in the drug formulation, batch size, process, equipment or manufacturing site, which affects the identity, strength, quality, purity and potency of the finished product.

Therefore, any change must be fully evaluated prior to implementation to determine its impact on the quality of the finished product.

A. Assessment of the Effects of the Change

The effects of the change must be measured or assessed since these changes may relate to affect the safety or effectiveness of the drug product. The assessment of the effects of the change on the identity, strength, quality, purity and potency of the drug product can be done by

1. Conformance to specifications

An assessment of the effects of a change should include a determination that the drug substance, in-process materials, and or drug product affected by the change conform to the approved specifications. A specification is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) to confirm the quality of drug substances, drug products.

Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the specification, will meet the listed acceptance criteria.

2. Additional testing

In addition to confirming that the material affected by the changes continues to meet its specification, It is recommended to perform additional stability profiles. The type of additional testing that should be performed would depend on the type of change, the type of drug substance and/or drug product and the effect of the change on the quality of the drug product. For an Instance: Evaluation of the hardness or friability of a tablet after certain changes.

b. Equivalence

On testing, we should usually assess the extent to which the change has impact on the identity, strength, quality, purity, and potency of the drug product. Usually, this is accomplished by comparing test results from before and Post change material and determining if the test results are equivalent or not.

c. Adverse effect

A change within a given parameter can have varied adverse effects depending on the type of dosage form and route of administration of the product.

For example:

A change in the container-closure system of a solid oral dosage form will have less impact on the drug product than it would for a semisolid or oral liquid dosage form where the primary packaging component becomes critical for the shelf life of the finished product. A process change recommended could cause the testing, when appropriate, to assess the impact of the change. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability and/or formation of a new degradant that requires qualification or identification. Therefore we must assess the change and get appropriate information that supports the continued safety and efficacy of the drug product. A small change in the concentration ratio of an inactive ingredient may have less impact on an immediate release drug product than it would for a modified release product, where that same ingredient may adversely affect the release rate, thereby impacting bioequivalence.

CONCLUSION

Alternate vendor development is a necessary for maintaining the continuous supply of the demanded product in the market. Before making AVD we have to look the changes and the evaluation of those changes and also reasons for changes. The regulatory authorities should over look the appropriate documentation for the changes of vendor from old to new. Selecting and evaluating the right suppliers is the quintessential aspect of strategic purchasing and supply chain management that can affect manufacturing firms. The primary objectives of supplier selection and evaluation include reducing costs, attaining real-time delivery, ensuring world class quality, mitigating risks, and receiving better services.

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