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POST APPROVAL CHANGES IN GENERIC DRUG PRODUCTS AND MARKETED DRUG PRODUCTS ACCORDING TO USFDA: A REVIEW

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ABSTRACT

The post approval changes are the changes made to generic and marketed drug products that have received an approval and to provide the data to support a change which would be considered suitable and sufficient to allow a determination of the impact of the change on the quality of the approved products as it relates to safety, efficacy and effective use of the products. After the approval of NDA or ANDA, the applicant may make post approval changes, provided the changes are reported to the FDA under the appropriate categories. Section 506 A of the Federal Food, Drugs and Cosmetics act and 21 CFR 314.70 provide for three reporting categories of the post approval changes namely: major change, moderate change and minor change. There are many reasons for making changes to pharmaceutical products after the original regulatory approval is obtained. Company change control procedures should detail how changes are evaluated and implemented as well as how the change impacts stability and what data will be needed to support the change. The regulatory group will determine the strategy for submission based on a review of the technical assessment of the change and the appropriate regulatory guidance.

KEYWORDS: NDA, ANDA, Post Approval Changes, Regulatory Approval, Generic Drugs, Marketed Drugs.

1. INTRODUCTION[1-5]

Definition for post approval activities: Post-approval activities are equally important throughout the lifecycle of a product. After got the approval of Abbreviated New Drug Application (ANDA) a product need to go through processes like submission of Final content of labeling, Electronic Drug Registration and Listing, Pharmacovigilance activities like ADER, FAR, PAS for any changes in the approved drug product for undisturbed and smooth commercial distribution of product.FDA have it own guidance and CFR for all these activities. Post-approval requirements for marketing applications, and requirements for the production of commercial products, are similar for products approved under either a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA).

Post approval changes: The changes which are reported after the approval of the drug product by the NDA or ANDA are known to be post approval changes. Hence FDA guidelines have proposed under Section 506A of the Act and § 314.70 provide for four reporting categories of post approval changes they are as followed.

A. Major Change

B. Moderate Change- It is categorized into 2 types

- The change requiring the submission of Supplement- Changes Being Effected in 30 Days
- The change requiring the submission of Supplement- Changes Being Effected

C. Minor Change

Major Change

a. 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 efficacy of the drug product.

b. A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called and should be clearly labeled as Prior approval supplement.

c. An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons like drug shortage or in case if there is a delay would impose an extraordinary hardship on the applicant.

Moderate Change

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.

The moderate change is categorized into 2 types based on the type of supplement being filed.

a. Supplement-Changes being affected in 30Days (CBE- 30supplement): A CBE-30 supplement involves certain moderate changes that require the submission of the supplement to FDA at least 30 days before the distribution of the drug product made using the change.

b. Supplement- Changes Being Effected (CBE-0 supplement): A CBE-0 supplement involves certain moderate changes that allow distribution to occur as soon as FDA receives the supplement.

Minor Change

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 efficacy of the drug product. The applicant must describe minor changes in its next Annual Report.

Upon regulatory approval of a new drug product, an applicant may propose post approval changes to the product for various reasons, such as continuous improvement, compliance with compendial standards, and new suppliers or manufacturers for different components of the drug product. To do so, an applicant must notify FDA about each post approval change via supplement or annual report, and also assess its effects before distributing a drug product made with such a change. The majority of the post-approval changes received by FDA is chemistry, manufacturing, and control (CMC) changes that may affect the following aspects of drug substances and/or drug products: components and composition, manufacturing sites, manufacturing process, specifications, container closure system, labeling, and multiple related changes. An applicant needs to submit a post approval change request in the form of a supplemental (abbreviated) new drug application (sNDA/sANDA, or supplement), or needs to describe the changes in an annual report. These post-approval CMC changes may directly or indirectly affect the drug product quality and safety, and thus need to be evaluated by FDA using a risk- and science-based approach.

In our earlier blog on US Food and Drug Administration's (FDA) current thinking on post-approval changes, we discussed, what application types do the FDA's industry guidance on post-approval changes to drug substances applies to and what types of changes does it emphasize. As there are multiple changes discussed in the guidance, decoding each type of change, studying the possible effects and keeping the agency informed about them is crucial to maintain continued marketability of the drug product. Elaborating on the changes, the guidance further explains what exactly each type of change entails. To give you a detailed account of each change, here we discuss them in detail as opined by the FDA.

Change is defined as "A change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labeling and product information". Changes to approved products should be evaluated to assess their impact on product quality, safety and efficacy/effectiveness. These changes should be documented properly. Depending on the degree of impact, some changes may simply need the company to document the change being evaluated. Different mechanisms exist in different jurisdictions for reporting these changes and these can vary from an annual report to an amendment/variation application to a new license application. Manufacturers should consult the guidance documents specific to the jurisdiction in order to follow the proper compliance procedures.

Based on the potential risk to product identity, strength, quality, purity or potency, postapproval CMC changes can be divided into four reporting categories.

- Prior Approval Supplement (PAS)—to report major changes that have substantial potential to adversely affect the drug product. Major changes need regulatory approval prior to distributing the drug product made using the proposed changes.
- Supplement Changes Being Effected in 30 Days (CBE 30)—to report moderate changes that have moderate potential to adversely affect the drug product at least 30 days prior to distributing the drug product made using the proposed changes. If FDA informs the applicant about missing information within 30 days of receiving a CBE 30, product distribution must be delayed until the CBE 30 is satisfactorily amended.
- Supplement-Changes Being Effected (CBE 0)—to report certain moderate changes for which product distribution can occur when FDA receives the supplement. If found not approvable upon regulatory review, FDA may order the applicant to cease the distribution of the drug product made using the proposed changes.

- Annual Report—to report minor changes that have minimal potential to adversely affect the drug product. An applicant must describe minor changes in its next annual report.

Sufficient supporting information needs to be submitted to FDA to justify the proposed changes. Different review timelines and strategies are used for different reporting categories.

The various post approval changes are observed in.

- Components and composition
- Manufacturing sites
- Manufacturing process
- Specifications
- Container closure system
- Labelling
- Miscellaneous changes and
- Multiple related changes

2. POST APPROVAL CHANGE MANAGEMENT[6-10]

A post-approval change management describes specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified. Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the Marketing Authorization Holder will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality.

In US, EU, Saudi Arabia, Singapore and India Post approval changes are designated as:

US: Scale Up and Post Approval Changes

EU: Variations

Saudi Arabia: Variations

Singapore: Variations

India: Post Approval Changes

Grading the Changes

According to the area of consideration (e.g. approval conformity or validation status), it may be necessary to use different change procedures as a base. This is the way many companies deal with changes to printed packaging material (information for use, folding cartons, and labels) in accordance with a special change control procedure, because these changes occur

relatively frequently in practice and the process sequences can be standardized easily. In these cases, the sequences and the criteria used are not independent, but are carefully matched to suit and coordinate with each other.

Table 1: Grading the Change.

	Changes requiring control		**Not Requiring Control**
	Major Changes	**Minor Change**	
Significance of change	Influences product quality or process reliability	Influences a unit requiring control	No relevance to GMP or authorization
Possible measures (selection)	Official license New approval Revalidation	Amendment Review Documentation	No relevance to GMP or authorization
Examples	Change of manufacturer: other synthesis route of a starting material (other impurities) Removal of processes to another site Change in the product composition Change to the process parameters	Replacement of apparatus part of the same design Change of cleansing agent for floors Change of laundry for work clothing (nonsterile or antibiotics area) Introduction of co-sales right	Change to working times Renovations in administration area Installation of air conditioner in staff room Introduction of electronically readable plant ID cards

(1) Components and composition

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes requiring a prior approval supplement, unless exempted by regulation or guidance.

The deletion or reduction of an ingredient intended to affect only the color of the drug product may be reported in an annual report.

Manufacturing sites

Example under reporting category of major change (Prior approval supplement)

A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.

Example under reporting category of moderate change (supplement changes being effected in 30days)

A move to a different manufacturing site for the primary packaging of

(1) Any drug product that is not otherwise listed as a major change and

(2) modified-release solid oral dosage form drug products.

Example under reporting category of moderate change (supplement changes being effected)

Move to a different manufacturing site for the manufacture or processing of the final intermediate.

Example under reporting category Minor Changes (Annual Report)

A move to a different manufacturing site for secondary packaging.

(3) Manufacturing process

Example under reporting category of major change (Prior approval supplement)

Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.

Example under reporting category of moderate change (supplement changes being effected in 30days)

For the drug substance, redefinition of an intermediate, excluding the final material, as the starting material.

Example under reporting category of moderate change (supplement changes being effected)

A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.

Example under reporting category of minor Changes (Annual Report)

A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.

4) Specifications

Example under reporting category of major change (Prior approval supplement)

Establishing a new regulatory analytical procedure including designation of an alternative analytical procedure as a regulatory procedure.

Example under reporting category of moderate change (supplement changes being effected in 30 days)

Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

Example under reporting category of moderate change (supplement changes being effected)

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

Example under reporting category of minor Changes (Annual Report)

Tightening of acceptance criteria.

(5) Container closure system

Example under reporting category of major change (Prior approval supplement)

A change in the primary packaging components for any drug product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).

Example under reporting category of moderate change (supplement changes being effected in 30days)

Changes in the size or shape of a container for a sterile drug substance.

Example under reporting category of moderate change (supplement changes being effected)

A change in or addition or deletion of a desiccant.

Example under reporting category of minor Changes (Annual Report)

A change in the size and/or shape of a container for a non sterile solid dosage form.

(6) Labeling

Example under reporting category of major change (Prior approval supplement)-

Changes based on post-marketing study results, including, but not limited to, labeling changes associated with new indications and usage.

Example under reporting category of moderate change (supplement changes being effected)

Addition of an adverse event due to information reported to the applicant or Agency.

Example under reporting category of minor Changes (Annual Report)

Labeling changes made to comply with an official compendium.

7) Miscellaneous changes

Example under reporting category of major change (Prior approval supplement)

Addition of a stability protocol or comparability protocol.

Example under reporting category of moderate change (supplement changes being effected in 30 days)

Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be submitted in a changes-being-effected-in-30-days supplement even if the extension is based on data obtained under a protocol approved in the application.

Example under reporting category of moderate change (supplement changes being effected)- No changes have been identified.

Example under reporting category of minor Changes (Annual Report)

An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application.

(8) Multiple related changes

For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the submission be in accordance with the most restrictive of the categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the submission be in accordance with the reporting category for the individual changes.

Reporting Categories

- A major change – substantial potential.
- Moderate change - moderate potential.

- Minor change – minimal 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.

3. POST APPROVAL CHANGES – US[11-16]

In US post approval changes are designated as Scale Up and Post Approval Changes(SUPAC), the changes are categorized into three level.

Level I: Major Changes

Level II: Moderate Changes

Level III: Minor Changes

Table 2: Classification of Post Approval Changes.

Type of Changes	Rules	Type of application
Major Change	21 CFR 314.70(b)	Prior Approval Supplement
Moderate Change	21 CFR 314.70(c)(5)	Changes Being effected in 30 days
	21CFR 314.70(c)(6)	Changes Being effected
Minor change	21 CFR 314.70(d)	Annual report/notification

a. 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 efficacy of the drug product.

b. A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called and should be clearly labeled as Prior approval supplement.

c. An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons like drug shortage or in case if there is a delay would impose an extraordinary hardship on the applicant.

Moderate Change

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.

The moderate change is categorized into 2 types based on the type of supplement being filed.

a. Supplement-Changes being affected in 30Days (CBE- 30supplement): A CBE-30 supplement involves certain moderate changes that require the submission of the supplement to FDA at least 30 days before the distribution of the drug product made using the change.

b. Supplement- Changes Being Effected (CBE-0 supplement): A CBE-0 supplement involves certain moderate changes that allow distribution to occur as soon as FDA receives the supplement.

Minor Change

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 efficacy of the drug product. The applicant must describe minor changes in its next Annual Report.

US: Scale Up and Post Approval Changes

The scale-up process and the changes made after approval in the composition, manufacturing process, manufacturing equipment, and change of site have become known as Scale-Up and Post approval Changes, or SUPAC. Changes are being made in the manufacturing process and chemistry of a drug product following approval and continue throughout its life. Depending upon foreseen (or unforeseen) requirements, there can be changes in the raw materials, process, equipment or manufacturing site, and batch size which ultimately affect quality attributes of a drug or finished product. Therefore, there is a need to anticipate and fully evaluate the impact of any kind of change on the quality of a drug or finished product. The intensity of the adverse effect produced by a particular change depends on the type of dosage form.

Scientific Rationale

- To expedite the processes of post approval.
- Changes of drug products.
- FDA can assure their safety and effectiveness.
- Lower the regulatory burden for industry.

PURPOSE OF GUIDANCE

This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the post approval period, to change.

1) The components or composition

2) The site of manufacture

3) The scale-up/scale-down of manufacture

4) The manufacturing (process and equipment) of an immediate release oral formulation.

The FDA has issued various guidance for SUPAC changes designated as.

A. SUPAC-IR (for immediate-release solid oral dosage forms),

B. SUPAC-MR (for modified-release solid oral dosage forms), and

C. SUPAC-SS (for non-sterile semisolid dosage forms including creams, ointments, gels, and lotions).

These guidelines provide recommendations for post approval changes in

(1) The components or composition,

(2) The site of manufacture,

(3)The scale-up of manufacture, and

(4) The manufacturing (process and equipment)

CONTAINER CLOSURE SYSTEM

Table 3: Summary Of Major, Minor And Moderate Changes.

Major changes	Moderate changes	Minor changes
For liquid and semisolid dosage forms, a change in polymeric materials (e.g., plastic, rubber) of primary packaging components.	A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a non sterile drug product in a unit-of-use container.	A change in the size and/or shape of a container for a non sterile solid dosage form.
Single unit dose container to a multiple dose container size and shape of a container.		A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams) of non sterile solid dosage form in a multiple-unit container.

Table 4: Summary of Major, Minor and Moderate Changes.

Major changes	Moderate changes	Minor changes
Changes based on post marketing study results, including, labeling changes associated with new indications and usage.	Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.	Changes in the layout of the package or container label that are consistent with FDA regulations Editorial changes, such as adding a distributor's name.

Table 5: Miscellaneous Changes.

Major changes	Minor changes	Moderate changes
Changes to an approved stability protocol. An extension of an expiration dating period based on data obtained under a new or revised stability testing protocol that has not been approved in the application. Changes to a drug product under an application that is subject to validity.	Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product	An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application

Table 6: Post approval changes in IR solid dosage forms.

Changes		Level	Dissolution requirements
Composition	Total excipients changes≤5%	Level 1	Dissolution release requirements
	Total excipients changes ≤10%	Level 2	Dissolution profile similarity in multiple media, unless active pharmaceutical BCS 1+ drug product dissolve>85% in 0.1N HCL in 15min
	Total excipients changes>10%	Level 3	In vivo bioequivalence
Site	Within same facility	Level 1	Dissolution release requirements
	Within same campus	Level 2	Dissolution release requirements
	Different campus	Level 3	Dissolution profile similarity in field medium
Batch size	Up to 10x	Level 1	Dissolution release requirements
	Beyond 10x	Level 2	Dissolution profile similarity in field medium
Equipment	Automation of transfer to alternate equipment	Level 1	Dissolution release requirements
	Different design or operating principle	Level 2	Dissolution profile similarity in field medium
Batch size	Changes within field and validated ranges	Level 1	Dissolution release requirements
	Changes within field and validated ranges	Level 2	Dissolution profile similarity in field medium
	Major changes	Level 3	In vivo bioequivalence

RESULTS

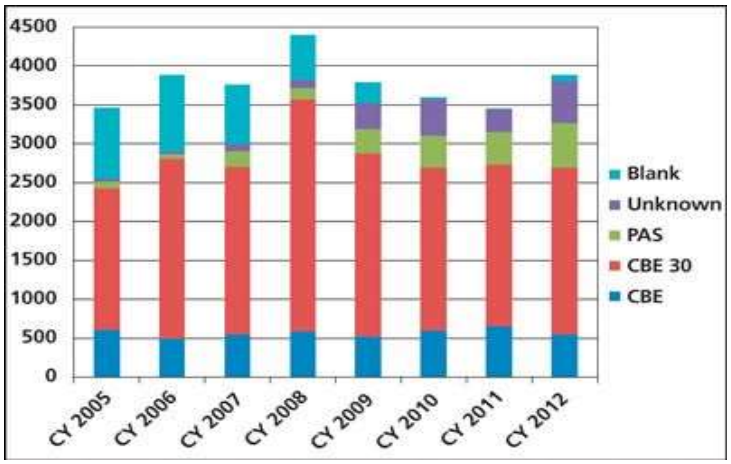

Figure 1: summary of supplements based on reporting categories from FDA(2005-2012).

Table 7: Summary of the elevation of applicant claimed moderate risk changes to high risk reporting categories upon FDA's risk assessment.

Calendar Year	CBE elevated to PAS	CBE 30 elevated to PAS
2005	25	30
2006	8	62
2007	77	279
2008	19	132
2009	3	109
2010	12	118
2011	18	134
2012	24	126

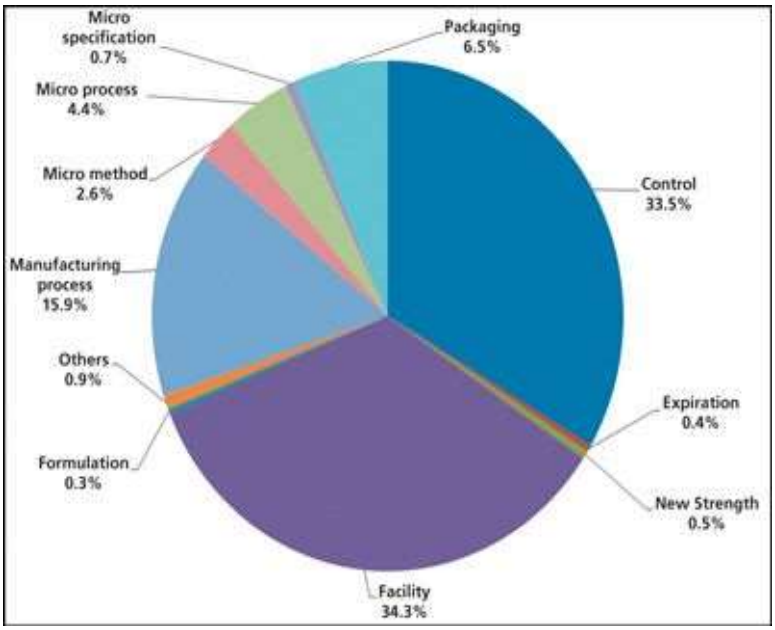

Figure 2: commonly seen CMC changes.

Table 8: Further descriptions about three main cohorts of post approval chemistry, manufacturing and controls (CMC) changes, reported to FDA in calendar year 2012.

CMC Changes	Description
Facility (34.3%)	This cohort introduces new facility(ies) to marketed generic drug products. New facilities may include testing facility, packaging site, manufacturing site for drug substance and/or drug product, and inactive ingredient source.
Control (33.5%)	This cohort introduces changes to controls of drug substance and/or drug product, such as specifications, in-process control, and stability protocol.
Manufacturing Process (15.9%)	This cohort introduces changes to manufacturing process of drug substance and/or drug product, such as scale up/down, equipment change, alternative manufacturing process, and new synthetic route for drug substance.

Table 9: PASs submitted in FY 2018 through FY 2022.

Submission Type	Performance Goal
Standard PASs or PAS Major Amendments	90% reviewed within 6 months if preapproval inspection not required
	90% reviewed within 10 months if preapproval inspection required
Priority PASs or PAS Major Amendments	90% reviewed within 4 months if preapproval inspection not required
	90% reviewed within 8 months if preapproval inspection required and applicant submits a complete and accurate Pre-Submission Facility Correspondence (PFC) no later than 60 days prior to the date of the PAS or amendment submission, which remains unchanged
	90% reviewed within 10 months if preapproval inspection is required and applicant fails to submit a complete and accurate PFC no later than 60 days prior to the date of the PAS or amendment submission, or information in a complete and accurate submitted PFC changes
Standard and Priority PAS Minor Amendments	90% reviewed within 3 months of submission date

4. CONCLUSION

Knowledge of these differences will enable the sponsor of NDA, ANDA to develop the CMC strategy to implement change successfully in US. it provides detailed analysis of the current US regulations and guidance documents for post approval change management in marketed drugs and generic drugs. It also provides information regarding the submissions to be submitted for filing a change for its approval. it also provides an analysis of the approaches described FDA draft guidance and post approval change management of CMC changes generic drug products and marketed drug products.

FDA receives more than 3500 supplements to marketed generic drugs each year. Proposed postapproval CMC changes directly impact product quality and performance, and eventually patient safety. Given the increasing importance of generic drugs in the US pharmaceutical supply chain, FDA is allocating more resources to ensure the timely evaluation of these postapproval changes. It is also applicants' responsibility to improve submission quality according to risk- and science-based principles, and to enhance lifecycle management of generic drugs using proper quality metrics (e.g., process capability). The authors believe that the findings presented here can provide valuable reference for the generic industry to submit high quality supplements, and for FDA to more efficiently manage and review them.

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