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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.

Introduction

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 to

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.

Aim and Objectives

Aim

The aim of this study explains about post approval changes of the drugs according to the USFDA.

Objectives

1. The main objective of the study is about filing the changes happened in the dosage forms after its approval and type of changes made for safety and efficacy of the drug.
2. To get the knowledge on different applications for filing the changes which are going to be approved.
3. To know the type of submissions required to file a change.
4. To get a sound knowledge on process filing post approval changes.
5. To know the submissions provided along with the changes made.
6. To know the changes made for generic and marketed drugs and its filing for the supplemental changes.

Methodology

The method begins with the scope and objective of the various dosage forms for granting the post approval changes regarding to USFDA. Accordingly, information was collected from regulatory authorities, their guidelines and expert opinion. From the entire study, results were obtained and discussion was made on the results and finally conclusion was drawn. Research methodology is a way to systematically achieve the study objectives. In this section a short explanation of following is given:

- ❖ Data collection
- ❖ Sources of data
- ❖ Literature review
- ❖ Study parameters
- ❖ Internet using the web page content

Data Collection

The study is the result of exclusive research over the topic to expedite the results. At most large amount of secondary data collection was done by means of following sources.

Sources of Data

In this comparative study mainly secondary sources of data have been referred to which include the following:

- Textbooks
- Journal articles
- Websites of different regulatory authorities and institutions
- Guideline and guidance documents issued by the regulatory agencies of countries incorporated in the study.

Literature Review

Typically covered the regulatory directives published officially by government/regulatory authorities within the on-line journals, newspaper articles, market research reports available from on-line library and other resources.

Study Parameters

The following parameters were selected for the understanding and studying the development so as to harmonize the requirements.

1. The comparison study of solid, liquid and semisolid dosage forms for granting the MA.
2. Development strategy and scaling.
3. Current regulatory and development pathway.

The methodology for this study was performed as follows:

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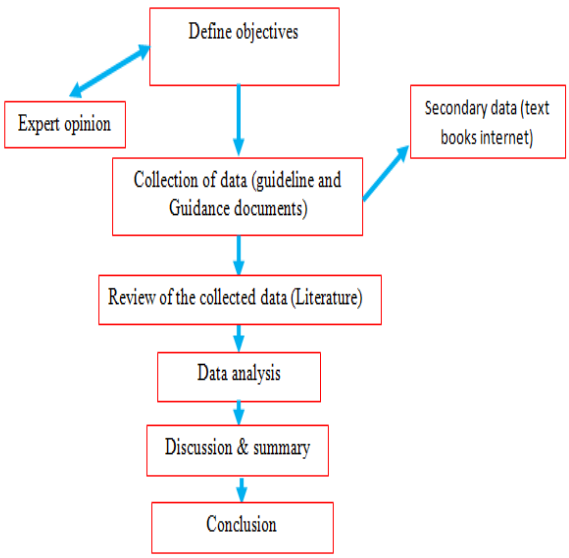


Figure 1: Schematic representation of methodological process

Type of the Study

The study was conducted with an objective carried out to establish the type of dosage form selected and the formulation proposed are satisfactory for the granting of

marketing authorization. All the required guidelines have been pooledup and translated from their local language to English.

Internet Using the Web Page Content

The literature is collected using numerous search engines such as Pharmabiz, RAPS, Science direct, IMS & BMI articles, Google scholar and many more.

Study and Discussion:

Regulatory guidelines are the backbone of the present study; the complete study is based on the guidelines and/or regulations which are published by Regulatory Agencies of each country.

Pharmaceutical Regulatory Agencies

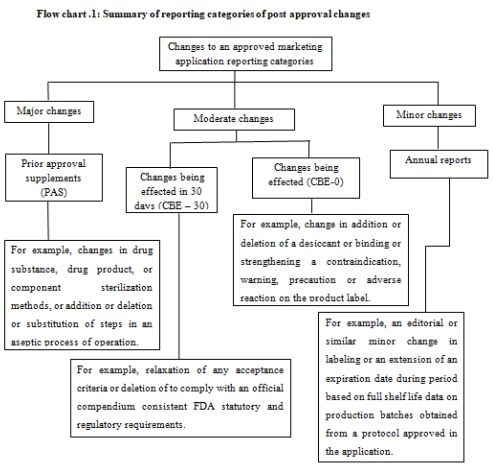
Regulatory authority and organizations are responsible in operational drug regulation essential to ensure the safety, efficacy and quality of drug products and/or substances. Regulatory bodies provide strategic and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world

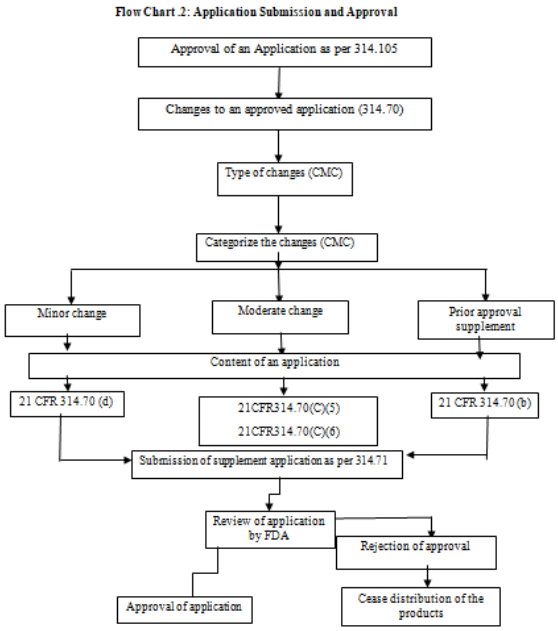
The guidance applies only to the holders of the application types listed below.

- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- New Animal Drug Application (NADA)
- Abbreviated New Animal Drug Application (ANADA)
- Drug Master File (DMF)
- Veterinary Master File (VMF)

The guidance does not apply to the holders of biologics license applications (BLAs) or master files cross-referenced in the BLAs. Also, it does not address complex active ingredient and it does not address post-approval changes to,

- Peptides, oligonucleotides and radiopharmaceuticals
- Drug substances isolated from natural sources
- Drug substances produced by procedures involving biotechnology
- Non-synthetic steps (such as fermentation) for semi-synthetic drug substances





Tab 01: SUMMARY OF CHANGES AND ITS REPORTING CATEGORIES

Change type	Conditions to be fulfilled	Supporting data	Reporting category
New equipment with different operating principles and different product contact materials	none	✓ In – process control testing info ✓ Process validation study reports ✓ One commercial batch comparison ✓ E and L information ✓ Compare/contrast operating principles	Moderate
	No impact to manufacturing process or product quality	All of the above except One commercial batch comparision E and L information	Minor

A Case Study on Post Approval Changes for A Marketed Drug Product

These drugs are also known as branded or innovator drugs invented by pharmaceutical companies to prevent them from being copied or reverse engineered by other companies.

1. **Facility Changes, Scale Changes and Equipment Changes**

Health authority. It should be noted that while making these changes, adjustments done to process parameters should only be limited to those needed to accommodate new equipment. A detailed account of facility, scale and equipment changes are as follows:

1. **Facility Changes:**

Facility changes are the changes in location of site of manufacture of intermediates and unfinished and final drug substances for both the company owned and the contract manufacturing facilities. The applicant or DMF holder is responsible for ensuring that any new facility is aligned with current good manufacturing practice (cGMP) regulations. Typical facility changes that must be reported are, but not limited to:

- Addition of a new contract manufacturing facility for an intermediate by the drug substance manufacturer or an existing contract manufacturer
- Addition or relocation of an in-house intermediate manufacturing facility to a different campus
- Transfer of new contract manufacturing facility for an intermediate by the drug substance manufacturer or an existing contract manufacturer
- The addition or relocation of an in-house intermediate manufacturing facility to a different campus
- Transfer of an additional manufacturing step to a facility already being used got the other manufacturing steps
- Change of facility for the final purification or final manipulation of the drug substance
- Addition of an alternative manufacturing facility for the drug substance

B. **Scale Changes:**

Scale changes are the changes pertaining to the batch size outside the validated scale for intermediates, and the finished/unfinished drug substance. The section is relevant to changes of scale that use equipment of the following characteristics.

- Same equipment as listed in the current master batch record (MBR)
- Equipment that differs only in capacity from the equipment listed in current MBR
- Equipment of same construction material, design and operating principle as equipment listed in the current MBR

C. **Equipment Changes:**

It is related to changes in equipment that is of a different construction material, design or operating principle than the equipment listed in current MBR. Changes in equipment at an existing manufacturing facility must be reported. In case the organization has a contract manufacturer, a quality agreement must be made between the parties to ensure that changes in equipment made at the contract manufacturer are reported to the master file holder. A change to new equipment with different construction material, design or operating principle has greatest potential to adversely affect the physical properties of the drug substance if this changed equipment is used during or after the final step or after subsequent processing procedures such as,

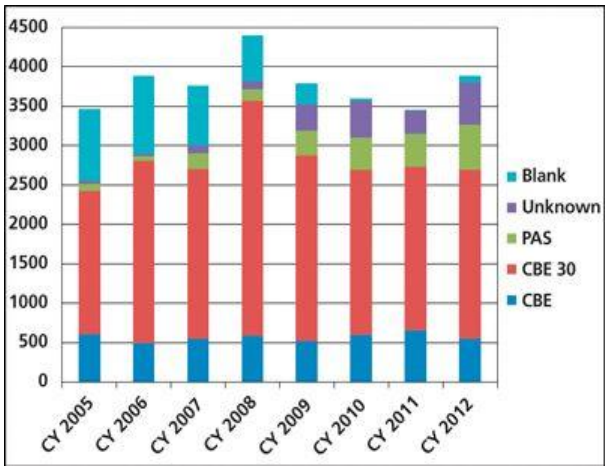
- Isolating the drug substance
- Drying the drug substance
- Reducing the particle size of the drug substance

Results

For Generic Drug Products

On average, OGD received more than 3500 supplements each year within the survey period, and the yearly number of supplements submitted to OGD stayed relatively constant. Figure 4 shows a distribution summary for these supplements based on reporting categories designated by FDA upon review. As shown, the number of CBEs and CBE 30s received per year remained similar at ~20% and ~65%, respectively. However, the number of high-risk changes (i.e., PAS) appeared to be on the rise and they currently constitute approximately 10% of all the incoming supplements.

Figure: 4: summary of supplements based on reporting categories from FDA (2005-2012)



There is a discrepancy between the numbers/percentages of supplements submitted by applicants and FDA in regard to reporting categories. This is mainly due to the difference in risk assessment for certain changes between applicants and FDA.

As a result, FDA evaluated some supplements to reflect an apparently higher risk with a given change. Reporting category elevation statistics are summarized in **Table 1**. Also, some supplements were downgraded upon review, such as CBE 30 downgraded to CBE or annual report. The proper filing category designation is crucial especially after implementing the Generic Drug User Fee Amendments of 2012 (GDUFA). As prescribed by the GDUFA legislation, a proper amount of fee (e.g., $25,760

for fiscal year 2013, and $31,930 for fiscal year 2014) needs to be paid to FDA upon submitting a PAS (major changes) , while no fee is required for submitting CBE 30, CBE, and annual reports. In addition, different review timelines are assigned to different reporting categories. In other words, proper supplement filing may significantly save resources and improve regulatory efficiency for both the applicant and FDA.

Table 2. 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

Applicants and FDA, therefore, need to conduct rigorous risk assessment for each proposed CMC change to determine and safeguard the proper filing category of a supplement, and to ensure that a supplement is processed accordingly. It should be noted that within a given supplement with multiple changes, one high-risk change automatically elevates the entire supplement into a high-risk reporting category, which is independent of the number of low-risk changes accompanying the high-risk change.

Figure 5 summarizes commonly seen CMC changes, using data from calendar year 2012 to show a typical distribution of these changes. It is noticeable that three cohorts (i.e., facility, control, and manufacturing process) constitute nearly 85% of the proposed CMC changes in calendar year 2012. Itprovides further clarifications for these cohorts. Typically, postapproval changes in these cohorts are costly for applicants and resource consuming for both applicants and FDA, and may even delay product commercialization or lead to product recalls.

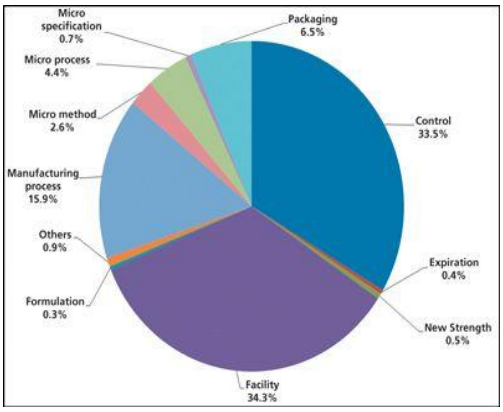


Figure 5 : commonly seen CMC changes

To better manage such a high volume of post approval CMC changes for generic drugs, FDA established a dedicated review team, the Supplement Review Team (SRT), in May 2012. The objectives of the SRT include: to increase the consistency and efficiency reviewing post approval CMC changes; to enhance the collaboration among multiple disciplines within FDA; and to improve communication between FDA and applicants to foster a risk- and science-based regulatory environment. Following a risk- and science-based approach, SRT reviews post approval changes in two steps. The first step is to conduct risk assessment of proposed CMC changes to designate an appropriate reporting category for the overall supplement; the second step is to conduct an in-depth scientific review of the supplement. As mentioned previously, the first step may result in different reporting category designations of a supplement between applicants and FDA.

Table 3: 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.

As observed above, applicants have reported more major changes (i.e., PASs) in recent years. On one hand, some major changes are being introduced to marketed generic-drug products due to various intended reasons, such as continuous improvements, adoption of new equipment and technologies, and reducing in-process control thanks to enhanced process understanding. On the other hand, some major changes are proposed due to various unintended reasons, such as out-of-specification (OOS) results, inability to scale up an approved manufacturing process, and new drug substance source due to a broken supply chain. Although applicants may not have control over some unintended situations (e.g., supply chain issues), improved process understanding and proper lifecycle management of generic drugs may reduce the number of high-risk changes. For instance, some costly CMC changes can be avoided or eliminated by better

understanding the drug product and/or manufacturing process especially in the premarket phase, and by using proper quality metrics to adequately monitor and control product manufacturing and quality in the lifecycle management.

For Marketed Drug Products

PAS to an approved ANDA should identify on the first page of the submission that it is a PAS. To facilitate processing, FDA recommends that the applicant provide the following information on the first page of the submission:

1. A statement indicating whether the PAS is for a new-strength product
2. A statement indicating whether the PAS is for a request for proprietary name review.
3. A statement indicating whether the PAS is for a Risk Evaluation and Mitigation Strategy (REMS) or a REMS modification.
4. A statement indicating whether the submission is an amendment to a PAS, and whether it is a major or minor amendment
5. A statement indicating whether the PAS contains any manufacturing or facilities changes
6. A list of the specific review disciplines to review the PAS (Chemistry, Biopharmaceutics, Labeling, DMF, Bioequivalence, Microbiology, or Clinical)
7. If expedited review is requested, the label Expedited Review Request should be placed prominently at the top of the submission. The submission should include a basis for the expedited review request.

Summary of supplements based on reporting categories from FDA (2012-2017)

FDA agreed to meet for reviewing and acting on PASs submitted in FY 2015 through FY 2017.Specifically, FDA agreed to:

- Review and act on 60% of complete PASs that do not require inspection within 6 months from the date of submission for receipts in FY 2015.
- Review and act on 60% of complete PASs that require inspection within 10 months from the date of submission for receipts in FY 2015.
- Review and act on 75% of complete PASs that do not require inspection within 6 months from the date of submission for receipts in FY 2016.
- Review and act on 75% of complete PASs that require inspection within 10 months from the date of submission for receipts in FY 2016.
- Review and act on 90% of complete PASs that do not require inspection within 6 months from the date of submission for receipts in FY 2017.

Table 4: 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 4 months if preapproval inspection not required
Priority PASs or PAS Major Amendments	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

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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No Declared

Conflict of Interest

Authors are declared that no conflict of interest.

Inform consent and Ethical Considerations

Not Applicable.

Author Contribution

All authors are contributed equally.

References

1. Evans GW, Friede AI. The Food and Drug Administration's regulation of prescription drug manufacturer speech: A first amendment analysis. Food and Drug Law Journal. 2003 Jan 1;58(3):365-437.
2. FDA C. Guidance for Industry, Changes to an Approved NDA or ANDA.
3. CMCCC C. FDA. Guidance for Industry—Changes to an Approved NDA or ANDA. Drug Information Branch, CDER, FDA (November 1999).
4. Marzo A, Porro E, Barassi A. Generic drugs: myths, facts, and limitations. Italian Journal of Medicine. 2012 Sep 1;6(3):146-52.
5. Craddock K. Improving Generic Drug Approval at the FDA. Mich. J. Envtl. & Admin. L.. 2017;7:421.
6. Karst KR. Letting the Devil Ride: Thirty Years of ANDA Suitability Petitions under the Hatch-Waxman Act. William Mitchell Law Review. 2014;40(4):3.
7. Barlas S. FDA strategies to prevent and respond to drug shortages: finding a better way to predict and prevent company closures. Pharmacy and Therapeutics. 2013 May;38(5):261.
8. Ganeshan S, Freund C. FDA Submission Requirements. InGood Clinical Practices in Pharmaceuticals (pp. 1-21). CRC Press.
9. CDER F. Guidance for Industry, PAC-ATLS: Postapproval Changes—Analytical Testing Laboratory Sites. US Department of Health and Human Services (April 1998).
10. FDA U. Guidance for Industry. Nonsterile semisolid dosage forms, scale-up and postapproval changes: chemistry, manufacturing, and controls; in vitro release testing and in vivo bioequivalence documentation. Center for Drug Evaluation and Research (CDER). 1997.
11. FDA, Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (Rockville, MD, Sep. 1997).
11. FDA, Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (Rockville, MD, Nov. 1995).