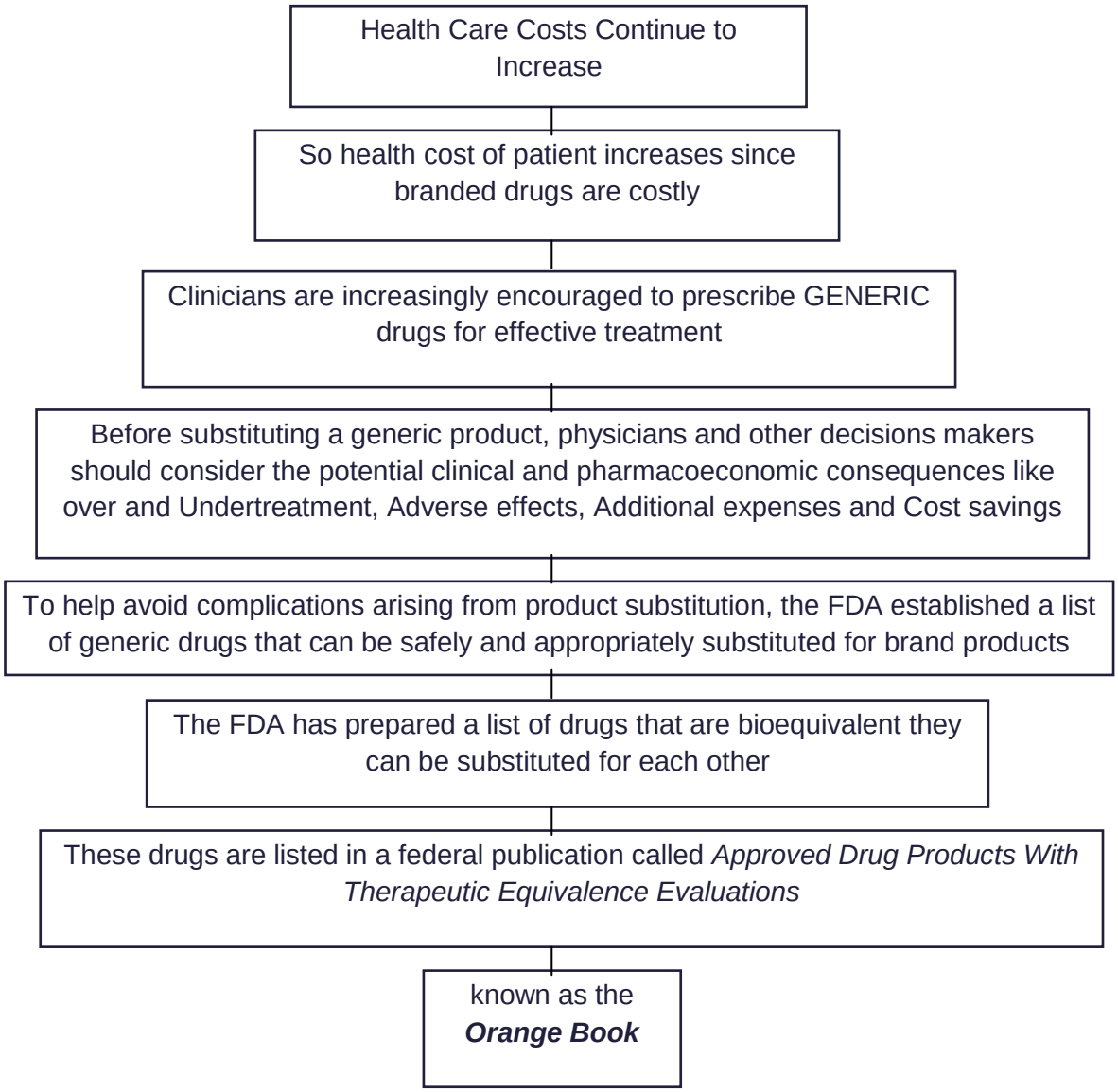
Basics in drug approval process with ref. to: Orange Book, FOI, IIG, DMF, Historical aspects with various phases of drug development and approval, CMC

TABLE OF CONTENT: -

1.NEED OF THE ORANGE BOOK



2.INTRODUCTION

A. BRIEF DEFINITION

- Orange book is a publication by the Food and Drug Administration which contains a list of approved drug products with therapeutic equivalence evaluations. It is prepared by the Orange Book Staff, Center for Drug Evaluation and Research (CDER).
- It identified drug products on the basis of ***safety and effectiveness*** by the Food and Drug Administration under the Federal Food, Drug, and Cosmetics Act.
- Drugs marketed only on the basis of safety (covered by Drug Efficacy Study Implementation i.e. DESI review e.g. Donnatal Tablets and Librax capsules) or pre-1938 drugs (e.g. Phenobarbital) are not included in this publication.

- The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons.
- The list is independent of any current regulatory action against a drug product.
- Therapeutic equivalence evaluations have also been mentioned in the list to provide public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs.

B. HISTORY

YEAR	ACTION
May 31, 1978	The Commissioner of the Food and Drug Administration sent a letter to officials of each state stating FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multi-source prescription products.
January, 1979	The list was distributed (included only currently marketed prescription drug products approved by FDA through NDAs and ANDAs under the provision of section 505 of the Act)
January 12, 1979	A complete discussion of the background and basis of FDA's therapeutic equivalence evaluation policy was published in the Federal Register (44 FR 2932)
October 31, 1980	The final rule (includes FDA's response to the public comments on the proposal) was published in the Federal Register (45 FR 72582). The list incorporated appropriate corrections and additions.

C. OBJECTIVES

1. To allow review of patterns of access and usage
2. To allow discovery of use of unusual privileges
3. To allow discovery of repeated attempts to bypass protections
4. To serve as a deterrent by its existence
5. To supply an additional form of user assurance

3.CONTENTS OF THE ORANGE BOOK

PREFACE TO THIRTIETH EDITION	
1.	**INTRODUCTION**
1.1	Content and Exclusion
1.2	Therapeutic Equivalence-Related Terms

C.	Uniform Terms
PATENT AND EXCLUSIVITY INFORMATION ADDENDUM	
A.	Patent and Exclusivity Lists
B.	Patent and Exclusivity Terms

1. INTRODUCTION

1.1 Content and exclusion

The List is composed of four parts:

- Approved prescription drug with therapeutic equivalence evaluations;
- Approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs;
- Drug products with approval under Section 505 of the Act administered by the Center for Biologics Evaluation and Research; and
- A cumulative list of approved products that have been discontinued from marketing.

The List also includes:

- Indices of prescription and OTC drug by trade or established name (if no trade name exists) and by applicant name (holder of the approved application).
- The latter list includes applicants' names as abbreviated in this publication
- An *Addendum* contains drug patent and exclusivity information for the Prescription and OTC Drug Product Lists, and for the Drug Products with Approval under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research.
- It includes only full approval products and not tentative approval products.

The List excludes:

- Prior to the 6th Edition, the publication had excluded OTC drug products with approval under Section 505 of the Act administered by the Center for Biologics Evaluation and Research.
- Distributors or re-packagers of products

1.2 Therapeutic-Equivalence Related Terms

Pharmaceutical Equivalents:

Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules).

Pharmaceutical Alternatives:

Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules).

Therapeutic Equivalents:

Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

Bioavailability:

This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

Bioequivalent Drug Products:

This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions.

1.3 Statistical criteria for Bio-equiavalence

- Under the Drug Price Competition and Patent Term Restoration Act of 1984, (Hatch-Waxman Act) manufacturers seeking approval to market a generic drug product must submit data demonstrating that the drug product is bioequivalent to the pioneer (innovator) drug product. A major premise underlying the 1984 law is that bioequivalent drug products are therapeutically equivalent, and therefore, interchangeable.

- Methods used to define bioequivalence as per 21 CFR 320.24 includes
  - Pharmacokinetic (PK) studies,
  - Pharmacodynamic (PD) studies,
  - Comparative clinical trials, and
  - In-vitro studies

- The choice of study used is based on the site of action of the drug and the ability of the study design to compare drug delivered to that site by the two products.

- The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedures

- **Two situations are tested with this statistical methodology:**

- The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable.

- The second of the two one-sided tests determines whether a brand-name product when substituted for a generic product is significantly less bioavailable.

- Based on the opinions of FDA medical experts, a difference of greater than 20% for each of the above tests was determined to be significant, and therefore, undesirable for all drug products.

- Numerically, this is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio

of the average response (AUC and Cmax) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

- For statistical reasons, all data is log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90% confidence interval for each pharmacokinetic parameter (Cmax and AUC).

- This system of assessing bioequivalence of generic products assures that these substitutable products do not deviate substantially in in-vivo performance from the reference product. The primary concern from the regulatory point of view is the protection of patient against approval of products that are not bioequivalent.

1.4 Reference Listed Drug

- A reference listed drug (21 CFR 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.
- FDA has identified in the Prescription Drug Product and OTC Drug Product Lists those reference listed drugs to which the *in vivo* bioequivalence (reference standard) and, in some instances, the *in vitro* bioequivalence of the applicant's product is compared.
- By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs.
- The reference listed drug is identified by the symbol "+" in the Prescription and Over-the-Counter (OTC) Drug Product Lists.
- The Prescription and OTC Drug Product Lists identify reference drugs for oral dosage forms, injectables, ophthalmics and topical products.

1.5 General Policies and Legal Status

- The list contains public information and advice for product selection.
- These evaluations do not constitute determinations that any product is in violation of the Act or that any product is preferable to any other.

1.6 Practitioner / User Responsibilities

- Professional care and judgement should be exercised in using the list.

- Practitioner should be aware of the multi-source and single-source drug products.

  - **Multisource Drug Product** means those pharmaceutical equivalents available from more than one manufacturer. For such products, a therapeutic equivalence (TE) code is included and, in addition, product information is highlighted in bold face and underlined.

  - **Single-Source Drug Product** is also included on the list but no therapeutic equivalence code is included with such products. If only one approved product is available for particular active ingredient, dosage form, route of administration, and strength then it is known as single-source drug product.

- Products on the List are identified by the names of the holders of approved applications (applicants) who may not necessarily be the manufacturer of the product:

- Applicants: (1) Manufacturer

(2) Contract Manufacturer
(3) Repackager/Distributor or Marketer

- Every product on the list is subject at all times to regulatory action.

1.7 Therapeutic Equivalence Evaluation Codes:

- The coding system for therapeutic equivalence evaluations is constructed users to determine quickly whether the Agency has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter).
- The two basic categories into which multisource drugs have been placed are indicated by the first letter as follows

Code 'A'

Drug product that FDA considers to be <u>therapeutically equivalent</u> to other pharmaceutically equivalent products, i.e., drug products for which:

1) There are no known or suspected bio-equivalence problems. These are designated as **AA, AN, AO, AP** or **AT**, depending on the dosage form; or

2) Actual or potential bio-equivalence problems have been resolved with adequate in-vivo and/or in-vitro evidence supporting bio-equivalence. These are designated **AB.**

Drug product designated with **code 'A'** fall under the two main policies:

1) A therapeutically equivalent rating is assigned to pharmaceutically equivalent products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated **AA**, **AN**, **AO**, **AP**, or **AT**, depending on the dosage form, as described below); or

2) For those DESI (Drug Efficacy Study Implementation) drug products and for post-1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through *in vivo* and/or *in vitro* studies the bioequivalence of the product to a selected reference product (these products are designated as **AB**).

<u>Code Index:</u>

AA: Products in conventional dosage forms not presenting bio-equivalence problems

AB, AB1, AB2, AB3: Products meeting necessary bio-equivalence requirements
(In certain instances, a number is added to end of the AB code to make a three character code, which is assigned only in situations when more than one reference listed drug of the same strength has been designated under the same heading. Two or more reference listed drugs are generally selected only when there are at-least two potential reference drug products which are not bio-equivalent to each other)

AN: Solutions and powder for aerosolization

AO: Injectable oil solutions

AP: Injectable aqueous solutions and intra-venous non-aqueous solutions

AT: Topical products

Code 'B'

Drug product that FDA at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products, i.e.

Drug products for which actual or potential bio-equivalence problems have not been resolved by adequate evidence of bio-equivalence. Often the problem is with specific dosage forms rather than with active ingredients. These are designated as **BC, BD, BE, BN, BP, BR, BS, BT, BX** or **B***

Drug product designated with **code 'B'** fall under the three main policies:

1) The drug products contain active ingredients or are manufactured in dosage forms that have been identified by the Agency as having documented bio-equivalence problems or a significant potential for such problems and for which no adequate studies demonstrating bioequivalence have been submitted to FDA; or
2) The quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or
3) The drug products are under regulatory review.

Code Index:

B*: Drug products requiring further FDA investigation and review to determine therapeutic equivalence

BC: Extended release dosage forms (capsules, injectables and tablets)

BD: Active ingredients and dosage forms with documented bio-equivalence problems.

BE: Delayed release oral dosage forms

BN: Products in aerosol-nebulizer drug delivery systems

BP: Active ingredients and dosage forms with potential bio-equivalence problems

BR: Suppositories or enemas that delivers drug for systemic absorption

BS: Products having drug standard deficiencies

BX: Drug products for which the data are in-sufficient to determine therapeutic equivalence

1.8 Description of special situations:

Certain drugs listed in the orange book present special situations that merit further discussion. Following is a description of those special situations:

Amino-acid and Protein Hydrolysate injections:

These products differ in the amount and kinds of amino-acids they contain, and therefore, are not considered pharmaceutical equivalents. For this reasons, these products are not considered therapeutically equivalent. At the same time, the Agency believes that it is appropriate to point out that where nitrogen balance is the sole therapeutic objective and individual amino acid content is not a consideration, pharmaceutical alternatives with the same total amount of nitrogen content may be considered therapeutically equivalent.

Follitropin alpha and beta:

Based on available data derived from physico-chemical tests and bio-assay, follitropin alpha and follitropin beta are indistinguishable

Gaviscon® tablets:

- Gaviscon® is an OTC product which has been marketed since September 1970. The active ingredients in this product, aluminum hydroxide and magnesium trisilicate, were reviewed by the Agency's OTC Antacid Panel and were considered to be safe and effective ingredients (Category I) by that Panel.
- However, the tablet failed to pass the antacid test which is required of all antacid products. The Agency, therefore, placed the tablet in Category III for lack of effectiveness.
- A full NDA with clinical studies was submitted by Marion Laboratories, Inc., and approved by FDA on December 9, 1983.
- Gaviscon®'s activity in treating reflux acidity is made possible by the physical-chemical properties of the inactive ingredients, sodium bicarbonate and alginic acid.
- Therefore, *all ANDAs which cite Gaviscon® tablets as the listed drug must contain the inactive ingredients sodium bicarbonate and alginic acid.*
- A full NDA will be required to support the effectiveness of the drug product if different inactive ingredients are to be substituted for sodium bicarbonate or alginic acid or if different proportions of these ingredients are to be used.

Patent certification (s) Reference listed drug based upon a suitability petition

An abbreviated new drug application that refers to a Reference Listed Drug (RLD) approved pursuant to a suitability petition must demonstrate that the proposed product is bioequivalent to the RLD, and it must include appropriate patent certification(s) and an exclusivity statement with respect to the listed drug which served as the basis for the approved suitability petition.

Waived exclusivity

- If a new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (Act) qualifies for exclusivity under sections 505(c)(3)(D) and 505(j)(5)(D), the exclusivity is listed in the Patent and Exclusivity Section of the Orange Book.
- If a drug product has received this exclusivity, the FDA will delay the approval of a 505(b)(2) application or an abbreviated new drug application (ANDA) under section 505(j) of the Act until the expiration of the exclusivity.

- If the listed drug is also protected by one or more patents, the approval date for the 505(b)(2) application or ANDA will be determined by the latest expiring patent or exclusivity listed in the Orange Book.

1.9 Therapeutic Equivalence Code Change for a Drug Entity

- The Agency will use the following procedures when, in response to a petition or on its own initiative, it is considering a change in the therapeutic equivalence code for approved multi-source drug products.
- Such changes will generally occur when the Agency becomes aware of new scientific information affecting the therapeutic equivalence of an entire category of drug products in the List (e.g., information concerning the active ingredient or the dosage form), rather than information concerning a single drug product within the category.
- These procedures will be used when a change in therapeutic equivalence code is under consideration for all drug products found in the Prescription Drug Product List under a specific drug entity and dosage form.
- The change may be from the code signifying that the drug does not present a bioequivalence problem (e.g., **AA**) to a code signifying a bioequivalence problem (e.g., **BP**), or vice versa. This procedure does not apply to a change of a particular product code (e.g., a change from **BP** to **AB** or from **AB** to **BX**).
- Before making a change in a therapeutic equivalence code for an entire category of drugs, the Agency will announce in the *Introduction* to the Cumulative Supplement that it is considering the change and will invite comment.

1.10 Change of the Therapeutic Equivalence Evaluation for a Single Product

The aforementioned procedure does not apply to a change in a single drug product code. For example, a change in a single drug product's code from **BP** to **AB** as a result of the submission of an acceptable bioequivalence study ordinarily will not be the subject of notice and comment.

Likewise, a change in a single drug product's code from **AB** to **BX** (e.g., as a result of new information raising a significant question as to bioequivalence) does not require notice and comment.

1.11 Discontinued section

Approved products are added to the Discontinued Section of the Orange Book when the applicant holder notifies the Orange Book staff of the products' not marketed status.

Products may also be added if annual reports indicate the product is no longer marketed or other Agency administrative action (e.g., Withdrawal of an Application).

1.12 Changes to the Orange Book

- Every effort is made to ensure the Annual Edition is current and accurate.
- Applicant holders are requested to inform the FDA Orange Book Staff (OBS) of any changes or corrections.
- When products are no longer marketed, OBS should be informed
- The OBS can be contacted by email at drugproducts@cder.fda.gov.
- Changes in drug product to be sent by

FAX: 301-827-7337;

MAIL: FDA/CDER Orange Book Staff
Office of Generic Drugs, HFD-610
7500 Standish Place
Rockville, MD 20855-2773

1.13 Availability of the edition:

Commencing with the 25th edition, the Annual Edition and current monthly Cumulative Supplements are available in a Portable Document Format (PDF) at the EOB home page, http://www.fda.gov/cder/ob/default.htm, by clicking on the Annual Edition.

2. HOW TO USE THE DRUG PRODUCT LISTS

2.1 Key Sections for Using the Drug Product Lists

This part of the publication contains illustrations, along with Drug Product Lists, indices, and lists of abbreviations and terms which facilitate their use

- **Illustration:** Depicts the format found in the Prescription Drug Product List
- **Drug Product Lists:** The Prescription and OTC drug product lists, arranged alphabetically by active ingredient (s), contains product identification information (active ingredients, dosage forms, routes of administration, product names, application holders, strengths) for single and multiple ingredient drug products. Also shown are the application number and drug product number.
- **Product Name Index:** This is an index of Prescription and OTC Drug Products by established or trade names. These terms are listed in Appendix A
- **Product Name Index Listed by Applicant:** This is an index of Prescription and OTC Drug Products that cross references applicants to drug products. These terms are listed in Appendix B.
- **Uniform terms:** To improve readability, uniform terms are used to designate dosage forms, routes of administration and abbreviations used to express strengths. These terms are listed in the Appendix C.

4. CUMULATIVE SUPPLEMENT

This Cumulative Supplement is one of a series of monthly updates to the Approved Drug Products with Therapeutic Equivalence Evaluations.

The Cumulative Supplement provides information on newly approved drugs and, if necessary, revised therapeutic equivalence evaluations and updated patent and exclusivity data. The Addendum contains appropriate drug patent and exclusivity information required of the Agency by the "Drug Price Competition and Patent Term Restoration Act of 1984" for the Prescription, OTC, and Drug Products with Approval under Section 505 of the Act Administered by the **Center for Biologics Evaluation and Research Lists.**

APPLICANT NAME CHANGES : It is not practical to identify in the Cumulative Supplement each and every product involved when an applicant transfers its entire line of approved drug products to another applicant, or when an applicant changes its name. Therefore, the cumulation of these transfers and name changes will be identified in this section only. Where only partial lines of approved products are transferred between applicants, each approved product involved will appear as an applicant name change entry in the Cumulative Supplement.

5. GREEN BOOK

- The Generic Animal Drug and Patent Restoration act requires that each sponsor of an approved animal drug must submit to the FDA certain information regarding patents held for the animal drug or its method of use.

- The Act requires that this information, as well as a list of all animal drug products approved for safety and effectiveness, be made available to the public.

- This list must be updated monthly under the provisions of the Act.

- The list, known as "the Green Book" was therefore first published in January 1989. Updates have been added monthly since then.

Online Green Book contains 8 Sections:

Section 1: Arrangement of sponsors by trade names, New Animal Drug Application (NADA) number
Section 2: Active Ingredients
Section 3: Patent Information
Section 4: Exclusivity periods
Section 5: Products subject to notice of hearing
Section 6: Voluntary withdrawals
Section 7: Suitability petition actions
Section 8: 2007 monthly updates

BLUE BOOK

- It was a FDA publication named "Requirements of the Laws and Regulations Enforced by the US Food and Drug Administration"
- It has been discontinued as of October 2002
- In its place there is a wealth of compliance information on the FDA website.

6. STUDY QUESTIONS

UNIVERSITY QUESTIONS:

September 2005

1) Define: Pharmaceutical Equivalents, Pharmaceutical Alternatives and Therapeutic equivalents. What are the criteria for these equivalents? (Internals July 2006)
2) What are the statistical criteria for Bio-equivalence

September 2006

1) What are Orange Book, Green Book and Blue Book? Discuss the coding system for Therapeutic Equivalence Evaluation and how it can be changed giving suitable illustration? (Internals July 2006)

OTHER QUESTIONS:

1) Write a introductory note on Orange Book?
2) How changes to the orange book can be made?
3) What do you mean by single source and multiple source products? Of these two, TE code is assigned to which category?

7. REFERENCES

- http://www.fda.gov/cder/orange/obannual.pdf
- http://www.fda.gov/cder/orange/obcs.pdf

FREEDOM OF INFORMATION (FOI)

TABLE OF CONTENT:

1. Introduction to Freedom of Information:

The 1996 amendments to the Freedom of Information Act (FOIA) mandate publicly accessible "electronic reading rooms" with agency FOIA response materials and other information routinely available to the public, with electronic search and indexing features.

Before submitting a FOIA request, please check to see if the information you are looking for is already available on FDA's Web site. You can use our search engine to help you find what you're looking for.

If you wish to visit an FDA Public Reading Room in person, they are located at:

- Division of Freedom of Information, 5600 Fishers Lane, HFI-35, Room 6-30, Rockville, MD 20857
- Division of Dockets Management, 5630 Fishers Lane, Room 1061, Mail Stop HFA-305, Rockville, MD 20852.

Hours of operation for both sites are 9 a.m. to 4 p.m., Monday through Friday.

For a general overview of the Freedom of Information Act see the U.S. Department of Justice's FOIA homepage.

FOIA Service Centers

- AoA - Administration on Aging
- ACF - Administration for Children and Families
- AHRQ - Agency for Healthcare Research and Quality
- CDC - Centers for Disease Control and Prevention
- CMS - Centers for Medicare & Medicaid Services
- HRSA - Health Resources and Services Administration
- IHS - Indian Health Service
- NIH - National Institutes of Health
- OIG - Office of Inspector General
- OS - Office of the Secretary
- PSC - Program Support Center
- SAMHSA - Substance Abuse and Mental Health Services Administration

2. Electronic Reading Room:

This index contains categories of frequently requested FDA documents. Before submitting an FOIA request, please check to see if the records you seek are already available on an FDA Web site. You can use this index to locate a specific category of documents. In addition, you can check specific FOI sites, which have been established by the following agency offices:

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVM)
- Dockets Management Branch (DMB)
- Office of Regulatory Affairs

3. CATEGORIES OF DOCUMENTS:

- ➔ Advisory committee transcripts
- ➔ Application Integrity Policy Test
- ➔ Information on commissioning
- ➔ Compliance policy guides

- Compliance program guidance manual
- Department list
- Directory of public affairs specialist
- Directory of state officials
- Assurance list for clinical investigation
- Enforcement reports
- Guides to inspection
- Guide to international inspection and travel
- Import alerts
- Import refusal reports
- Investigations operation manual
- Lab information bulletins
- Laboratory procedures manual
- Medical devices reports
- New animal drug application FOI summaries
- Notice of initiation of disqualification proceedings and opportunity to explain (NIDPOE)
- Notice to opportunity for hearing
- Products approval
- Regulatory procedures manual
- Warning letters

A handbook for requesting information and records from FDA

The guidance given in this handbook is intended to facilitate requests for both public information and records not originally prepared for distribution by FDA. This handbook has been updated in response to the Electronic Freedom of Information Act Amendments of 1996.

Obtaining public information

Certain documents that are prepared for public distribution—such as press releases, consumer publications, speeches, and congressional testimony—are available from FDA without having to file a Freedom of Information Act (FOIA) request. Many of these documents are available on FDA's Internet site (http://www.fda.gov/default.htm).

4. OBTAINING INFORMATION THROUGH FOIA:

FOIA allows anyone to request copies of records not normally prepared for public distribution. FOIA pertains to existing records only and does not require agencies to create new records to comply with a request. It also does not require agencies to collect information they do not have or to do research or analyze data for a requestor. In addition, FOIA requests must be specific enough to permit an FDA employee who is familiar with the subject matter to locate records in a reasonable period of time.

Under FOIA, certain records may be withheld in whole or in part from the requestor if they fall within one of nine FOIA exemptions. Six of these exemptions most often form the basis for the withholding of information by the FDA:

Exemption 1: Protects certain records related solely to FDA's internal rules and practices.

Exemption 2: Protects information that is prohibited from disclosure by other laws.

Exemption 3: Protects trade secrets and confidential commercial or financial information.

Exemption 4: Protects certain interagency and intra-agency communications.

Exemption 5: Protects information about individuals in personnel, medical, and similar files when disclosure would constitute a clearly unwarranted invasion of privacy.

Exemption 6: Protects records or information compiled for law enforcement purposes when disclosure

(A) Could reasonably be expected to interfere with enforcement proceedings;

(B) Would deprive a person of a right to a fair trial or an impartial adjudication;

(C) Could reasonably be expected to constitute an unwarranted invasion of personal privacy;

(D) Could reasonably be expected to disclose the identity of a confidential source;

(E) Would disclose techniques and procedures for law enforcement investigations or prosecutions, or would disclose guidelines for law enforcement investigations or prosecutions, if such disclosure could reasonably be expected to risk circumvention of the law; or

(F) Could reasonably be expected to endanger the life or physical safety of an individual.

In the event FDA relies on one or more FOIA exemptions to deny a requestor access to records, a letter stating the reasons for denying the records will be sent to the requestor. The letter will also notify the requestor of the right to appeal the agency's denial determination. More specific information on these exemptions and on other aspects of our FOIA program is contained in FDA's FOIA implementation regulations, 21 CFR Part 20.

5. How to Make an FOIA Request:

All FOIA requests must be in writing and should include the following information:

A. Requestor's name, address, and telephone number.

B. A description of the records being sought. The records should be identified as specifically as possible. A request for specific records that are releasable to the public can be processed much more quickly than a request for "all information" on a particular subject. Also fees for a more specific and limited request will generally be less.

C. Separate requests should be submitted for each firm or product involved.

D. A statement concerning willingness to pay fees, including any limitations.

Questions relating to FOI requests may be addressed to the Division of the Freedom of Information Offices at 301-827-6567.

All FOIA requests must be in writing. At this time, FDA does not accept FOIA requests sent via e-mail. Requests should be mailed to the following address:

Food and Drug Administration
Division of Freedom of Information (HFI-35)
Office of Shared Services
Office of Public Information and Library Services
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: fax number 301-443-1726 or 301-443-1719. If experience difficulty sending a fax, please call (301) 443-2414.

6. FREEDOM OF INFORMATION (FOI) REFERENCE SHEET:

This table descripts the types of information that are releasable through the Freedom of Information (FOI) process from FDA

(Contents Revised: June 23, 1997) ELEMENTS	PREMARKET APPROVAL (PMA) Documents 21 CFR 814.9	INVESTIGATIONAL DEVICE EVALUATION (IDE) Documents 21 CFR 812.38	PREMARKET NOTIFICATION (PMN/510k) 21 CFR 807.95
Appeals	Only through FOI Staff, HFZ-82	Only through FOI Staff, HFZ-82	Only through FOI Staff, HFZ-82
Adverse Effects / Reaction Reports in PMA's, IDE's & 510(K)'s	Released by ODE, to the patient only, after receipt of written request. If requested by an attorney or family member; need notarized authorization from the patient.	Not releasable, except to provide a patient with their own report	Released by ODE, to the patient only, after receipt of written request. If requested by an attorney or family member; need notarized authorization from the patient.
Approval Letters	Letter available through Dockets Management with the SS&E package or on the Internet	Not Releasable	Only releasable only by FOI Staff, HFZ-82
Approvable Letters	Generally not releasable. See FOI Staff.	N/A	N/A
Bench/Clinical Data	Not Releasable	Not Releasable	Not Releasable
Consent Forms	Releasable only to those participants in the PMA study if reviewer is able to identify the individual in the document. If requested by an attorney or family member, it must be accompanied by a notarized authorization from the patient.	Releasable only to those participants in the IDE study if reviewer is able to identify the individual in the document. If requested by an attorney or family member, it must be accompanied by a notarized authorization from the patient.	Releasable only to those participants in the 510k study & if reviewer is able to identify the individual in the document. If requested by an attorney or family member, it must be accompanied by a notarized authorization from the patient.
Certifications of Documents	Only through FOI Staff, HFZ-82	Only through FOI Staff, HFZ-82	Only through FOI Staff, HFZ-82

Denials	Only through HFZ-82 and coordinated through General Counsel	Only through HFZ-82 and coordinated through General Counsel	Only through HFZ-82 and coordinated through General Counsel
Labeling	Contained in summary of safety and effectiveness (SS&E) and released by Dockets Management; some may be found on the Internet	N/A or Not Releasable	Releasable by FOI HFZ-82 after PDN
Manufacturer's Standard Operating Procedures (SOP), In-house Quality Assurance Procedures	Not Releasable	Not Releasable	Not Releasable
Minor Deletions	Only through HFZ-82	N/A	Only through FOI Staff, HFZ-82
Not Substantially Equivalent Document	N/A	N/A	May be releasable, see FOI Staff
Patient Records	Releasable only to those participants in the PMA study if reviewer is able to identify the individual in the document. If requested by an attorney or family member, it must be accompanied by a notarized authorization from the patient.	Not releasable except to provide a patient with their own report	Not releasable except to provide a patient with their own report
PMA Supplements	Review for proprietary information prior to release	N/A	N/A
Recession Letters	Releasable only after recession is effective	May be releasable, see FOI Staff	Releasable only after recession is effective
Reviewer's Notes	Review for proprietary information prior to release	Not Releasable	Review for proprietary information prior to release

Substantially Equivalent Letter	N/A	N/A	Available on the Internet as of 7/97, otherwise only releasable through FOI, HFZ-82
Summary of Safety and Effectiveness (SSE)	Releasable through ODE or Dockets Management (with a Docket Number); approvals after 9/96 on Internet	N/A	Available on the Internet for 510(K)'s found SE after March 1996. Voluntarily submitted by manufacturer and intended for public release. Note that the SS&E were not required prior to 4-18-91.
Withdrawn Submission	Not Releasable, see FOI Staff	N/A	Not Releasable - see FOI Staff
Withdrawn Letter	Not Releasable - see FOI Staff	Not Releasable - see FOI Staff	Not Releasable - see FOI Staff

7. References:

- http://www.fda.gov/foi

8. Study Questions:

1. How to make an FOIA request?
2. Write in brief about freedom of information.

INACTIVE INGREDIENT GUIDE (IIG)

1. INTRODUCTION:

- IIG is a part of FOI Special Topics, which comes under Drug Information division of CDER.
- IIG was prepare on January 1996
- PDF version available on FDA from March 2000 – scanned document
- Divided in 8 Parts – alphabetically.
- Total Pages 155
- IIG consist of all the inactive ingredient present in approved drug product or conditionally approved drug products currently marketed for human use.
- IIG is compile by DDIR – Division of Drug Information Resources.

2. PURPOSE:

- Once Inactive Ingredient appears in currently approved drug products for particular route of administration, the Inactive Ingredient would not usually be considered NEW and may require less extensive review.

3. INACTIVE INGREDIENT:

- 21 CFR 210.3 (b) 8 defines Inactive Ingredient as any component other than Active Ingredient.
- Only those which are present in Final dosage form.
- Not include any processing material used, which removed afterwards and not present in Final dosage form.
- The Ingredient, which is Physically or Chemically combined with Active ingredient to facilitate DRUG TRANSPORT are considered as Inactive Ingredient.
- Reactant in Radiopharmaceuticals are Inactive Ingredient.

Contaminants

- IIG does not represents contaminant found in approved drug products.

Synonyms

- Since many Ingredient have Synonyms, if one can not find any particular Ingredient, he may contact Drug Information Officer, who can assist with the help of Dictionary maintained by DDIR.

Proprietary Name

- DDIR does not always include Proprietary names of Ingredient in IIG.
- In such situations, one has to search data for such ingredient under individual component entries.

Toxics

- If any ingredient of IIG is found to be Carcinogenic or Teratogenics or Embryotoxic, please NOTIFY to DDIR
- DDIR draws attention of medical officers and pharmacological reviewer towards that specific Inactive Ingredient

Color Additives

- Specially listed at last in Appendix
- Certification Branch of Division of Color Technology had classified colors.
    - Permanently listed color additives
    - Provisionally listed color additives
    - Desisted color additives
- Consult 21 CFR 74 and 82 for detail information on color additives

4. IIG DESCRIPTION:

NAME	ROUTE / DOSAGE FORM	CAS NO.	NDA COUNT	LAST NDA APPROVAL DATE	POTENCY RANGE

NAME

- Alphabetically listed Starting from ACACIA to ZINC SULFATE
- Then few excipients as per Numerical starting
- e.g. 1,1,1 – TRICHLOROETHANE

ROUTE / DOSAGE FORM

- Route; Dosage form; specific
- i.e. Oral; Tablet; Delayed action, Enteric Coated
- Alphabetical order: Buccal, I.M., I.V., Ophthalmic, Oral, Topical

CAS No.

- Chemical Abstract Service No. - 9 digit
- Helpful in Computer-assisted search with the National Library of Medicine's Online Databases

NDA COUNT

- Total No. of NDA filed, in which Inactive Ingredient currently appears

LAST NDA APPROVAL DATE

- Date of obtaining Last NDA approval, Helps to find Latest NDA

POTENCY RANGE

- Minimum to Maximum Value of Excipient used
- i.e. 0.5 mg – 5 mg
- In many excipient Potency Range is given in Percentage of final product
- i.e. 0.5 % - 5 %

STRUCTURE

- Chemical Structures of Inactive Ingredient are not mentioned in IIG.
- If anyone requires for review, it can be obtained from DDIR Chemist.

5. REFERENCE:

- **www.fda.gov/cder/drug/iig/default.htm**

6. QUESTIONS:

1. What is IIG and what is its purpose?
2. Give IIG description.
3. Write in brief about IIG.

DRUG MASTER FILE (DMF)

TABLE OF CONTENT:-

I. INTRODUCTION

A **Drug Master File (DMF)** is a submission to the Food and Drug Administration (FDA) that may be **used to provide confidential detailed information** about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

The submission of a DMF is **not required by law or FDA regulation** and a DMF is **submitted solely at the discretion of the holder (**a person who owns a DMF)**.**

The information contained in the DMF may **be used to support** an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an **Export** Application, or amendments and supplements to any of these. But a DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application.

Drug Master Files are provided for in 21 CFR 314.420. This guideline is intended to provide DMF holders with procedures acceptable to the agency (FDA) for preparing and submitting a DMF.

DMF's are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new DMF.

II. DRUG MASTER FILE CONTENTS

{A}TYPES OF DRUG MASTER FILES

There are five types of DMF's:

TYPE I: Manufacturing Site, Facilities, Operating Procedures, and Personnel

NOT MORE APPLICABLE. (WITHDRAWN BY FDA)

A Type I DMF is **recommended for a person outside of the United States** to assist FDA in conducting on site inspections of their manufacturing facilities. The DMF should describe the manufacturing site, equipment capabilities, and operational layout.

The description of the site should include acreage, actual site address, and a map showing its location with respect to the nearest city. An aerial photograph and a diagram of the site may be helpful.

A diagram of major production and processing areas is helpful for understanding the operational layout. Major equipment should be described in terms of capabilities, application, and location. Make and model would not normally be needed unless the equipment is new or unique.

TYPE II: Drug Substance, Drug Substance Intermediate & Material used in their preparation OR Drug Product

A Type II DMF should, in general, be **limited to a single drug intermediate, drug substance, drug product, or type of material used in their preparation.**

(1) Drug Substance Intermediates, Drug Substances, and Material used in their preparation

Summarize all significant steps in the manufacturing and controls of the drug intermediate or substance.

(2) Drug Product

Manufacturing procedures and controls for finished dosage forms should ordinarily be submitted in an IND, NDA, ANDA, or Export Application. If this information cannot be submitted in an IND, NDA, ANDA, or Export Application, it should be submitted in a DMF.

FOLLOWING GENERAL POINTS INCLUDED IN TYPE II DMFs.

1. Manufacturing Section
2. Quality Controls
    a. Inputs (Raw/Pkg. Materials)
    b. Intermediates & In-process
    c. Finished Drug Substance
3. Validations
4. Stability data
5. Impurities
6. Pkg. & Labeling

1. MANUFACTURING SECTION IN DMFs

- **Data of inputs (Raw Materials/Packaging Materials) & Sources**
    - ★ **List all RMs & PMs with sources**
    - ★ **Identify Key Starting Materials (KSMs)**
    - ★ **Complex materials do not qualify as KSMs**
        - Should be easily available
        - Structurally simple
        - If KSMs are complex molecules, extensive data are required
    - ★ **If <u>complex KSMs</u> are outsourced, FDA can ask:**
        - ♦ **Detailed mfg. Process**
        - ♦ Quality data (including impurities & residual solvent levels);
        - ♦ Justification / Evidence on how carryover of impurities from KSMs to finished API is controlled

- **Manufacturing Process details**
    - ★ **Synthetic scheme (KSMs to end product)**
        - Show structures of all intermediates also
    - ★ **Process Flow Diagram**
        - List all inputs and all unit operations
    - ★ **Detailed Process Write up**
        - ♦ Batch formula (commercial-scale)
        - ♦ Probable yields
        - ♦ Critical operating parameters
        - ♦ Purification procedures employed
        - ♦ Equipment
        - ♦ End Points of critical operations (no ambiguity)

- **Important note:**
    - ✓ 3 consecutive commercial scale batches shall be mfd. and charged for stability studies.
    - ✓ It required to produced REPRODUCIBILITY

2. QUALITY CONTROLS' SECTION IN DMFs

- ★ **Objective: To ensure quality at every stage of process:**
    - Inputs (Raw/Pkg. Materials)
    - Intermediates & In-process
    - Finished Drug Substance

- ★ Gradual increase in checks as the process progresses
- ★ Specifications & Test methods for all above
- ★ Complete Analytical Data of study batches (Certificates of Analyses)
- ★ Sampling Procedures adopted
    - [Idea: Ensure "homogeneity of test lots"]
- ★ **Analytical Reference Standard (ARS):**
    - **(**Preparation, Purification & Qualification with Pharmacopoeial STD.)
    - **If Non-Pharmacopoeial:** Extensive testing
- ★ **Test batches vs. ARS:** IR/UV/NMR/XRD

3. ANALYTICAL VALIDATIONS

- ★ **Done accordance to Reference Guidelines:** ICH Q 2 A & B
- ★ Validation **of In-house methods is must**
- ★ **Validation of P'copoeial methods** is also expected to assess suitability (w.r.t. molecule nature, nature & levels of impurities, instruments used etc.)
- ★ **Assay/Impurities' determination**/OVI estimation
- ★ **Forced Degradation Studies** (Hydrolytic, Oxidative, Acidic, Alkali, photo-degradation etc.): Establish stability indicating methods
- ★ **Three consecutive commercial scale batches**
- ★ **Accelerated studies** (40° C / 75% RH): **3 months satisfactory data. :**You can claim 2 yr. Shelf-life (if fails, 30°/65% RH for 12 months)
- ★ **Long term studies** (25° C / 60 % RH): Must continue to confirm shelf-life
- ★ Stability study samples **must be packed** in simulated market containers (miniatures)
- ★ Study shall **include all susceptible parameters** (e.g. impurities, potency etc.), i.e. OVI, BD etc. can be omitted
- ★ **All validated methods** shall be used, especially for impurities and assay, stability indicating methods are must
- ★ **Label unidentified impurities**, if increasing significantly.
- ★ **Decision** on identification & qualification

4. IMPURITIES' SECTION

- **Objective:** To prove that quality obtained is by design of process, not by chance
- **Explain:**
    - How carry over of impurities from SMs / in-process stage to API is controlled
    - How residual solvents are thrown away in various stages of process
- **Justifications for limits applied**

5. PACKING & LABELING

- ★ Detailed description of complete packing configuration
    - List out primary & secondary pkg. Materials
- ★ Food-grade certification of inner-most pkg. Material
- ★ Stability sample packing must be identical
- ★ Specifications & Test methods for all packing materials
- ★ Specimen label must be submitted
- ★ Clear mention of recommended storage conditions (temperature, light protection etc.)
- ★ Never switch-over to alternate packing, unless stability established & approved

TYPE III: Packaging Material

Each packaging material should be identified by the intended use, components, composition, and controls for its release.

The names of the suppliers or fabricators of the components used in preparing the packaging material and the acceptance specifications should also be given.

The specification should be provided as described in "Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics**."(Covered under Regulatory Aspects of Pharm. Packaging)**

BUT REMEMBER THAT,

Responsibility for compatibility and safety of packaging components in finished drug product is the responsibility of the AUTHORISED PARTY (AP).

It is not the responsibility of DMF HOLDER.

TYPE IV: Excipient, Colorant, Flavor, Essence, or Material used in their preparation

Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods. Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross reference to another document.

TYPE V: FDA Accepted Reference Information

FDA **discourages the use of Type V DMF's** for miscellaneous information, duplicate information, or information that should be included in one of the other types of DMF's.

If any holder wishes to submit information and supporting data in a DMF that is **not covered by Types I through IV**, a holder must first submit a letter of intent to the Drug Master File Staff (for address, see D.5.a. of this section). FDA will then contact the holder to discuss the proposed submission.

Each DMF **should contain only one type of information** and **all supporting data**. Supporting information and data in a DMF can be cross referenced to any other DMF.

2. General Information and Suggestions

A. Environmental Assessment

Type II, Type III, and Type IV DMF's should contain a commitment by the firm that its facilities will be operated in compliance with applicable environmental laws.

B. Stability

Stability study design, data, interpretation, and other information should be submitted, when applicable, as outlined in the "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics."

C. Format, Assembly and Delivery

- An original and duplicate are to be submitted for all DMF submissions.
- Drug Master File holders and their agents/representatives should retain a complete reference copy that is identical to, and maintained in the same chronological order as, their submissions to FDA
- The original and duplicate copies must be collated, fully assembled, and individually jacketed.
- Each volume of a DMF should, in general, **be no more than 2 inches thick**. For multivolume submissions, number each volume. For example, for a 3 volume submission, the volumes would be numbered 1 of 3, 2 of 3, and 3 of 3.

Some basic terminologies:

HOLDER: The person /company who submits DMF.

AGENT: The person / company who represents a DMF HOLDER.
(*Also called Representative*.)

APPLICANT / CUSTOMER / AUTHORISED PARTY (AP): The person / company who references the DMF.

APPLICATION: Investigational New Drug Application (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA)

SUPPLEMENT TO AN ANDA / NDA: A report of change in an approved ANDA / NDA.

AMENDMENT TO AN APPLICATION: Additional information to…

an existing IND,
a pending ANDA / NDA
a pending ANDA / NDA supplement**.**

III. SUBMISSIONS TO DRUG MASTER FILES

Each DMF submission should contain **a transmittal letter, administrative information about the submission, and other specific information.**

The DMF **must be in the English language**. Whenever a submission contains information in another language, an accurate certified English translation must also be included.

Each page of each copy of the DMF **should be dated and consecutively numbered.** An **updated table of contents** should be included with each submission.

A. Transmittal Letters

The following should be included:

A.1. Original Submissions

A. Identification of submission: Original, the type of DMF as classified in Section III, and its subject.
B. Identification of the applications, if known, that the DMF is intended to support, including the name and address of each sponsor, applicant, or holder, and all relevant document numbers.
C. Signature of the holder or the authorized representative.
D. Typewritten name and title of the signer.

A. 2. Amendments

A. Identification of submission: Amendment, the DMF number, type of DMF, and the subject of the amendment.
B. A description of the purpose of submission, e.g., update, revised formula, or revised process.
C. Signature of the holder or the authorized representative.
D. Typewritten name and title of the signer.

B. Administrative Information

Administrative information should include the following:

B.1. Original Submissions

A. Names and addresses of the following:

(1) DMF holder.
(2) Corporate headquarters.
(3) Manufacturing/processing facility.
(4) Contact for FDA correspondence.
(5) Agent(s), if any.

B. The specific responsibilities of each person listed above.

C. Statement of commitment.
A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

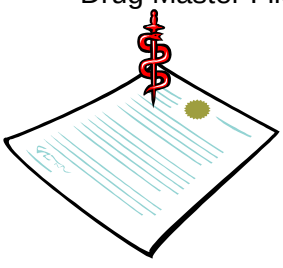
B.2. Amendments

A. Name of DMF holder.
B. DMF number.
C. **Name and address for correspondence**.
D. **Affected section** and/or **page numbers** of the DMF.
E. **The name and address of each person** whose IND, NDA, ANDA, DMF, or Export Application relies on the subject of the amendment for support.
F. **The number of each IND, NDA, ANDA, DMF, and Export Application** that relies on the subject of the amendment for support, if known.
G. **Particular items** within the IND, NDA, ANDA, DMF, and Export Application that are affected, if known.

U.S. standard paper size (8-1/2 by 11 inches) is preferred.

Delivery to FDA

Drug Master File submissions and correspondence should be addressed as follows:



Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

An original DMF submission will be examined on receipt to determine whether it meets minimum requirements for format and content. If the submission is administratively acceptable, FDA will acknowledge its receipt and assign it a DMF number

IV. AUTHORIZATION TO REFER TO A DRUG MASTER FILE

Letter of Authorization (LOA) to FDA:

Letter of authorization means a written statement by the holder or designated agent or representative permitting FDA to refer to information in the DMF in support of another person's submission.

When are letters of authorization needed?

Before the Agency can review information in your DMF, you must send an LOA to the applicant who is incorporating information by reference from your DMF (21 CFR 314.420(b)).

The applicant must include a copy of the LOA in their submission (21 CFR 314.50(g) (1)).

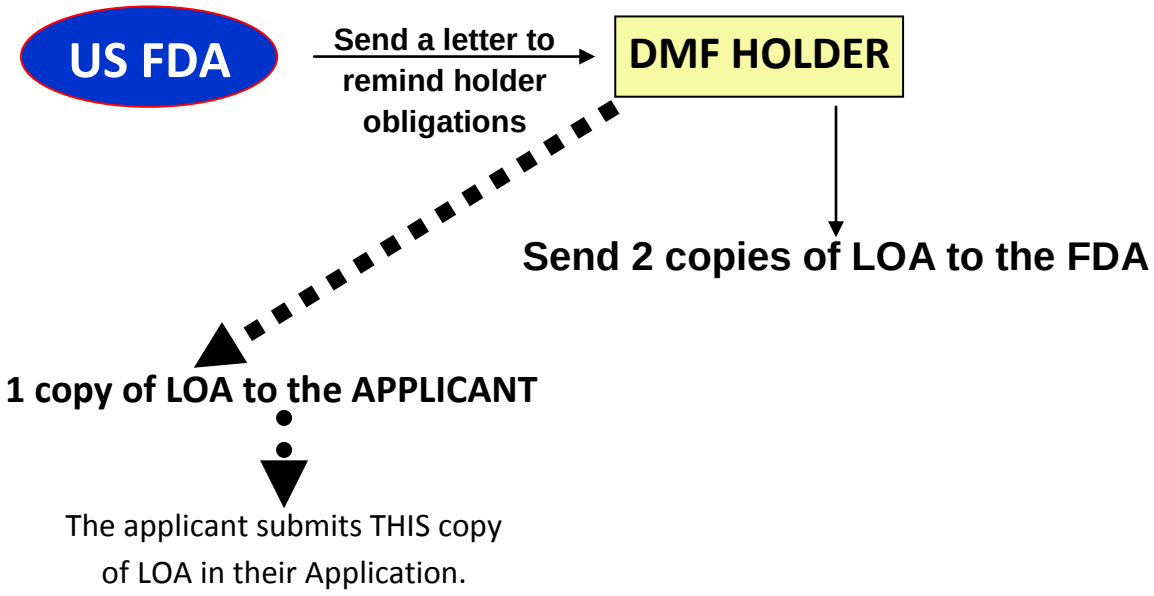
The LOA permits FDA to access the information in your DMF.

The LOA is required even if the applicant is also the holder of the DMF. A copy of the LOA should also be submitted to your DMF.

- **The letter of authorization should include the following:**

1. The date.
2. Name of DMF holder.
3. DMF number.
4. Name of person(s) authorized to incorporate information in the DMF by reference.
5. Specific product(s) covered by the DMF.
6. Submission date(s) of 5, above.
7. Section numbers and/or page numbers to be referenced.
8. Statement of commitment that the DMF is current and that the DMF holder will comply with the statements made in it.
9. Signature of authorizing official.
10. Typed name and title of official authorizing reference to the DMF

The DMF will be reviewed ONLY when it is referenced in an Application or another DMF.



IMPORTANCE OF LOA

- ✓ Sending LOA is the only mechanism which triggers the review procedure of DMF.
- ✓ A letter of authorization permits the FDA to reference the DMF.
- ✓ If the holder cross references its own DMF, the holder should supply following information in a LOA.
  - -DMF number
  - -Specific product(s) covered by the DMF
  - -Section numbers and/or page numbers to be referenced

Copy to Applicant, Sponsor, or Other Holder

The holder should also send a copy of the letter of authorization to the affected applicant, sponsor, or other holder who is authorized to incorporate by reference the specific information contained in the DMF. The applicant, sponsor, or other holder referencing a DMF is required to include a copy of the DMF holder's letter of authorization in the application.

General Format for LOA.

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: DMF #XXXXX, Type III
Hairless Cap Liner

Dear Sir or Madam:

By copy of this letter, DRUG HOLDER “X” is authorizing APPLICANT ABC to incorporate by reference into their NDA/ANDA/IND/SUPPLEMENTAL NDA our DMF #XXXXX, DATE, Section WXYZ, Pages 105-115.

We hereby authorize your office to review the aforementioned specific information in DMF #XXXX in considering the application filed by APPLICANT ABC.

The component/material furnished will be manufactured in accordance with DMF #XXXX and in compliance with CGMPs.

This DMF holder states that DMF #XXXXX is current and will comply with all statements made within it.

Sincerely,
XYZ

V. Drug Master File Review

A DMF IS NEVER APPROVED OR DISAPPROVED.

The agency will review information in a DMF only when an IND sponsor, an applicant for an NDA, ANDA, or Export Application, or another DMF holder incorporates material in the DMF by reference. As noted, the incorporation by reference must be accompanied by a copy of the DMF holder's letter of authorization.

If FDA reviewers **find deficiencies** in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder. At the same time, FDA will notify the person who relies on the information in the deficient DMF that additional information is needed in the supporting DMF.

The general subject of the deficiency is identified, but details of the deficiency are disclosed only to the DMF holder. When the holder submits the requested information to the DMF in response to the agency's deficiency letter, the holder should also send a copy of the accompanying transmittal letter to the affected persons relying on the DMF and to the FDA reviewing division that identified the deficiencies. The transmittal letter will provide notice that the deficiencies have been addressed.

VI. HOLDER OBLIGATIONS

Any change or addition, including a change in authorization related to specific customers, should be submitted in duplicate and adequately cross referenced to previous submission(s). The reference should include the date(s), volume(s), section(s), and/or page number(s) affected.

A. Notice Required for Changes to a Drug Master File

A holder must notify each affected applicant or sponsor who has referenced its DMF of any pertinent change in the DMF (21 CFR 314. 420(c)).

Notice **should be provided well before making the change** in order to permit the sponsor/applicant to supplement or amend any affected application(s) as needed.

B. Listing of Persons Authorized To Refer to a Drug Master File

A DMF is required to **contain a complete list of persons authorized** to incorporate information in the DMF by reference [21 CFR 314.420(d)].

The holder **should update the list in the annual update**. The updated list should contain the holder's name, DMF number, and the date of the update. The update should identify by name (or code) the information that each person is authorized to incorporate and give the location of that information by date, volume, and page number.

Any person whose authorization has been withdrawn during the previous year should be identified under a suitable caption.

If the **list is unchanged on the anniversary date**, the DMF holder should also submit a statement that the list is current.

C. Annual Update

The holder should **provide an annual report on the anniversary date** of the original submission.

If the **subject matter of the DMF is unchanged**, the DMF holder should provide a statement that the subject matter of the DMF is current.

Failure to update or to assure FDA annually that previously submitted material and lists in the DMF remain current can cause delays in FDA review of a pending IND, NDA, ANDA, Export Application, or any amendment or supplement to such application; and FDA can initiate procedures for closure of the DMF

D. Appointment of an Agent

When an agent is appointed, the holder should submit a signed letter of appointment to the DMF giving the agent's name, address, and scope of responsibility (administrative and/or scientific).

Domestic DMF holders do not need to appoint an agent or representative, although foreign DMF holders are encouraged to engage a U.S. agent.

E. Transfer of Ownership

To transfer ownership of a DMF to another party, **the holder should so notify FDA** and authorized persons in writing. The letter should include the following:

1. Name of transferee
2. Address of transferee
3. Name of responsible official of transferee
4. Effective date of transfer
5. Signature of the transferring official

6. Typewritten name and title of the transferring official.

The **new holder should submit**:

1. A letter of acceptance of the transfer
2. An update of the information contained in the DMF, where appropriate.
3. Any change relating to the new ownership (e.g., plant location and methods) should be included.

MAJOR REORGANIZATIONOF A DRUG MASTER FILE

A holder who plans a major reorganization of a DMF is encouraged to submit a detailed plan of the proposed changes and request its review by the Drug Master File Staff.

The staff should be given sufficient time to comment and provide suggestions before a major reorganization is undertaken.

VII. CLOSURE OF A DRUG MASTER FILE

A holder who wishes to close a DMF should submit a request to the Drug Master File Staff stating the reason for the closure.

The request should include a statement that the holder's obligations.

The Agency may close a DMF that does not contain an annual update of persons authorized to incorporate information in the DMF by reference and a list of changes made since the previous annual report. The holder will be notified of FDA's intent to close the DMF.

VIII. OPEN PART OF DRUG MASTER FILES

European Drug Master File Procedure for Active Substances

The DMF contains information which includes valuable know-how which should be kept Confidential and submitted to the authorities only.

Therefore, it should be divided into 2 parts:

1. An Applicant's part **(OPEN PART)**

2. An Active Substance Manufacturer (ASM) Restricted Part. **(CLOSED PART)**

1. OPEN PART (APPLICANT'S PART) OF DMFs:

The applicant's part (OPEN PART) of a DMF is provided by the ASM to the applicant directly and becomes part of the application for marketing authorization.

The applicant's part of the DMF is still a confidential document which cannot be submitted to third parties without the written agreement of the ASM.

The applicant must be supplied by the ASM with sufficient information to be able to take Responsibility for an evaluation of the suitability of the active substance specification to control the quality of the substance.

This normally includes a brief outline of the manufacturing method, information on potential impurities originating from the manufacturing method, from the isolation procedure

(natural products) or from degradation and, where applicable, information on the toxicity of specific impurities.

2. CLOSED PART (ASM RESTRICTED PART) OF DMF

Detailed information on the individual steps of the manufacturing method such as reaction conditions, temperature, validation and evaluation data for certain critical steps of the manufacturing method, etc. and on quality control during manufacture may contain valuable know-how. Such information may therefore be supplied to the authorities only.

	ASM Restricted Part	**Applicant's Part**
Name(s) and site(s) of manufacturer(s)	+	+
Specification and routine tests		+
Nomenclature		+
Description		+
Manufacturing method		
Brief outline (flow chart)		+
Detailed description	+	
QC during manufacture	+	
Process validation and evaluation of data	+	
Development chemistry		
- Evidence of structure (if needed)		+
- Potential isomerism		+
Physico-chemical characterization		+
Analytical validation		+
Impurities		+
Batch analysis (incl. impurities)		+
Stability (where necessary)		+

DMF Retirement Procedure:-

If a DMF has no activity (amendment or annual report) in three years FDA will initiate retirement procedure.

Note: LOA is not counted for activity.

- ✓ FDA sends overdue notice letter (ONL) to holder and/or agent using most recent address.
- ✓ If no response in 90 days, one copy of DMF is sent to Federal Records Center (FRC) and the other is destroyed.

Differences between Applications and DMFs

Applications	DMFs
1.COMES UNDER REGULATORY STATUS. MUST BE FILED BY APPLICANT.	1.NOT COME UNDER REGULATORY STATUS.IT IS NOT MANDATORY TO FILE A DMF.
2. EACH APPLICATION AND ITS SUPPLEMENT ARE ENTERED INTO A COMMON DATABASE.	2. DMFs ARE ENTERED IN TO DATABASE AS PER THEIR TYPES. (SEPARATE DATABASE FOR EACH TYPE OF DMF)
3.SUBMITTED TO A PARTICULAR REVIEW DIVISION.	3.SUBMITTED TO CDR.
4. ASSIGNMENT TO A REVIEWER AND EACH SUBMISSION HAS A DUE DATE.	4.NO ASSIGNMENT TO A REVIEWER, NO DUE DATE.
5.REVIEW PROCEDURE QUITE DIFFERENT THAN DMF.	5.DMFs ARE REVIEWED ONLY WHEN REFERENCED BY APPLICATION OR ANOTHER DMF
6.IF THE ANNIVERSARY DATE FOR ANNUAL UPDATE IS MISSED FDA SENDS A REMINDER.	6.IF THE ANNIVERSARY DATE FOR ANNUAL UPDATE IS MISSED FDA WILL NOT SEND A REMINDER.

CHANGES IN DMF SYSTEM:-

- Over the past decade, there have been some changes in the DMF system to help make it work better.
- However some things remain the same.

I. Changes in the DMF System and Procedures (Internal changes):-

- ✓ Creation of Review Cover Form
- ✓ Creation of Type II Review Format
- ✓ Implementation of Re-review Policy
- ✓ Creation of Central Review File
- ✓ Revision of Database View

Changes in the DMF System and Procedures (External changes):-

- ✓ Elimination of Type I DMFs
- ✓ Post-Approval Changes Guidance and
- ✓ Creation of DMF List Website
- ✓ Creation of DMFQUESTION
- ✓ Establish Position of DMF Expert

UNCHANGED THINGS OF DMF:-

- ✓ No review of DMF on receipt of it.
- ✓ Review only when referenced in application.
- ✓ All of the DMF is still confidential.
- ✓ DMFs are neither approved nor disapproved.
- ✓ The holder still has the responsibility to notify customer of changes.

SUMMARY

- ✓ The DMF system presents challenges for both the industry and the FDA.
- ✓ Some of the changes have made the system smoother (hopefully for both industry and FDA).
- ✓ Problems can be minimized:
  - – With full understanding of their responsibilities and adherence to Guidances on the part of holders and applicants.
  - – With adherence to policies and procedures on the part of reviewers.

IX. Study Questions??????

1. What are DMFs? Describe various types of DMFs.
2. Write a short note on type II DMFs.
3. Give details about latter of authorization.
4. What are the differences between DMFs and APPLICATIONS?
5. What are the open and closed parts of DMF as per European guidelines?
6. Describe the submission, review and retiring of DMF.
7. State and explain the contents of Drug Master File. (uni. Exam.....2005)
8. Short note on DMF.....(uni. Exam.....2006,07)

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- www.emea.eu.int/htms/vet
- http://www.fda.gov/cder/Offices/ONDQA/presentations/shaw.pdf

HISTORICAL ASPECTS OF VARIOUS PHASES OF DRUG DEVELOPMENT AND APPROVAL PROCESS

TABLE OF CONTENT:-

1. INTRODUCTION:-

Each year many new prescription drugs are approved by the Food and Drug Administration (FDA). The process of developing and bringing new drugs to market is important for primary care physicians to understand.

The process starts with preclinical testing. For drugs that appear safe, an investigational new drug application is filed with the FDA. If approved, clinical trials begin with phase 1 studies that focus on safety and pharmacology. Phase 2 studies examine the effectiveness of the compound. Phase 3 is the final step before submitting a new drug application (NDA) to the FDA. An NDA contains all the information obtained during all phases of testing. Phase 4 studies, or postmarketing studies, are conducted after a product is approved. Recent changes in legislation have streamlined the approval process. Critics contend that these changes have compromised public safety, resulting in the need to recall several products from the market. Proponents claim that changes in the approval process help patients with debilitating diseases, such as acquired immunodeficiency syndrome, that were previously denied critical medication because of bureaucratic regulations.

The Food and Drug Administration (FDA) is responsible for assuring that foods and cosmetics are safe and that medicines and medical devices are both safe and effective. To carry out this responsibility, the FDA monitors more than $1 trillion worth of products, representing about $0.25 of every $1.00 spent annually by American consumers. Balancing the efficacy and safety of these products is the core public health protection duty of the FDA. This mission requires examining efficacy as determined from well-controlled trials, effectiveness as determined from actual use in uncontrolled settings, and safety for both prescription and over-the-counter pharmaceuticals before approving a medication for market. During the past decade alone, more than 500 new prescription drugs have been approved by the FDA.

Physicians face the continual challenge of learning about new products approved by the FDA. The process of developing new drugs and bringing new drugs to market has important practice implications yet is poorly understood by most primary care physicians. Understanding how clinical trials are conducted is important when physicians consider the use of a new medication for patients in their own practices. For example, the medical literature or a pharmaceutical representative might refer to a phase 3 or phase 4 study. This Table provides a brief description of these terms and others used throughout this article. Understanding these terms will help the physician understand the risks involved in using a new medicine and the role of clinical trials in evaluating safety and effectiveness. Primary care physicians who might receive invitations to participate in clinical trials need to understand the risks involved for patients and the importance such investigations play in determining efficacy and safety issues of newly released medications. Finally, physicians who challenge the cost of new medications might benefit from a more complete understanding of the time, cost, and complex issues involved in having a new product approved by the FDA.

The purpose of this article is to present a concise overview of the drug approval process. It will briefly review the history of the FDA and follow the journey of a new product from early development until approval by the FDA for prescription use.

2. HISTORICAL PERSPECTIVE OF DRUG DEVELOPMENT AND ITS APPROVAL:-

Misfortune, disaster, and tragedy have triggered most of the advances in drug regulation. At the turn of the 19th century, the marketing of medicines was not controlled, and corruption, exploitation, and fraud were rampant. Public disclosures about the unsanitary conditions in meat-packing plants and concerns about worthless or even dangerous medicines led to the enactment of the **Food and Drug Administration Act of 1906**. This law (1) required that drugs meet official standards of strength and purity, (2) defined the terms *adulterated* and

misbranded, and (3) prohibited the shipment for sale of misbranded and adulterated foods, drinks, and drugs.

The FDA gained little power from this legislation, and it did not prevent the **accidental deaths of 107 persons in 1937** from the patent medicine marketed as "elixir sulfanilamide." A well-intentioned chemist used diethylene glycol as a solvent to make a liquid formulation of sulfanilamide that would be easier for children to take. Although the toxicity of diethylene glycol was known at the time, the manufacturer was not aware of it. **Existing law did not require that manufacturers demonstrate a drug's safety**, and 240 gallons of the elixir were released into the marketplace.

As a consequence of this event, Congress enacted the Federal Food, Drug and Cosmetic Act of **1938**, marking the birth of the modern FDA. **The new act required that a manufacturer (not the FDA) prove the safety of a drug before it could be marketed**, **authorized factory inspections, and established penalties for fraudulent claims and misleading labels**. Following the 1938 Act, the FDA began to distribute public notices (known as trade correspondences) to the industry regarding the labeling and dispensing of drugs. It was in these public notices that the FDA first distinguished medications that should be available only by prescription. Specifically it required that all drugs either carry a label with adequate information for consumer use or a caution label. The caution label warned consumers that the drug should be used only by or on prescription of a physician.

At this point the decision about which drugs should receive a caution label was largely at the discretion of the manufacturer**. In 1951**, the Durham-Humphrey Amendment set forth the basis for distinguishing between prescription and nonprescription drugs. The amendment specified that three classes of drug be available by prescription: habit-forming drugs, drugs considered unsafe for use except under expert supervision because of toxicity or other potential harmful effects, and drugs limited to prescription use only under a manufacturer's new drug application.

In 1961, an Australian obstetrician, William McBride, reported an increase of fetal malformations in association with the hypnotic drug **Thalidomide**. Although thalidomide was heavily marketed in Western Europe, approval of this drug was delayed by the FDA in the United States and never made it to market. This near catastrophe, however, highlighted the need for more stringent laws, and **in 1962**, Congress passed the Kefauver-Harris Amendment. This act not only required that manufacturers prove to the FDA that a drug is safe but, for the first time, required that the manufacturer provide evidence that the product was effective for the claims made in labeling. Effectiveness needed to be established through adequate and well-controlled investigations by qualified researchers.

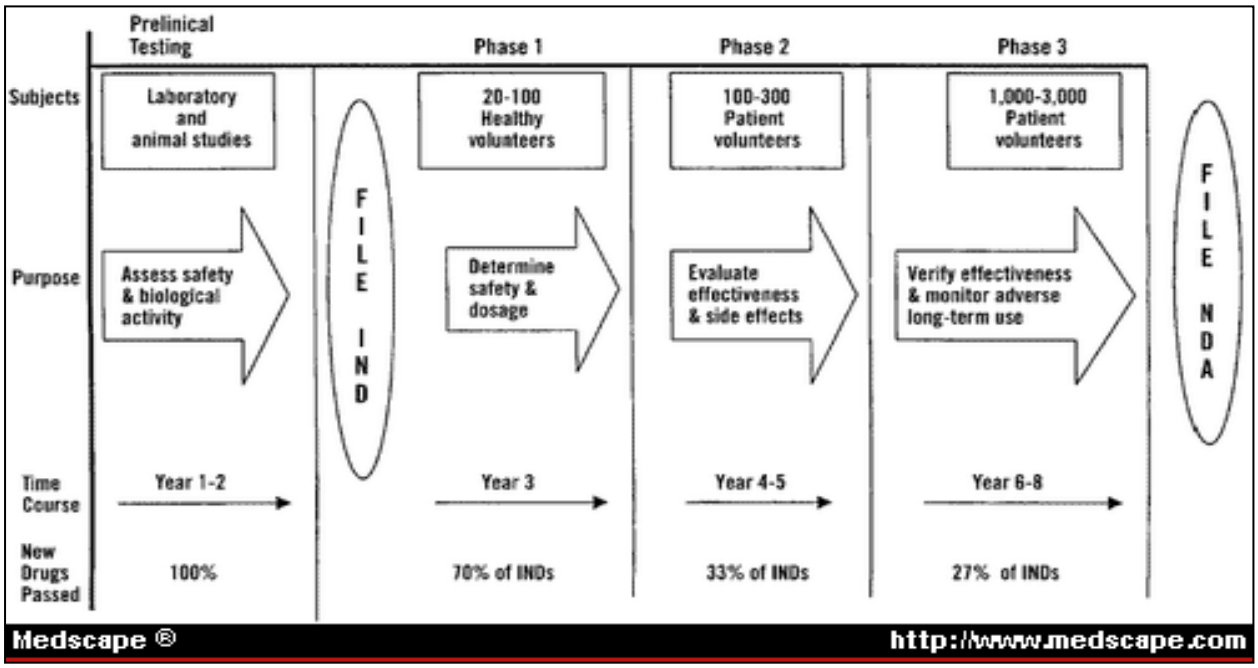
In the late 1970s there was concern about the quality of scientific data submitted to the FDA. This concern led to the establishment of good laboratory practices and guidelines for clinical trials to assure the quality and integrity of the safety data filed with the FDA. Important elements of the guidelines included the qualifications of the investigator, the study facilities, study management, safeguards for the safety and rights of patients, adherence to the research protocol, record keeping, and study monitoring. Many of these guidelines have now become regulation, such as the need to provide informed consent and the basic elements of informed consent, and essentially spell out the requirements for institutional review boards (IRBs).

In 1987, partially in response to the human immunodeficiency virus (HIV) epidemic, new regulations were developed to accelerate approval for high-priority medications. Before then, drugs were approved based on their effect on the illness or on survival. Accelerated approval allowed the FDA to judge drugs using a surrogate endpoint, or the effect of the drug on a physiologic process or marker associated with a disease. For example, CD4 cell counts could be used to measure the effectiveness of an antiviral medication in treating

HIV-infected patients. This new standard allowed the FDA to approve a promising drug without completing a full clinical trial.

3. DRUG DEVELOPMENT:-

Drug development can generally be divided into phases. The first is the preclinical phase, which usually takes 3 to 4 years to complete. If successful, this phase is followed by an application to the FDA as an investigational new drug (IND). After an IND is approved, the next steps are clinical phases 1, 2, and 3, which require approximately 1, 2, and 3 years, respectively, for completion (Table). Importantly, throughout this process the FDA and investigators leading the trials communicate with each other so that such issues as safety are monitored. The manufacturer then files a new drug application (NDA) with the FDA for approval. This application can either be approved or rejected, or the FDA might request further study before making a decision. Following acceptance, the FDA can also request that the manufacturer conduct additional postmarketing studies. Overall, this entire process, on average, takes between 8 to 12 years. Figure 1 summarizes the drug approval process.



It is not surprising that from conception to market most compounds face an uphill battle to become an approved drug. For approximately every 5,000 to 10,000 compounds that enter preclinical testing, only one is approved for marketing. A 1993 report by the Congressional Office of Technology Assessment estimated the cost of developing a new drug to be $359 million. Newer figures place the cost at more than $500 million.

The first step, a preclinical phase, is to find a promising agent, which involves taking advantage of the advances made in understanding a disease, pharmacology, computer science, and chemistry. Breaking down a disease process into its components can provide clues for targeting drug development. For example, if an enzyme is determined to be a key component of a disease process, a researcher might seek ways to inhibit this enzyme. Advances in basic science might help by ascertaining the active enzyme site. Numerous compounds might be synthesized and tested before a promising agent emerges. Computer modeling often helps select what compounds might be the most promising.

The next step before attempting a clinical trial in humans is to test the drug in living animals, usually rodents. The FDA requires that certain animal tests be conducted before humans are exposed to a new molecular entity. The objectives of early in vivo testing are

to demonstrate the safety of the proposed medication. For example, tests should prove that the compound does not cause chromosomal damage and is not toxic at the doses that would most likely be effective. The results of these tests are used to support the IND application that is filed with the FDA. The IND application includes chemical and manufacturing data, animal test results, including pharmacology and safety data, the rationale for testing a new compound in humans, strategies for protection of human volunteers, and a plan for clinical testing. If the FDA is satisfied with the documentation, the stage is set for phase 1 clinical trials.

Phase 1 studies focus on the safety and pharmacology of a compound. During this stage low doses of a compound are administered to a small group of healthy volunteers who are closely supervised. In cases of severe or life-threatening illnesses, volunteers with the disease may be used. Generally, 20 to 100 volunteers are enrolled in a phase 1 trial. These studies usually start with very low doses, which are gradually increased. On average, about two thirds of phase 1 compounds will be found safe enough to progress to phase 2.

Phase 2 studies examine the effectiveness of a compound. To avoid unnecessarily exposing a human volunteer to a potentially harmful substance, studies are based on an analysis of the fewest volunteers needed to provide sufficient statistical power to determine efficacy. Typically, phase 2 studies involve 100 to 300 patients who suffer from the condition the new drug is intended to treat. During phase 2 studies, researchers seek to determine the effective dose, the method of delivery (eg, oral or intravenous), and the dosing interval, as well as to reconfirm product safety. Patients in this stage are monitored carefully and assessed continuously. A substantial number of these drug trials are discontinued during phase 2 studies. Some drugs turn out to be ineffective, while others have safety problems or intolerable side effects.

Phase 3 trials are the final step before seeking FDA approval. During phase 3, researchers try to confirm previous findings in a larger population. These studies usually last from 2 to 10 years and involve thousands of patients across multiple sites. These studies are used to demonstrate further safety and effectiveness and to determine the best dosage. Despite the intense scrutiny a product receives before undergoing expensive and extensive phase 3 testing, approximately 10% of medications fail in phase 3 trials.

If a drug survives the clinical trials, an NDA is submitted to the FDA. An NDA contains all the preclinical and clinical information obtained during the testing phase. The application contains information on the chemical makeup and manufacturing process, pharmacology and toxicity of the compound, human pharmacokinetics, results of the clinical trials, and proposed labeling. An NDA can include experience with the medication from outside the United States as well as external studies related to the drug.

After receiving an NDA, the FDA completes an independent review and makes its recommendations. The Prescription Drug User Fee Act of 1992 (PDUFA) was designed to help shorten the review time. This act allowed the agency to collect user fees from pharmaceutical companies as financial support to enhance the review process. The 1992 act specifies that the FDA reviews a standard drug application within 12 months and a priority application within 6 months. Application for drugs similar to those on the market are considered standard, whereas priority applications represent drugs offering important advances in addition to existing treatments. If during the review the FDA staff feels there is a need for additional information or corrections, they will make a written request to the applicant. During the review process it is not unusual for the FDA to interact with the applicant staff.

Once the review is complete, the NDA might be approved or rejected. If the drug is not approved, the applicant is given the reasons why and what information could be provided to make the application acceptable. Sometimes the FDA makes a

tentative approval recommendation, requesting that a minor deficiency or labeling issue be corrected before final approval. Once a drug is approved, it can be marketed.

Some approvals contain conditions that must be met after initial marketing, such as conducting additional clinical studies. For example, the FDA might request a postmarketing, or phase 4, study to examine the risks and benefits of the new drug in a different population or to conduct special monitoring in a high-risk population. Alternatively, a phase 4 study might be initiated by the sponsor to assess such issues as the longer term effects of drug exposure, to optimize the dose for marketing, to evaluate the effects in pediatric patients, or to examine the effectiveness of the drug for additional indications. Postmarketing surveillance is important, because even the most well-designed phase 3 studies might not uncover every problem that could become apparent once a product is widely used. Furthermore, the new product might be more widely used by groups that might not have been well studied in the clinical trials, such as elderly patients. A crucial element in this process is that physicians report any untoward complications. The FDA has set up a medical reporting program called Medwatch to track serious adverse events (1-800-FDA-1088). The manufacturer must report adverse drug reactions at quarterly intervals for the first 3 years after approval, including a special report for any serious and unexpected adverse reactions.

Term	Definition
Clinical evaluation, phase 1	Examines the pharmacologic actions and safe dosage range of a drug; how it is absorbed, distributed, metabolized, and excreted; and its duration of action
Clinical evaluation, phase 2	Controlled studies in volunteers to assess the effectiveness of a drug. Simultaneous animal and human studies can continue to examine further the safety of the drug
Clinical evaluation, phase 3	Testing using a greater number of volunteer patients. The drug is administered by practicing physicians to those suffering from the condition the drug is intended to treat. These studies must confirm earlier efficacy studies and determine low-incidence adverse reactions
Clinical evaluation, phase 4	Studies conducted after FDA approval, during general use of the drug by medical practitioners. Also referred to as postmarketing studies
Fast-track drugs	Fast-track approval provided for drugs that meet unmet medical needs for patients with serious or life-threatening conditions
Labeling	Any information distributed about a drug by the manufacturer, even if it is not physically affixed to the product. In addition to package inserts, labeling includes such material as advertising
Misbranding	Anything in labeling that is "false or misleading in any particular" renders the product misbranded, making it subject to FDA regulatory action

4. RECENT DEVELOPMENT IN DRUG APPROVAL:-

The Food and Drug Administration Modernization Act of 1997 (**FDAMA**) extended the use of user fees and focused on streamlining the drug approval process. In 1999, the 35 drugs approved by the FDA were reviewed in an average of 12.6 months, slightly more than the 12-month goal set by PDUFA. This act also increased patient access to experimental drugs and facilitated an accelerated review of important new medications. The law ended the ban on disseminating information to providers about non-FDA-approved uses of medications. A manufacturer can now provide peer-reviewed journal articles about an off-label indication of a

product if the company commits to filing a supplemental application to establish the use of the unapproved indication. As part of this process, the company must still conduct its own phase 4 study. As a condition for an accelerated approval, the FDA can require the sponsor to carry out postmarketing studies to confirm a clinical benefit and product safety. Critics contend the 1997 act compromises public safety by lowering the standard of approval. Within a year after the law was passed, several drugs were removed from the market.

Among these medications were Mibefradil for hypertension, dexfenfluramine for morbid obesity, the Antihistamine Terfenadine, and Bromfenac Sodium for pain. More recently, additional drugs including Troglitazone were removed from the market. Although the increase in recalls might reflect the dramatic increase in drugs approved and launched, others argue that several safety questions were ignored. Another concern was that many withdrawn drugs were me-too drugs which did not represent a noteworthy advance in therapy. Persons critical of the FDA believe changes in the approval process, such as allowing some new drugs to be approved based on only a single clinical trial, expanded use of accelerated approvals, and the use of surrogate end points, have created a dangerous situation. Proponents of the changes in the approval process argue that there is no evidence of increased risk from the legislative changes, and that these changes improve access to cancer patients and those with debilitating disease who were previously denied critical and lifesaving medications.

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CHEMISTRY, MANUFACTURING & CONTROL (CMC)

TABLE OF CONTENT:-

1. INTRODUCTION

Chemistry, Manufacturing, and Controls (CMC) is a relatively small section (approximately 15–20%) of a typical New Drug Application (NDA), but it often becomes a reason for delay in the approval of NDA/Biologics Licensing Applications (BLAs). For Abbreviated New Drug Applications (ANDAs), however, the CMC section is significant (around 80–90%).

This section also becomes quite important in the postapproval life-cycle management of the products. It should be noted that the CMC section is made up of three distinctly different but overlapping disciplines /sciences: synthetic/fermentation chemistry, analytical chemistry, and formulation chemistry. Also, the CMC section continuously changes with clinical phases. Typically during clinical phase 1 trials, the CMC section is quite small and contains laboratory-scale manufacturing experience for the drug substance and the drug products with quite simple analytical methodologies. During clinical phase 2 trials, the CMC section evolves to pilot-scale manufacturing of the drug substance and the drug products, and the specifications and analytical methodologies become more sophisticated. End of phase 2 (EOP2) usually becomes a pivotal point in the drug development since at this point decisions and major commitments are made to as to whether to go forward with the phase 3 clinical development and marketing authorization application (NDA/BLA). EOP2 means for the CMC section a major shift in planning and execution. The drug substance and drug product manufacture typically need to be moved to commercial site at a commercial scale, and the specifications and the analytical methodologies need to be upgraded and finalized. So, one can see that the CMC section is a ‘‘moving target.’’

After the completion of clinical phase 3 studies, an NDA/BLA is submitted to the U.S. Food and Drug Administration (FDA) for review and approval. The CMC section of an NDA/BLA should contain all the relevant developmental information that bridges phase 1 through 3 leading up to the NDA/BLA submission.

This chapter will systematically analyze and describe the FDA organization, its various regulations and guidances, the industry process by which CMC information is generated and submitted, and various ways to compress timelines and secure timely approvals of NDA/BLAs and ANDAs. As this chapter is being written, it is expected that the CMC review and approval process for new chemical entities and possibly biotechnologically produced drugs and generic drugs at the FDA may undergo a paradigm change. However, the basic principles behind obtaining approval of NDAs/BLAs/ANDAs in a timely manner remain the same. It is anticipated that ICH Q8 (Development Pharmaceutics) and ICH Q9 (Risk Assessments) will reflect the paradigm shift at the agency.

2.CMC CONTENT

A) DRUG SUBSTANCE

1.	Drug Substance Summary	Contributing author to overview
2.	Description, Physical & Chemical Characteristics	
2.1	Nomenclature	
2.2	Structural Formula	
2.3	Physical & Chemical Characteristics	including: Solubility profile Partition coefficient Dissociation coefficient Optical rotation Thermal properties Crystal morphology

		Particle size distribution, others as appropriate
2.4	Solid State Forms (Polymorphs, Hydrates or Solvates)	Comparative evaluation of analytical methods for determination of Physical properties Stability Potential impact on bioavaibility Controls (if needed) to assure specified form or ratio of forms
2.5	Reference Standard	Preparation and characterization with respect to identity and purity
2.6	Elucidation of Structure	Analytical proof of structure (and Stereochemistry) including: Spectroscopic data Optical rotation X-ray diffraction Thermal analysis Elemental analysis Chemical (purity) data
3.	Manufacturer(S)	
4.	Method of Manufacture	
5.	Container/Closure System	Quality Controls for packaging components and materials
6.	Process controls	
6.1	Quality Requirements for starting materials	Specification and Methods
6.2	Reagents, Solvents and Auxiliary Materials	Quality Control for identity and purity
6.3	In-Process Controls	Specification and Methods
6.4	Prime Intermediate(s)	Specification and Methods
7.	Impurities	Characterization of potential and observed impurities (by-and degradation products)
8.	Regulatory Controls for drug substance	
8.1	Specification	Tests, Limits & Methods used for release and stability testing of finished drug substance
8.2	Rational for Specification	Choice of routine tests Development of methods Justification of proposed limits & omitted test Qualification of specified impurities
8.3	Method Validation	
8.4	Analytical Data	Release results and impurity profiles for: Registration batches

		Supportive batches (toxicology, clinical and development)
9.	Stability	
9.1	Overview of Stability	Summary of primary and supportive data Potential and observed degradation pathway(s) and product(s)
9.2	Batch Description	
9.3	Package Description(s)	Relative to bulk package
9.4	Development Protocols	Storage condition, time points, tests: stress, Accelerated and Long term studies Shipping studies
9.5	Analytical Methods	Description of stability indicating methods Comment on different (if any) versus NDA specifications and methods
9.6	Data	
9.7	Conclusions	Recommended storage condition Proposed retest period Special precaution
9.8	Post Approval Commitment	Sampling Plan/Frequency Commercial stability protocol

B) DRUG PRODUCT

1.	Drug Product Summary	Contributing author to review
2.	Development Pharmaceutics	Contributing author for development data
3.	Batch tracking	
4.	Components	
5.	Compositions	
6.	Specification for Inactive Ingredients	Reference for compendial items Additional requirements for compendial Items, if any specification and methods for non-compendial items
7.	Manufacture(S)	
8.	Method of Manufacture	
9.	Container/Closure System	Bulk and Market packages Quality controls for packaging components and materials
10.	Regulatory Control for drug product	
10.1	Specifications	Tests, Limits & Methods used for release and stability testing of finished drug substance

10.2	Rationale for Specification	Choice of routine tests Development of methods Justification of proposed limits & omitted test Qualification of specified impurities
10.3	Method Validation	
10.4	Analytical Data	Results, Impurity Profiles and Dissolution Profiles, if applicable, for: Registration batches Supportive batches (Clinical and Development)
11.	Stability	
11.1	Overview of Stability	Summary of Primary and Supportive data Potential and observed degradation pathway(s) and product(s)
11.2	Batch Descriptions	
11.3	Package Descriptions	Bulk and Proposed market packages
11.4	Results of Studies	
11.5	Development Protocol	Stress, Accelerated & Long term studies Bulk containers Shipping studies Reconstitution studies, if applicable
11.6	Analytical Method	Description of stability indicating methods Comment on difference (if any) versus NDA Specification & Method
11.7	Data	
11.8	Statistical Analysis	
11.9	Conclusion	Recommended Storage condition Proposed Expiration Date Special Precaution
11.10	Post Approval Commitment	Sampling Plan/Frequency Commercial Stability Protocol

C ENVIRONMENTAL ASSESMENT

D METHOD VALIDATION

1	Exhibit Samples	List of reference standards and exhibit samples of drug substance and drug products to be provided to FDA laboratory
2	Certificates of Analysis	For all listed standards and samples
3	Raw Data	For Exhibit Samples: Sample chromatograms and spectra Raw data from actual analysis Example calculation
4	Method Validation Reports	

3. CURRENT U.S. FDA ORGANIZATION

The U.S. Food and Drug Administration is one of the most important customers for pharmaceutical companies. In order to understand the review and approval process for the CMC section of NDAs and ANDAs, one should be familiar with the regulatory authority and the process in the United States. The U.S. FDA is an agency within the Department of Health and Human Services, and it regulates biologics, drugs, food, devices, and veterinary products. It is made up of eight centers/ offices. The biologics such as vaccines and blood products are regulated by the Center for Biologics Evaluation and Research (CBER). The Center for Drug Evaluation and Research (CDER), which is the largest of the five centers in the FDA, regulates drugs that include NDAs and ANDAs. The devices are regulated by the Center for Device and Radiological Health (CDRH). Animal products are regulated by the Center for Veterinary Medicines (CVM). The Center for Food Safety and Applied Nutrition (CFSAN) regulates foods and nutritional products. The National Center for Toxicological Research (NCTR) regulates all types of toxicological research. The Office of the Commissioner (OC) and the Office of Regulatory Affairs (ORA) provide administrative and management support.

The CDER organization consists of therapeutic area–based review divisions. Each review division has the primary responsibility of reviewing submissions and provides an action that could involve approval, approvable, nonapproval, request for more information, etc. The review divisions are staffed by the division director, medical reviewers, pharmacologists, chemists, bio-statisticians, bio-pharm reviewers, project manager staff, etc. The chemistry and bio-pharm reviewers report to the Office of Pharmaceutical Sciences (OPS). The Office of Generic Drugs (OGD) also reports to OPS. The OGD has two divisions of chemistry, each made up of five teams. This division of OGD is based on major therapeutic classes. As this chapter is being written, by the middle of 2005 the chemists from review divisions will be combined into one new drug chemistry group under the Office of New Drug Chemistry. The objective behind this change is consistency in reviews and better time management. This step is a predecessor to other CMC review and approval practices changes being planned at the agency.

Various regulations as published in the 21 Code of Federal Regulations (CFR), guidances and points to consider (PTC) published by FDA, the Manual of Practices and Procedures (MaPP) published by FDA, and guidelines published by the International Committee on Harmonization (ICH) are important documents that become the foundation of scientifically and regulatorily sound CMC submission documents.

4. FDA AND ICH CMC/QUALITY REGULATIONS AND GUIDANCES

FDA regulates new drugs as well as generic drugs under the Federal Food, Drug, and Cosmetic Act enacted by the U.S. Congress. The law, among other things, ensures that drugs and devices are safe and effective for their intended uses and all labeling used is truthful, accurate, informative, and not deceptive. Chapter five and specifically subchapter A of the Act provides for Drugs and Devices. The interpretation of the Act is provided in the Code of Federal Regulations (CFR), which is published annually. There are 50 titles/sections in CFR, and title 21 specifically provides interpretation of the Federal Food, Drug, and Cosmetic Act. Typically the regulations are brief and often difficult to fully interpret for actual implementation. FDA issues guidances and PTCs, which provide further interpretation of the regulations. FDA also publishes MaPPs, which are approved detailed instructions to FDA reviewers in order to standardize reviews of submissions.

The reader is encouraged to make use of all FDA guidances and manuals. If properly used, they will ensure the quality of CMC submission, which should result in approval by FDA.

5. SPONSOR COMPANY AND AGENCY PROCESSES TO SUCCESSFULLY DEVELOP THE CMC SECTION OF NDAs AND ANDAs BASED ON QbD AND ICH/FDA REGULATIONS

The activities at the sponsor company in regards to CMC development from pre-IND through various phases of INDs leading up to the NDA and, in the case of generic drugs, the process leading up to ANDA determine one's success or failure. The product one delivers to FDA is the CMC submission, and its scientific quality determines its successful approval by the agency.

5.1. Pre-IND Phase

In this very early phase of drug development some basic work is performed. Preliminary solubility in various solvents, stability, and other important structural elucidations and characterizations are typically determined, which become the basis for future development of the new molecular entity. Of course, limited work is done at this stage, since the failure rate for new molecular entities (NMEs) is quite high. The CMC information from this stage typically becomes the basis for development pharmaceutics, and as the drug development progresses, additional tests and information are carried out.

5.2. IND Phase 1

This phase is still an early phase of product development and a limited and necessary effort is typically made. Since CMC is a multi-functional section, it will be highly beneficial to put together multi-functional teams consisting of scientists from drug substance synthesis, formulation, analytical, regulatory, writing group, etc. This team of people becomes responsible and accountable for putting together the CMC section of the IND and following the new drug's progress through phases 2 and 3 and making sure an NDA is filed on a quality submission.

In some instances, a sponsor may want to request a pre-IND meeting, which could be in the form of a teleconference, with the agency to seek advice and/or clarification. The agency requires that a briefing document be submitted by the sponsor at least 4–6 weeks prior to the meeting. The briefing document should contain relevant information on the drug substance and drug product and concise questions about which the sponsor seeks advice from the agency. FDA requires limited CMC information in a phase 1 IND. The main emphasis is on the safety of the volunteers and patients, and hence the sponsor is required to make a connection between preclinical material and the proposed clinical material from impurity and bioavailability points of view. (It is conceivable that the material used in the preclinical safety studies was not as bioavailable as the clinical material posing a safety risk to the patients.) Also, if the clinical material has any impurity with safety implications, the agency will want to know more about it. At the time of submitting an original IND, very limited stability information is required. A commitment to generate concurrent stability data during the course of a clinical trial and reporting the data in most cases should suffice. It is the sponsor's responsibility to make sure that the NME is stable in the dosage form when given to patients. During this early phase of clinical development, the analytical methods should be capable of determining the assay, impurities, etc., with specificity, accuracy, and precision. A formal validation of methods typically is not required at this early stage of development. Of course, as the drug development progresses, the analytical methods should be progressively validated so that they ensure strength, identity, purity, potency, and quality (SIPPQ) of the product. The sponsor must wait for a period of 30 days before initiating studies on human volunteers and patients. During this period the agency determines whether the sponsor could proceed with proposed studies, and if it has any objection it will instruct the sponsor not to initiate the study (known as clinical hold) until the deficiencies are satisfactorily addressed. The agency has issued a guidance as to the format and the content of the CMC section of IND, and the reader is encouraged to read and apply it to fullest extent as possible.

5.3. IND Phases 2 and 3

IND phases 2 and 3 are pivotal and become the basis for successfully obtaining approval of NDAs, because under these phases critical CMC information that supports SIPPQ is generated, drug substance and drug product manufacturing are optimized, bioavailability of the drug product is established, and primary stability data for the drug substance and the drug product are generated. The multifunctional team plays a critical role in advancing the NME through phases 2 and 3 leading up to NDA submission. Based on input from the clinical studies through phase 2, the safe and effective dose of the drug is chosen and various QbD parameters for the drug substance and drug product are introduced in the product development. The agency requires that during phases 2 and 3 the sponsor inform the agency of any new patient safety–related information in the form of IND amendments. These amendments to the IND typically do not require a waiting period; however, if the new information is significantly different from the original and if it affects the safety of the patients in the clinical trials, then the agency may advise the sponsor not to implement the change. The usual changes to the CMC, such as optimization to synthesis/manufacture of the drug substance, analytical methods, the drug product, new stability data, etc., could be submitted in IND annual reports to the agency. The sponsor could take advantage of the IND amendments to update the agency on the progress in the CMC and identification of critical issues and proposed/planned solutions to the issues. During phase 2, typically the drug substance and the drug product are produced in a large laboratory to pilot scale. At this phase, the drug substance synthesis/manufacturing, drug product formulation/ process, analytical test methods, etc. are fine-tuned and the principles of QbD and PAT may be introduced and implemented. The end of phase 2 or the beginning of phase 3 becomes a pivotal point in the overall drug development process. At this point the NME has shown a certain threshold for safety and desired efficacy and the drug development picks up the speed with which confirmation of clinical results from phases 1 and 2 are reached in a larger patient population in phase 3. The CMC has to match the increased clinical activity of phase 3 by gearing up all three disciplines: drug substance synthesis and manufacturing, drug product formulation and manufacturing, and analytical testing. Typically phase 3 clinical trials are conducted on many hundreds to thousands of patients, leading to marketing application. In this phase the CMC section has to match the expanded clinical trials leading towards commercial distribution. In phase 3, the CMC section should focus on two important aspects of development: combining information and data from all three phases and bridging those with the future commercial product. FDA has issued a guidance for CMC information requirements for phases 2 and 3. The bridging study will be discussed in the next section.

5.4. Successful Bridging of Pre-IND, Phase 1, Phase 2, and Phase 3 with Commercial Product

One of the secrets of obtaining approval of NDAs and BLAs from a CMC perspective is successfully bridging the CMC information and data from preclinical through the three phases of IND and the commercial product. Bridging of critical information on strength, identity, purity, potency, and quality starting from the preclinical phase leading up to commercial product is of utmost importance.

All relevant drug substance and drug product characterization information from all phases of development should be bridged to come up with a complete picture of strengths and weaknesses of the drug substance and the drug product. Key characteristics such as impurity profile, solubility of the drug substance, dissolution-friability balance (DFB) for SODF, accelerated/forced degradation to understand the mechanistic aspects of degradation, design of experiments, etc., should be bridged to get a complete picture of the drug product. The aforementioned information on the drug substance and the drug product from investigational phases is bridged to the planned commercial drug product. All of this bridging information, along with design of experimental data in which the boundaries of success and failures of all critical parameters (drug substance manufacturing processing parameters, formulation components, composition, processing equipment and parameters, in-process controls, specifications, etc.) are determined, become part of developmental

pharmaceutics and should be included in a New Drug Application. It should be emphasized that bridging in the form of evolution of analytical procedures starting from preclinical phase to phase 3 and commercial product testing should be thoroughly discussed in developmental pharmaceutics.

5.5. Developmental Pharmaceutics and Its Importance to CMC

As discussed above, Design of Experiments, Quality-by-Design, Process Analytical Technologies, bridging of all the phases of INDs, technology transfer, etc., become the basis for developmental pharmaceutics, which becomes the foundation of a good CMC section of NDAs and ANDAs. It provides an overview of the thoughts and rationale behind the product development and commercial product to the CMC reviewing staff at the agency and becomes an important tool in the review and approval process. The ICH CTD format also provides for a section for Development Pharmaceutics. ICH Q8 is on developmental pharmaceutics, and once this guidance (which is at early stages of its development at this time) is finalized, it should provide appropriate guidance to the industry.

5.6. Quality-by-Design and Process Analytical Technologies

As this chapter is being written, the Office of Pharmaceutical Sciences (OPS) under CDER is in the process of redesigning and introducing a paradigm shift in the CMC reviews and compliance investigations. It is expected that by the end of 2005 the Agency would have implemented the planned changes in CMC reviews and compliance investigations. The ICH through initiation of Q8 (Pharmaceutical Development) and Q9 (Risk Assessment) is also gearing up towards the same goal of OPS. Both ICH Q8 and Q9 will involve the concept of QbD. Qualityby-Design, which encompasses Process Analytical Technologies and embraces building quality in the process and product throughout the manufacturing process, may be summarized as follows:

QbD = Preprocess Controls (PPCs)
+ In-Process Controls (IPCs)
+ Post-Process Controls (POPCs)

PPCs: Preprocess controls (throughout the preclinical, the three phases of INDs, and for commercial production) such as thorough physical-chemical-biological characterization of the (a) drug substance and all its manufacturing/synthesis components and (b) excipients. The drug substance, starting materials, its other components (catalysts, solvents, etc.), key and pivotal intermediates, etc., should be thoroughly characterized. The pharmacopoeias provide fairly good chemical characterization, but do not provide thorough functional physical characterization, and it is up to the sponsor to develop that characterization. The drug substance physical and chemical characterization is of critical importance to successful Qualityby-Design. Some examples of PPCs are chemical purity of starting materials and intermediates, purification steps, drug substance particle size and specific surface area, density, excipient particle size and shape, density, etc.

IPCs: In-process controls is the heart of process analytical technologies. IPCs such as assay, purity, residual solvents, particle size, specific surface area, polymorphism, etc., are critical in the manufacturing of drug substance. For drug products, in-process controls such as granulation endpoints, moisture level, content uniformity, etc., are critical. Process analytical technologies could involve off-line, at-line, in-line, on-line testing of in-process parameters for drug substance and drug product. Carefully and strategically chosen in-process controls, if done in-line or on-line, may obviate final testing because of the large sample size.

PoPCs: Postprocess controls play an important role in QbD. Testing of final drug product per specifications, storage conditions, long-term and accelerated stability studies are components of PoPCs.

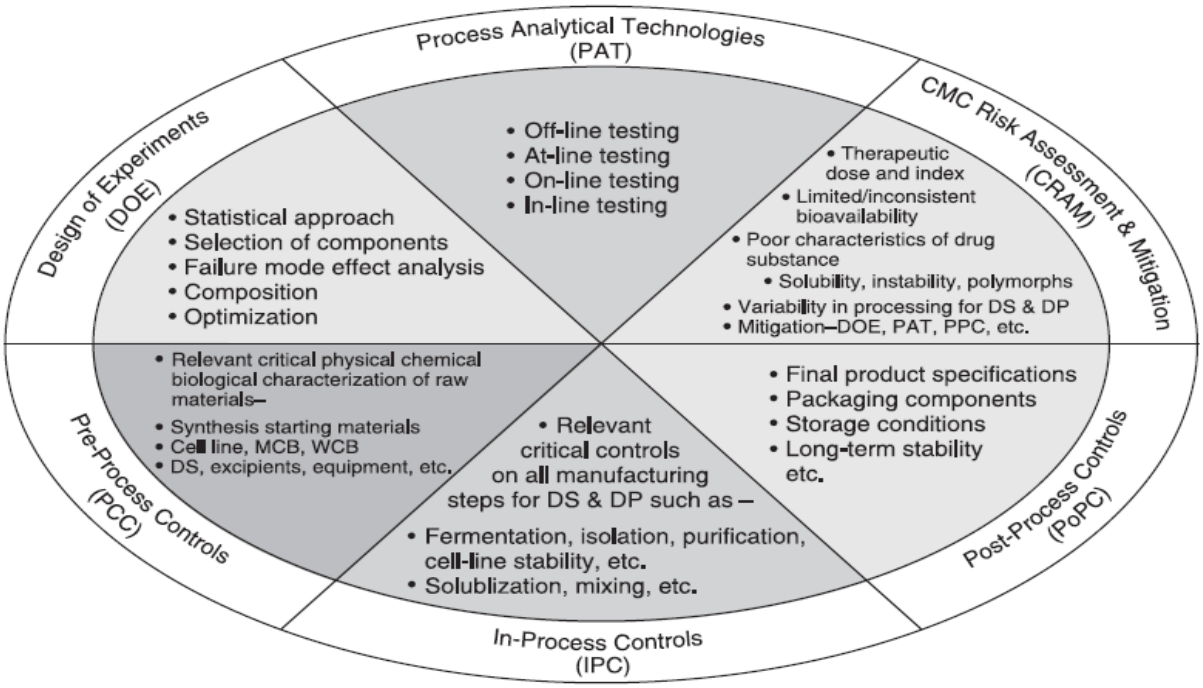

Figure 1 Quality-By-Design And Process Analytical Technologies Initiatives.

5.7. Sponsor-FDA Meetings

FDA allows several kinds of meetings with sponsors in order to assist and gather information. Meetings such as pre-IND typically are clinical oriented. For CMC section, end-of phase 2 and pre-NDA meetings are important for the CMC section of NDAs and BLAs. (FDA has issued a guidance on sponsor-FDA meetings.) The sponsor should submit a briefing document to the agency at least 6 weeks prior to the requested meeting, and the briefing document should contain relevant background information and questions on which the sponsor is seeking advice. The briefing document should not be voluminous. It should be a focused document that contains specific questions/ issues. The sponsor can easily enhance its NDA/BLA/ANDA submissions by taking advantage of these meetings.

5.8. NDA Submissions

NDA submission on a new drug should follow the FDA and ICH guidance. From a technical regulatory perspective, if all the work is done properly as described in sections a through h, the NDA submission should become fairly easy and result in approval in a timely manner. The submission should follow the FDA and ICH guidances, and moreover it should be reviewer friendly. The data should be presented in a clear-cut manner. One should remember that the product that the FDA sees from an applicant is the NDA/ANDA submission. The chemistry reviewers have a responsibility to make sure that the product they approve meets the regulatory requirements as prescribed in the Code of Federal Regulations. Submissions to the FDA should be accurate and of high quality.

All submissions to the FDA must meet four important criteria in order to secure approval the first time: (a) Adherence to Regulations and Guidances—strict adherence to FDA CMC regulations and guidances for format and content, which include those ICH quality guidelines that have reached step 5. It is possible to adopt an approach other than that provided by the FDA guidances; however, it is the applicant's responsibility to secure approval on the alternative approach from the FDA reviewing staff (for example, at EOP2 and/or Pre-NDA meeting). Careful and strategic implementation of guidance should be received from the reviewing staff at the FDA; (b) Introduction—submissions should have an introductory section that clearly provides the purpose, scope, and context of the submission that helps the reviewing team. This introduction should have a clear delineation of any agreement made prior to the submission. The introductory section should provide a higher level overview of the

submission, which will lead into the next section, where the nuts and bolts of the submission are provided. This section should end with a summary of the submission; (c) Body of the submission—this part of a submission is of utmost importance since it provides the main basis for approval. The chemistry review staff has to provide a rationale for their action (approval, nonapproval, approvable, etc.) and a good introduction and summary aids them in making their decision. The information provided in submissions must be focused, relevant, precise, accurate, complete, and of quality. When it comes to quality of the submission, one should adopt the philosophy of ''quality always.'' In this main body of the submission, one should pay special attention not to provide redundant and unrelated information, because it takes away from the reviewers' attention and wastes their precious time. The submission should have a logical flow of information and justified decisions based on scientific rationales. The logical flow of information and justified decisions along with clear objectives and findings that lead to clear conclusions provide a coherent submission. The main body of the submission should follow the time-tested organizational characteristics of a sound beginning, experimental details, organized results, discussion of results, and conclusions. Information should be provided with an appropriate combination of text, figures, tables, etc., which will provide a clear picture of the submission. The information should convey a clear message and conclusion and should follow the usual standards of quality (free of typographical and grammatical errors, clear legends, footnotes as
necessary for clarity, etc.); (d) A summary and conclusion section should be provided, including any short- or long-term commitments (such as placing batch(es) of drug product on long-term stability and reporting the data to the agency at a later date, etc.).

5.9. ANDA (505b2) Submissions

The ANDA submission on a generic drug should follow the FDA guidance. FDA has provided a clear-cut format and content guidance on the organization of an ANDA. Section VII of the guidance provides for detailed CMC requirements. The applicant should provide a statement on the components and composition of the product. This should be followed by information on raw materials (active ingredient and inactive ingredients), description of manufacturing facility, information on the outside/contract firms, manufacturing process and packaging instructions, in-process information, packaging material controls, controls for finished dosage form, analytical methods for the drug substance and drug product, stability of finished dosage form, and availability of samples. If the generic product is a parenteral product, the applicant must provide sterilization assurance information and data package. The above CMC section is somewhat similar to the NDA requirements, and if it follows the above recommendations, obtaining approval for an ANDA should be easy. The CMC section should be preceded by information on the bioavailability/ bioequivlaence of the dosage form in relation to the reference listed drug.

5.10. Quick and Complete Response (QCR) Team Approach to FDA Questions/Comments

Once an NDA or ANDA has been submitted by an applicant and filed (meaning accepted) by FDA, during and/or after the completion of the review, FDA might have questions/comments on the submission. The questions/comments may come verbally or in writing. In either case it is very important for the applicant to respond to the questions/comments in a timely, thorough, and accurate fashion. Often applicants form a team (such as QCR) that develops complete and timely responses that aide the agency's review process. The QCR team, if properly organized, could play an important role in obtaining the approval of NDAs in a timely manner.

6. UNDERSTANDING THE CMC REVIEW PROCESS

The CMC review process at FDA is quite transparent. The agency publishes its most current ONDC organization chart and several MaPPs. The primary CMC review chemists review the submissions and share their reviews with the chemistry team

leaders. Based on their reviews, they may issue information request letters. Alternatively, CMC reviews are further reviewed by CMC division directors and then ultimately by the director of ONDC. Once the reviews are finalized by the CMC reviewers and ONDC management, the review division director will issue appropriate letters (approval, nonapprovals, approvable, etc.). The CMC reviewers issue a review report, which includes their assessment and reasons for their recommendations. As stated earlier, the overall CMC review and approval processes may change in 2005 as a result of ICH Q8 and Q9. However, it should be remembered that the basics and fundamentals of CMC reviews (and compliance inspections) will focus on strength, identity, purity, potency, and quality, which are surrogates of safety and efficacy of drugs.
The OGD follows a similar review process. Of course, for ANDAs the final reviews stop at the OGD head level. The CMC reviewers have a legal responsibility to review and assess CMC submissions and to make sure that the submissions meet the law and regulations and the product meets the strength, identity, purity, potency, and quality requirements. If for some reason a product is recalled because of SIPPQ, then the reviewing staff that approved the product is in part responsible. Thus, understanding the review process and the responsibility of the reviewing staff is important in obtaining approval of NDAs/ BLAs.
As this chapter is being written, the Office of Pharmaceutical Sciences is planning for a paradigm change in the CMC reviews and compliance. The ICH through Q8 (Pharmaceutical Development) and Q9 (Risk Assessment) is also gearing up towards the same goal of OPS.

7. PROBLEMS AND CHALLENGES INVOLVED IN SECURING TIMELY APPROVALS AND POTENTIAL SOLUTIONS

Most delayed approvals are due to poor science contained in the submission and poor submission strategy. The poor science may be reflected in instability of the product or unacceptable levels of impurities or poor product bioavailability as measured by tablet dissolution, etc. A good product development plan based on the principles of QbD (see above) should result in an approvable submission. Judicial use of contacts with the agency and maximizing various FDA-sponsor meetings should avoid delays in the approvals of applications. Agency reviewers are available to assist the industry as long as it is done in a professional manner. The Agency is pushing for science based regulations and review practices. Applicants should take advantage of this new paradigm to secure approvals in a timely manner. As described in Sec. 4.8, the quality of submission is critical in securing approval of applications in a timely manner.

8. SUMMARY AND CONCLUSIONS

This chapter has offered some practical ways to develop a science-based, regulatory-friendly application that should be approved at first submission. By focusing on the fundamental scientific principles and FDA and ICH guidances, it is quite feasible to obtain approval of NDAs and ANDAs. In order to obtain approval of NDAs/ANDAs in a timely manner, one should focus on four pillars: (a) development of CMC based on QbD/PAT, (b) application of FDA and ICH CMC regulations and guidances, (c) bridging of phases 1 through 3 to a successful NDA, and (d) preparing sound CMC scientific and regulatory submissions.

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