DRUG PRODUCT PERFORMANCE: CONSIDERATIONS FOR INTERCHANGEABILITY OF MULTISOURCE DRUG SUBSTANCES AND DRUG PRODUCTS

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ABSTRACT

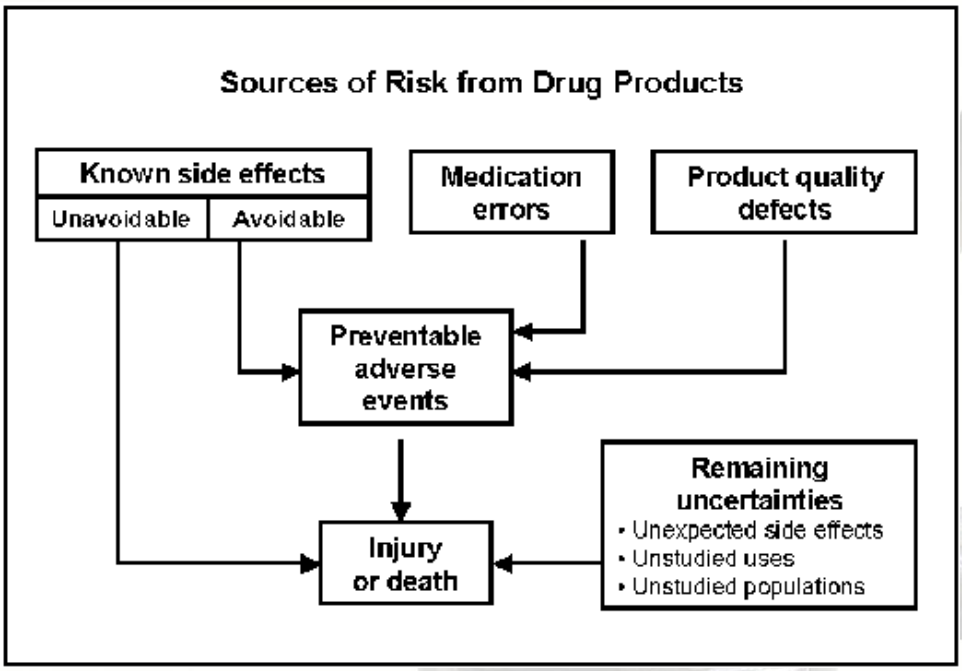
Drug product performance is measured by the release of the active pharmaceutical ingredient (API) from the drug product, leading to bioavailability of the API and achieving a desired therapeutic response. Multisource drug products contain the same API or drug substance and are manufactured in the same dosage form or drug product. Although these APIs and drug products may meet compendial (e.g., USP-NF) monograph standards of strength, quality, purity, and identity, these multisource drug products may not have the same drug product performance, in vivo. Quality standards are important attributes that must be built into the drug product. However, two multisource pharmaceutical equivalent drug products containing the same quality ingredients may not have the same in vivo drug product performance as demonstrated by bioequivalence. Quality performance of the drug product is affected by the physical properties of the active pharmaceutical ingredients, the quality and functionality of the excipients and the manufacturing process. The designation of multisource drug products as therapeutic equivalents for interchangeability (generic substitution) is a matter of governmental regulatory approval. Regulatory approval regulations for interchangeable multisources, does not necessarily mean that generic drug products are identical in all countries. The US Food and Drug Administration (FDA) has very strict rules for the approval and marketing of generic drug products. Only those multisource drug products that are pharmaceutical equivalent, bioequivalent, and therapeutic equivalent and have approval of an appropriate regulatory agency (e.g., FDA or EMEA), may be marketed as interchangeable, substitutable generic drug products.

INTRODUCTION

Multisource drug products are products marketed by more than one manufacturer that contain the same active pharmaceutical ingredient (API) or drug substance in the same dosage form and are given by the same route of administration. Many of these multisource drug products contain drug substances that meet *USP–NF* or other compendial monograph standards of strength, quality, purity, and identity. However, drug substances and drug products that solely meet the same *USP–NF* monograph standards should not be considered automatically as interchangeable products (1, 2). FDA (3) reported that *product quality defects* are an important component in the maintenance of drug product safety (Figure 1). Product quality defects are controlled through

good manufacturing practices, monitoring and surveillance. Drug product quality must be built into the manufacture of drug products. However, even with quality components, the drug product must demonstrate proper in vivo performance for safety and efficacy. Many multisource drug products are now available on the open market and internet websites. Drug product selection and drug product substitution are important responsibilities of the health practitioner to assure the patient is receiving a quality drug product that performs according to the approved product label.

Figure 1 - Types of Risks from Medicines



(Ref: CDER Report to the Nation: 2002, www.fda.gov/cder/reports/rtn/2002/rtn2002-3.HTM)

The objective of this article is to provide an understanding of interchangeability and substitutability of drug substances and drug products that are pharmaceutical equivalents and meet compendial monographs for quality. Additionally, this article provides an understanding of drug product performance and why drug substance and drug product performance are important in the manufacture of interchangeable, therapeutic equivalent, generic drug products including scale-up and post-approval changes (SUPAC) that relate to change(s) in a formulation after market approval.

DRUG PRODUCT PERFORMANCE

Drug product performance may be measured by the release of the active pharmaceutical ingredient (API) from the drug product, leading to bioavailability of the API and achieving a desired therapeutic response. Drug product performance can be measured by *in vivo* or *in vitro* methods. Table 1 differentiates drug product quality and drug product performance attributes. Quality product attributes are built into the product and help assure that the drug product is

manufactured consistently. If a newly manufactured batch meets specifications, the drug product is assumed to have the same drug product performance as the original production batches used in clinical studies and the batch is released for marketing.

Table 1 Drug Product Quality and Performance Attributes

PRODUCT QUALITY

- Chemistry, manufacturing and controls (CMC)
- Microbiology
- Identity, strength, quality, purity and potency of drug product

PRODUCT PERFORMANCE

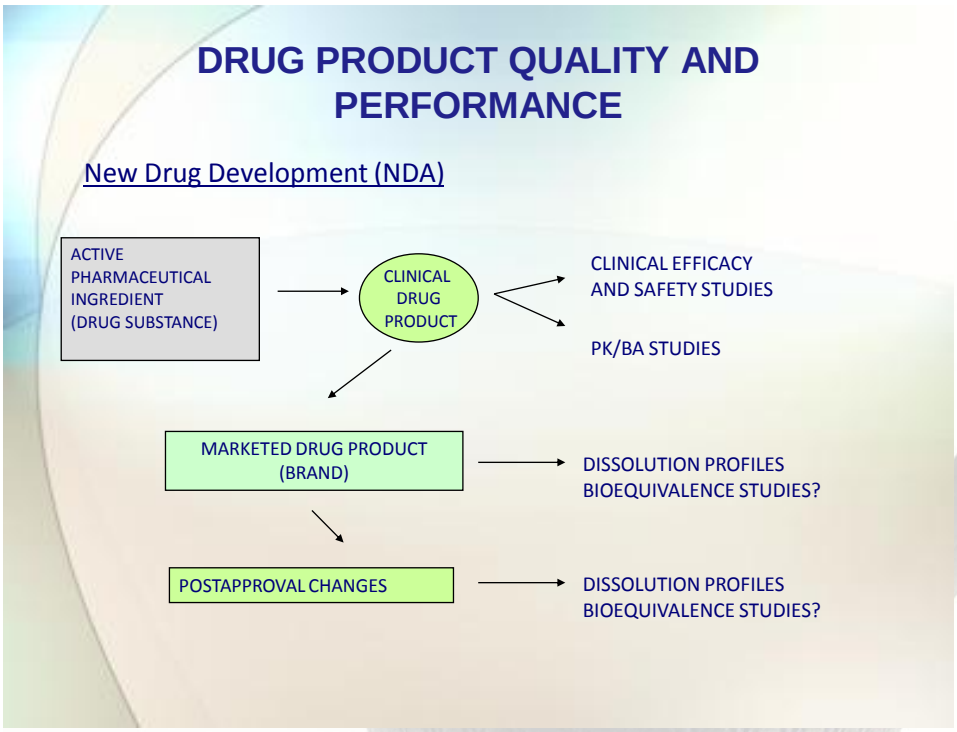
- Drug Product Performance, *In Vivo*
  - Bioavailability and bioequivalence
- Drug Product Performance, *In Vitro*
  - Drug release/drug dissolution

Bioequivalence is an *in vivo* measure of drug product performance. Bioequivalence compares the relative bioavailability of two pharmaceutical equivalent dosage forms. Bioavailability is defined as 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. The approaches for the determination and demonstration of bioequivalence of two pharmaceutically equivalent drug products containing drugs that are systemically absorbed are widely accepted by the scientific and regulatory agencies (4). Generally, the active drug substance and/or active metabolites are quantitatively determine in plasma after the administration of the drug product in normal, healthy subjects using a crossover study design. The basis of bioequivalence is determined by statistical comparison of the values for C_{max} (peak drug concentration) and of the values for $AUC_{(t)}$ -the area-under the curve of plasma drug concentration versus time.

NEW AND GENERIC DRUG PRODUCT DEVELOPMENT

Drug product performance is important in the development of new drug and generic drug products. The initial human safety and efficacy studies during new drug development may use a very simple formulation such as the active ingredient diluted with lactose and placed into a hard gelatin capsule. If the new drug demonstrates appropriate efficacy and safety, the manufacturer of the new drug will begin the development of a *to-be-marketed* drug product (e.g., compressed tablet). Since the initial safety and efficacy studies were performed using a different formulation (i.e., hard gelatin capsule), the sponsor must demonstrate that the *to-be-marketed* drug product has the same drug product performance as the original formulation (Figure 2).

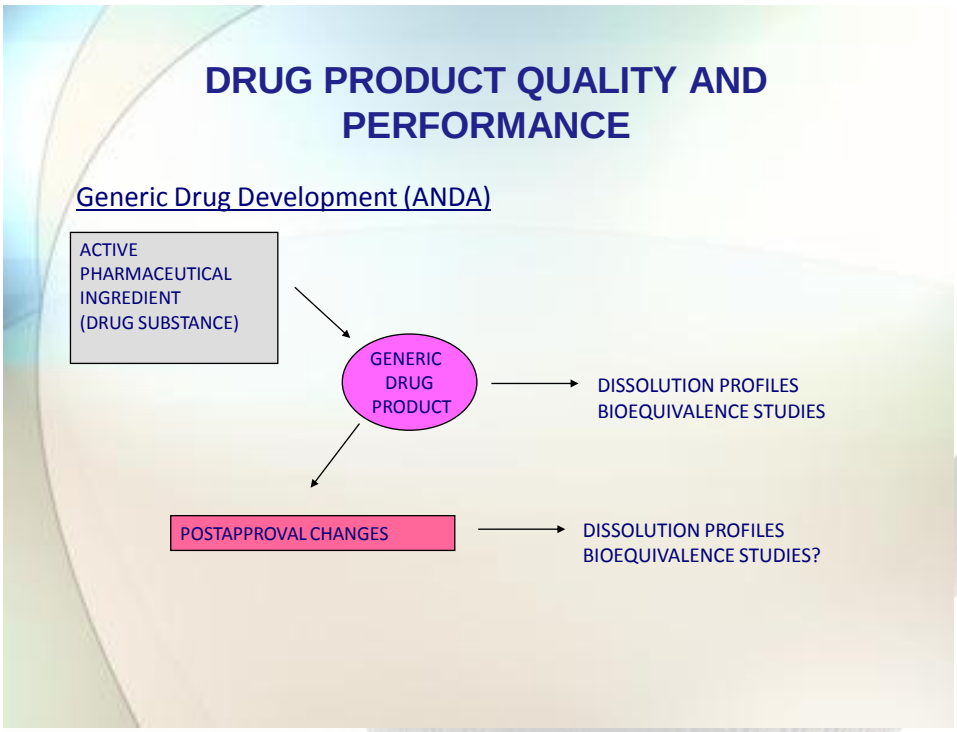
Figure 2



Thus, the marketed drug product that is approved by FDA may not have been used in the original safety and efficacy clinical studies. If this newly approved drug product is successful on the market, the manufacturer may perform several post-approval changes to the market formulation. These post-approval changes, often termed, SUPAC (scale-up and post approval change), could include a change in the supplier of the active ingredient, a change in the formulation, a change in the manufacturing process and/or a change in the manufacturing site (5,6). In each case, the manufacturer must demonstrate that drug product performance did not change and is the same for the drug product before and after the SUPAC change.

Drug product performance is also important in the development of generic drug products (Figure 3). As mentioned above, a generic drug product is a multisource drug product that is a pharmaceutical equivalent to the reference listed drug product (usually the brand or innovator drug product) and has proven equivalent drug product performance. Safety and efficacy clinical studies are not generally performed on generic drug products. Drug product performance comparison for oral generic drug products is usually measured by *in vivo* bioequivalence studies in normal healthy adult subjects under fasted and fed conditions. Drug product performance comparisons, *in vitro* may include comparative drug dissolution/release profiles.

Figure 3



PHARMACEUTICAL EQUIVALENTS

Pharmaceutical equivalence of drug substances and drug products is determined by the relevant regulatory agencies who review the manufacturer's submission that contains experimental evidence that the drug substances meet quality standards and perform similarly as measured by bioequivalence or other tests.

FDA defines *pharmaceutical equivalents* as drug products that contain : a) the same active ingredient(s), b) the same dosage form, c) the same route of administration, d) identical in strength and e) formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), Pharmaceutical equivalents may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling (7). Pharmaceutical equivalence, by itself, does not ensure bioequivalence or therapeutic equivalence.

PHARMACEUTICAL ALTERNATIVES

FDA considers pharmaceutical alternatives as drug products that contain the same therapeutic moiety but are different salts, esters, or complexes of that moiety or are different dosage forms or strengths (7). WHO considers pharmaceutical alternatives as products that contain the same molar amount of the same active pharmaceutical moiety(s) but differ in dosage form (e.g., tablets versus capsules), and/or chemical form (e.g., different salts or esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise

not pharmaceutically equivalent (8). Pharmaceutical alternatives may or may not be bioequivalent or therapeutically equivalent with the comparator product.

Different Salt Forms

Salt forms of drugs such as hydrochloride, phosphate, sulfate, potassium, and sodium, among others, are ionizable substances that have different ionization equilibrium between salt form and non-ionized form. Additionally, different salt forms of the same drug may have different aqueous solubility and may dissolve at different rates. For example, tetracycline phosphate or tetracycline hydrochloride equivalent to 250 mg tetracycline base are considered pharmaceutical alternatives. Sometimes pharmaceutical manufacturers can use different excipients and manufacturing processes to produce pharmaceutical alternatives that may be bioequivalent in vivo in relationship to the active moiety (e.g, tetracycline base) and therefore considered as clinically equivalent to the reference drug product.

Esters and Prodrugs

Prodrugs are often esters of the active pharmaceutical ingredient. Esters of fatty acids such as stearates and palmitates have been used extensively. Generally, the ester prodrug is inactive and must be hydrolyzed to the parent drug to exert its pharmacodynamic activity. Hydrolysis can proceed by enzymatic pathways via esterases in the tissues or plasma or by non-enzymatic means such as acid hydrolysis in the stomach. Both prodrug and the active drug resulting from hydrolysis in the gastrointestinal tract can be systemically absorbed at the same or different rate depending on the permeability of each drug entity. The systemic distribution of the intact pro-drug may differ from the distribution of the active drug. A drug product containing a pro-drug is considered by regulatory agencies as a different drug product compared to a product containing just the active drug substance.

BIOPHARMACEUTIC ASPECTS OF DRUG PRODUCT PERFORMANCE

Biopharmaceutics is the study of the interrelationship of the physical-chemical properties of the drug or a drug product in which the drug is given by a specified route of administration and the rate and extent drug that becomes available at the site of action in the body. The principles of biopharmaceutics is important the design of drug products and directly relates to drug product performance (Table 2).

Table 2 – Biopharmaceutic Considerations in Drug Product Development and Drug Product Performance

Drug Substance

- Chemical attributes of the drug substance
    - Different synthetic route
        - Different in impurity profile

- Different salts or esters
- Physical attributes of drug substance
  - Different polymorphic forms
  - Different particle size and particle size distribution

Drug Product

- Different drug release mechanism
- Different dosage forms
- Different excipients in the formulation
- Different manufacturing process

Drug Substance (Active Pharmaceutical Ingredient, API)

Due to patents and different approaches in chemical or biological synthesis, the drug substance may differ in various physicochemical properties. Depending on the synthetic route and method of purification, some drugs can exist in different polymorphic forms. A manufacturer may obtain a patent for a specific crystalline form of the drug substance. An alternative manufacturer of this drug substance may use a different synthetic route and method of purification, resulting in a crystalline form that is different from the patented form. Different crystalline forms of a drug substance may not have the same physical properties. Similarly, the hydrous form of a drug substance is not chemically and physically identical to its anhydrous form. However, in both of these cases, the two drug substances (e.g., crystalline versus non-crystalline or hydrous versus anhydrous) may be considered pharmaceutical equivalents if their *in vivo* performances are equivalent.

Different crystalline forms may dissolve at different rates, in vitro, and consequently, may affect *in vivo* drug product performance as measured by bioavailability. Generally, crystalline structures are more rigid and thermodynamically stable compared to amorphous forms that dissolve more quickly in vitro as well as in vivo. Particle size and the particle size distribution of the drug may also affect the rate of dissolution. Although mean particle size may be similar, a particle size distribution that contains a larger number of very fine (smaller) particles may dissolve more quickly and may be systemically absorbed more quickly than the same drug substance whose particle size distribution contains a greater number of larger particles. The effect of the physical chemical properties of the drug substance on drug product performance must be considered if the manufacturer of the drug product changes the supplier of the API or the API manufacturer changes the manufacturing process for the API.

Excipients

Drug products are finished dosage forms that contain the active pharmaceutical ingredient along with suitable diluents and/or excipients. Excipients are generally considered inert in that they have no pharmacodynamic activity of their own. However, excipients have different functional purposes and influence the performance of the drug product (9). Compressed tablets may consist of the active ingredient, a diluent (filler), a binder, buffering agents, disintegrating agent, and one

or more lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide), flavors, and sweetening agents may also be present. These excipients provide various functional purposes such as improving compression, improving powder flow, stability of the active ingredient, and other properties (Table 3). For example, diluents, such as, lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose are added where the quantity of active ingredient is small and/or difficult to compress.

The physical and chemical properties of the excipients, the physical and chemical properties of the active pharmaceutical ingredient, and the manufacturing process all play a role in performance of the finished dosage form. Each excipient must be evaluated to maintain consistent performance of the drug product throughout the product's life cycle.

The World Health Organization (WHO) states that "pharmaceutical equivalence does not necessarily imply bioequivalence and therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance" (8). However, amorphous and crystalline drug substances can be bioequivalent when manufactured in the same dosage form (e.g., oral tablet) if a manufacturer uses different excipients and manufacturing processes that produce bioequivalence in vivo.

Table 3. Common excipients for solid oral dosage forms

Excipient	Function in compressed tablet	Possible effect on drug product performance
Microcrystalline cellulose, lactose, calcium carbonate	Diluent	Very low dose drug (e.g, 5 mg) may have high ratio of excipients to active drug leading to a problem of homogeneous blending and possible interaction of drug with excipients
Copovidone, starch, methylcellulose	Binder	Binders give adhesiveness to the powder blend and can affect tablet hardness. Harder tablets tend to disintegrate more slowly.
Magnesium stearate	Lubricant	Lubricants are hydrophobic; over lubrication can slow dissolution of API
Starch	Disintegrant	Disintegrant allows for more rapid fragmentation of tablet in vivo, reducing disintegration time and allowing for more rapid dissolution.
FD&C colors and lakes	Color	
Various	Coating	Coatings may have very little effect (film coat) or have rate controlling effect on drug release and dissolution (e.g., enteric coat)

Manufacturing Process

Quality cannot be tested into drug products. Quality should be built in or should be designed and confirmed by testing. With a greater understanding of the drug product and its manufacturing process, regulatory agencies and pharmaceutical manufacturers are developing a systematic approach to achieve quality and drug product performance (4, 11, 12).

As discussed in ICH Q8 (R1), manufacturing should be based on sound scientific principles. Pharmaceutical development should include, at a minimum, the following elements:

- Defining the target product profile as it relates to quality, safety, and efficacy considering, e.g., the route of administration, dosage form, bioavailability, dosage, and stability
- Identifying critical quality attributes (CQAs) of the drug product so that those product characteristics that have an impact on product quality can be studied and controlled
- Determining the quality attributes of the drug substance and excipients and selecting the type and amount of excipients to deliver drug product of the desired quality
- Selecting an appropriate manufacturing process
- Identifying a control strategy

An enhanced quality by design (QbD) approach to product development additionally would include the following elements:

- A systematic evaluation, understanding, and refining of the formulation and manufacturing process, including:
    - Identifying by, e.g., prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs
    - Determining the functional relationships that link material attributes and process parameters to product CQAs

- Using the enhanced process understanding in combination with quality risk management to establish an appropriate control strategy that can include a proposal for design space(s) and/or real-time release.

Scale-up and Post-approval Changes

Scale-up and Post-approval Changes (SUPAC) relate to change(s) in a formulation after market approval (*4*, *5*). These may include a change in (1) the components or composition, (2) the site of manufacture, (3) the scale-up/scale-down of manufacture, and/or (4) the manufacturing (process and equipment) of a modified-release solid oral dosage form during the post-approval period.

Any scale-up and post-approval change can potentially affect the performance of the finished drug product. Moreover, changes in the manufacture of drug substance or excipients have the

potential to change the performance of the finished dosage form. FDA SUPAC guidances define (1) levels of change, (2) recommended chemistry, manufacturing, and controls (CMC) tests for each level of change, (3) recommended in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change, and (4) documentation that should support the change. The possibility that a change may affect the safety and performance of the drug product is tabulated by levels of change (Table 4).

Table 4: Levels of Change and Their Impact on Drug Product Performance

Change Level	Example	Comment
Level 1	Deletion or partial deletion of an ingredient to affect the color or flavor of the drug product.	Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
Level 2	Quantitative change in excipients greater that allowed in a Level 1 change.	Level 2 changes are those that could have a significant impact on formulation quality and performance.
Level 3	Qualitative change in excipients.	Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. A Level 3 change may require *in-vivo* bioequivalence testing.

The manufacturer must provide evidence that the performance of the product is not impaired because of the change.

INTERCHANGEABILITY OF MULTISOURCE DRUG PRODUCTS

The interchangeability of multisource generic drug products is a major concern for physicians, pharmacists, and others, who prescribe, dispense, purchase, or pay/reimburse for drugs. Because the formulation and method of manufacture of the drug product can affect its bioavailability and stability, the multisource generic drug manufacturer must demonstrate that the generic drug product is bioequivalent and therapeutically equivalent to the reference listed drug.

Generic Substitution and Interchangeability of Multisource Drug Products

Generic substitution is the process of dispensing a different brand or an unbranded therapeutically equivalent drug product in place of the prescribed drug product. The substituted drug product must be approved by the regulatory agency as a therapeutic equivalent. FDA lists therapeutic equivalents in the *Orange Book* (discussed below). In most cases, generic substitution does not require permission from the prescriber if the drug product has been approved by FDA and is listed as a therapeutic equivalent.

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. FDA classifies as therapeutically equivalent those products that meet the following general criteria:

- they are approved as safe and effective
- they are pharmaceutical equivalents because they
    - contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and
    - meet compendial or other applicable standards of strength, quality, purity, and identity
- they are bioequivalent because
    - they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or
    - if they do present a known or potential problem, they are shown to meet an appropriate bioequivalence standard
- they are adequately labeled
- they are manufactured in compliance with cGMP regulations.

WHO and certain countries may have different definitions of therapeutic equivalence. Drug products that are approved for marketing as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

Orange Book

FDA publishes *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the *Orange Book* (7). The *Orange Book* identifies drug products approved under the 1938 Federal Food, Drug, and Cosmetic Act by FDA on the basis of safety and effectiveness and contains therapeutic equivalence evaluations for approved multisource prescription drug products. The Orange Book does not include drugs approved under the Public Health Service Act (biologics), pre-1938 drugs, or drugs approved by FDA only on the basis of safety (those covered by the so-called ongoing DESI review). *Orange Book* evaluations serve as public information and advice to health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs.

Reference Listed Drug

The reference listed drug (RLD) is identified by FDA as the drug product on which an applicant relies when seeking approval of an Abbreviated New Drug Application (ANDA). The RLD generally is the brand-name drug that has been approved on the basis of a full New Drug Application (NDA) with substantial evidence of safety and efficacy. FDA designates 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 counterparts. Such variations could result if generic drugs were compared to different RLDs.

Therapeutic Equivalence Evaluations Codes

The Orange Book ratings provide the health practitioner a guide to generic drug substitution. The coding system for therapeutic equivalence evaluations in the *Orange Book* allows users to determine quickly whether FDA has evaluated a particular approved product as therapeutically equivalent to another pharmaceutically equivalent products (first letter) and provides additional information about the basis of FDA's evaluations (second letter) (Table 5). With few exceptions, the therapeutic equivalence evaluation date is the same as the approval date.

Table 5 - Orange Book Codes for Nifedipine Extended Release Tablets

TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
AB1	Yes	Nifedipine Tablet	Extended Release; Oral	90mg	Adalat Cc	Bayer Pharms
AB1	No	Nifedipine Tablet	Extended Release; Oral	90mg	Nifedipine	Biovail
BX	No	Nifedipine Tablet	Extended Release; Oral	90mg	Nifedipine	Martec USA LLC
AB2	Yes	Nifedipine Tablet	Extended Release; Oral	90mg	Procardia XL	Pfizer
AB2	No	Nifedipine Tablet	Extended Release; Oral	90mg	Nifedipine	Osmotica Pharm

Two separate branded Nifedipine Extended Release Tablet formulations (Adalat Cc and Procardia XL) are approved by FDA and are listed as separate RLD indicated by "Yes". A generic nifedipine extended release tablet formulation may be bioequivalent to one of the nifedipine extended release tablet formulation as indicated by AB1. The AB1 product is not interchangeable with the AB2 product.

The two basic categories into which multisource drugs have been placed are indicated by the first letter:

- Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products. These are drug products for which there are no known or suspected bioequivalence problems. These are designated AA, AN, AO, AP, or AT, depending on the dosage form.

- Actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence. These are designated AB.

FDA at this time considers some drug products not to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients. These are designated BC, BD, BE, BN, BP, BR, BS, BT, BX, or B*. The *Orange Book* should be consulted for a complete listing of therapeutically equivalent drug products.

Pharmaceutically Equivalent Drug Products

Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, are administered by the same route of administration, and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5-mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, and preservatives), expiration time, and, within certain limits, labeling.

Pharmaceutically equivalent or pharmaceutically alternative products may or may not be therapeutically equivalent. Only multisource pharmaceutical drug products that are approved by the regulatory agency as therapeutically equivalent are interchangeable. An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

Pharmaceutical Alternatives

Pharmaceutical alternatives are drug products that 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, 250-mg capsules versus tetracycline phosphate complex, 250-mg capsules; quinidine sulfate, 200-mg tablets versus quinidine sulfate, 200-mg capsules). Different dosage forms and strengths within a single manufacturer's product line are thus pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient.

Capsules versus Tablets

The bioavailability of the same drug substance from a tablet compared to another tablet may demonstrate bioequivalence. However, FDA currently considers a tablet and capsule containing the same active ingredient in the same dosage strength as pharmaceutical alternatives, and the two dosage forms cannot be interchanged. In contrast, several countries have concluded that bioequivalent capsules and tablets containing the same active ingredient in the same dosage strength are therapeutic equivalents and therefore can be interchanged.

Pharmaceutical Substitution

Pharmaceutical substitution is the process of dispensing a pharmaceutical alternative for the prescribed drug product. This occurs, for example, if ampicillin suspension is dispensed in place of ampicillin capsules or if tetracycline hydrochloride is dispensed in place of tetracycline phosphate. Pharmaceutical substitution generally requires the physician's approval.

Therapeutic Alternatives

Therapeutic alternatives are drug products that contain different active ingredients and are indicated for the same therapeutic or clinical objectives. Active ingredients in therapeutic alternatives are from the same pharmacologic class and are expected to have the same therapeutic effect when administered to patients for identical indications. In such cases, for example, ibuprofen may be given instead of naproxen, and cimetidine may be given instead of ranitidine.

Therapeutic Substitution

Therapeutic substitution is the process of dispensing a therapeutic alternative in place of the prescribed drug product. For example, amoxicillin may be dispensed instead of ampicillin for the treatment of a Staphylococcus infection or ibuprofen may be dispensed instead of naproxen for the treatment of pain. Therapeutic substitution also can occur when one NDA-approved drug is substituted for the same drug that has been approved by a different NDA, e.g., the substitution of Nicoderm® (nicotine transdermal system) for Nicotrol® (nicotine transdermal system).

Because these drug products are not therapeutic equivalents as defined above, they may not be marketed or labeled as interchangeable. Generally, the prescriber must be notified before a substitution is performed. However, in certain institutions such as in a hospital or nursing facility, a formulary may list drug products that can be interchanged without the need to contact the physician. In this case, a pharmacy and therapeutics committee has reviewed the products in the formulary and has listed those products that can be substituted.

CONCLUSIONS

USP–NF contains science-based standards for drugs, biologics, dietary supplements, and excipients used in dosage forms and products. A *USP–NF* monograph for an official substance or preparation includes applicable standards of strength, quality, purity, and identity, including the article's definition, and packaging, storage, and other requirements and specifications.

Multisource drug products may contain drug substances and drug products that meet *USP–NF* monograph standards of strength, quality, purity, and identity. Pharmaceutical equivalence per se does not ensure equivalent drug product performance as demonstrated by bioequivalence, nor does it ensure therapeutic equivalence. The approval of interchangeability of multisource, generic drug products depends on the review of an appropriate application (e.g., an ANDA) by an appropriate regulatory agency such as FDA.

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18 November 2010