The New Drug Approval Process: Basic Concepts

April 20, 2021

FDLI

Agenda

- What is a Drug?
- What is a New Drug?
- Legal Standard for Approval of New Drugs
- New Drug Approval Pathways

What is a Drug?

- Statutory and Regulatory Definitions
- The Key Principle: Intended Use
- Distinguishing Between Drugs and Other FDA Regulated Products

Statutory Definition of “Drug”

- Articles that are:
  - Recognized in USP, HPUS, NF
  - Intended for use in diagnosing, curing, mitigating, treating, or preventing disease
  - Intended to affect the structure or function of the body (but not a food)
  - Intended for use as a component of any of the above

FDCA 201(g)

Key Regulatory Definitions

- **Drug substance:** An active ingredient intended to furnish pharmacological activity or other direct effect in diagnosing, curing, mitigating, treating, or preventing disease, or to affect the structure or function of the body.
- **Drug product:** A finished dosage form (e.g., tablet, capsule, solution) that contains a drug substance, usually in association with other ingredients.

  21 CFR 314.3

Key Regulatory Definitions

- **Active ingredient:** The component intended to furnish pharmacological activity or other direct effect in diagnosing, curing, mitigating, treating, or preventing disease, or to affect the structure or function of the body.
- **Active moiety:** The molecule or ion, excluding portions that cause the drug to be an ester, salt, or other noncovalent derivative of the molecule, responsible for the physiological or pharmacological action.

  21 CFR 314.3

Intended Use

- Evidence of intended use
  - Expressions of the person responsible for labeling or circumstances surrounding the product's distribution
  - Look to, e.g., labeling claims, advertising, statements by company or its representatives
  - Can include circumstances under which the product is offered or used, but not labeled or advertised, if with manufacturer's knowledge
  - Manufacturer with knowledge that drug "is to be used" for a use other than manufacturer's intended uses must provide labeling for that use

Drug vs. Other FDA Regulated Products

- **Biologic:** Similar to a drug, is "applicable to the prevention, treatment, or cure of a disease or condition of human beings"

  PHSA 351(i)(1)

  - Approved and regulated under the Public Health Service Act, but also subject to the FDCA
  - Some products that fall within the definition of "biological product" were approved as drugs, but were deemed to be licensed as biologics in March 2020

Drug vs. Other FDA Regulated Products

- **Medical Device:** Like a drug, is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect structure/function of the body (FDCA 201(h))
  - Distinguished from a drug in that it does not achieve its primary intended purposes through chemical action within or on the body, or by being metabolized

Drug vs. Other FDA Regulated Products

- **Combination Product:** One of several types of products:
  - A product comprised of two or more regulated components (drug/device, biologic/device, drug/biologic, drug/device/biologic) that are combined or mixed and produced as a single entity
  - Two separate products that are packaged together; or
  - Separately packaged products that are labeled for use with each other

  FDCA 503(g); 21 CFR 3.2(e)
- The product's primary mode of action determines which FDA component has primary responsibility for product review

Drug vs. Other FDA Regulated Products

- **Food:** Articles used for food or drink, chewing gum, components of any such article (FDCA 201(f))
  - Per statutory definition of "drug," can be intended to affect the structure or function of the body
  - Specifically permitted health claims may be made, e.g., diets low in saturated fats and cholesterol may reduce the risk of heart disease (FDCA 403(r); 21 CFR 101 Subpart E)
  - "Medical food" is intended for use under physician's supervision for the dietary management of a disease or condition with distinctive nutritional requirements (21 USC 360ee(b)(3); 21 CFR 101.9(j)(8))

Drug vs. Other FDA Regulated Products

- **Dietary Supplement:** Product intended to supplement the diet that contains certain types of ingredients (e.g., vitamin, mineral, herb) and is intended for ingestion (FDCA 201(ff))
  - Can include products approved as drugs, if previously marketed as dietary supplement or food
  - Are permitted to have structure/function claims, with a disclaimer of no FDA review

Drug vs. Other FDA Regulated Products

- **Cosmetic:** Article intended to be applied to, or introduced into, the body to cleanse (but not a soap), beautify, promote attractiveness or alter appearance (FDCA 201(i))
  - Claims of effect on structure/function can be problematic, which is why you see claims to "reduce *the appearance of* wrinkles and fine lines"
  - FDA has taken the position that the presence of certain ingredients that are active ingredients in drugs make a product a drug, regardless of claims

Drug vs. Other FDA Regulated Products

- **Tobacco:** Product made or derived from tobacco and intended for human consumption, or any component, part or accessory, but not any such product that meets the statutory definition of drug, device or combination product (FDCA 201(rr))

Drug vs. Other FDA Regulated Products

- **Animal Drug:** Included within the statutory definition of "drug," which includes products intended for use in animals (FDCA 201(g))
  - Includes drugs intended for use in animals in the food chain, in animal feed, and in pets
  - Subject to separate standards regarding approval and other regulatory standards

What is a New Drug?

- Statutory Definition
- Grandfathered Drugs
- DESI Drugs
- Rx/OTC Drugs

Statutory Definition of “New Drug”

- A drug that is:
  - Not generally recognized by experts as safe and effective (GRAS/E), or
  - GRAS/E as a result of clinical data, but that has not been used to a material extent or for a material time

  21 USC 201(p)
- Does not include “grandfathered” drugs
- Most drugs that have not been approved

Grandfathered Drugs

- Drugs that were marketed under authority of the Food and Drugs Act of June 30, 1906, before enactment of the Food, Drug, and Cosmetic Act of 1938, the labeling of which "contained the same representations concerning its conditions of use" as the current labeling (FDCA 201(p))
- FDA interprets this very narrowly, such that very few drugs, if any, meet the standard
- Differences in formulation, dosage or strength, dosage form, route of administration, indications, or intended patient population render a product not grandfathered, in FDA's view
  - FDA Guidance: *Marketed Unapproved Drugs – Compliance Policy Guide Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs* (Sept. 2011)

DESI Drugs

- 1938 Act required demonstration of safety for approval, and allowed products that were “identical, related or similar” to an approved product to come to market without their own approval
- 1962 amendments to FDCA required proof of effectiveness, in addition to safety, and required all new drugs to have a product-specific NDA approval
- Products approved before 1962 (as safe) now had to be reviewed for effectiveness
  - Drug Efficacy Study Implementation (DESI) was the process for that review
  - Still ongoing more than 50 years later
  - As a matter of enforcement discretion, FDA does not pursue those products except in certain circumstances

Rx/OTC Drugs

- Default under FDCA is for products to be available OTC
- Prescription requirement is imposed if FDA determines that the product is not safe to use except under a healthcare practitioner's supervision, due to the product's toxicity or other potential harmful effect, method of use, or collateral measures (FDCA 503(b))
- Rx drugs that are new drugs – like all new drugs – require an approved application (NDA, ANDA, BLA)
- Some OTC drugs also require a product-specific approval to be marketed

Rx/OTC Drugs

- As part of the DESI review, FDA created a monograph system, under which certain categories of OTC drugs are determined to be GRAS/E under defined circumstances, and therefore not “new drugs”
- Groupings by therapeutic category, with active ingredients, strengths, dosage form, labeling defined
- Products that meet criteria are not “new drugs” and therefore do not require an approved application
- OTC monograph reform was enacted in 2020 as part of the CARES Act

Legal Standards for Approval of New Drugs

- Demonstrating Safety and Effectiveness
- Substantial Evidence
- Risk/Benefit Analysis

Demonstrating Safety and Effectiveness

- NDA must contain:
  - Preclinical and clinical data demonstrating that the product is safe and effective for the proposed use
  - Information about components of the product and its formulation
  - Detailed discussion of the manufacturing methods and facilities
  - Proposed labeling

FDCA 505(b)

Substantial Evidence

- FDA cannot approve an NDA if the agency determines that the application does not adequately demonstrate the product's safety for the intended use, or if "there is a lack of substantial evidence" that the drug is effective (FDCA 505(d)(5))
  - "Substantial evidence" means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts . . . On the basis of which it could fairly and responsibly be concluded by such experts" that the drug will be effective (FDCA 505(d))
  - Typically, this means at least two Phase III clinical trials, but the standard can be met by a single study "and confirmatory evidence" (id.)

Risk/Benefit Analysis

- Safety and effectiveness are not absolute
  - FDA balances the benefits and risks, in essence asking whether the product is sufficiently safe, given its effectiveness, or sufficiently effective, given its safety profile
  - FDA regulations explain that "[w]hile the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards." 21 CFR 314.105(c)

New Drug Approval Pathways

- Full New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- 505(b)(2) NDA

“Full” NDA → 505(b)(2)NDA → ANDA

- **Full NDA:** All data and information necessary to demonstrate safety and effectiveness are the sponsor’s, or the sponsor has obtained a right of reference to the data/information
- **505(b)(2) NDA:** Some data/information proving safety and effectiveness are not the sponsor’s, and the sponsor hasn’t obtained a right of reference
  - Typically rely on data in an already approved product to which the proposed product is similar, but can rely on literature
  - Provide additional, product-specific information to bridge the gap between the products

"Full" NDA → 505(b)(2)NDA → ANDA

- **ANDA:** Demonstrating sameness to an approved reference listed drug (RLD), from which safety and effectiveness of RLD is extrapolated to the generic product
  - Product generally must have the same active ingredient, in the same strength, dosage form, route of administration, same labeling, and be shown to be bioequivalent
  - There are exceptions permitted, e.g., "suitability petition" ANDA or labeling carve-out, but generally an approved generic is "A" rated to the RLD, which allows for substitution (under state law) at the pharmacy

Questions?

Bert Lao

Hogan Lovells

bert.lao@hoganlovells.com

+1 310 785 4712