The New Drug Approval Process: Basic Concepts

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Overview of Basic Concepts

- 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 Definition of "Drug"
21 U.S.C. § 321(g)(1)

- The Federal Food, Drug, and Cosmetic Act ("FDCA") defines "drug" to include:
  - (A) "articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them";
  - (B)"articles **intended for use** in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals";
  - (C) "articles (other than food) **intended to** affect the structure or any function of the body of man or other animals"; and
  - (D)"articles intended for use as a component of any article specified in clause (A), (B), or (C)"

Statutory Definition of "Animal Drug" 21 U.S.C. § 321(v)

- Animal drugs are meet the statutory definition of drugs
  - e.g., "articles (other than food) intended to affect the structure or any function of the body of man **or other animals**"
- "New animal drug" means "any drug intended for use for animals other than man"
  - Includes, in certain circumstances, animal feed

Statutory Definition of "Biological Product" 42 U.S.C. § 262(i)

- Defined in the Public Health Service Act ("PHSA")
  - "A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the **prevention, treatment, or cure of a disease or condition** of human beings"
- Generally biological products meet the definition of a "drug" in the FDCA
- Biological products may be produced through biotechnology in a living system (e.g., plant or animal cell), and have more complex structures than small molecule drugs, and therefore are often more difficult to characterize than small molecules

Other Drug Concepts and Definitions

- FDA regulations and guidance identify other key concepts, including, but not limited to:
  - "New drug" (21 U.S.C. § 321(p))
  - "Same drug" (21 C.F.R. § 316.3(b)(14))
  - "Drug product" (21 C.F.R. § 314.3)
  - "Drug substance" (21 C.F.R. § 314.3)
  - "Listed drug" (21 C.F.R. § 314.3)

Intended Use

- Key concept for how FDA regulates (and therefore, for regulatory stakeholders and practitioners)
- A product's intended use is an important threshold question that typically determines the FDA regulatory requirements applicable to a product
  - Statutory definition of a drug includes "articles **intended for use** in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" or "**intended to** affect the structure or any function of the body of man or other animals"

Intended Use

- A product's "intended use" is determined by the objective intent of the persons legally responsible for the product, including as shown by "labeling claims, advertising matter, or oral or written statements by such persons or their representatives" (21 C.F.R. § 201.128)
  - "Labeling" is defined broadly to include all labels and other written, printed, or graphic matter "accompanying" an article, and has been interpreted broadly to include, e.g., social media

Intended Use

- Examples of potential evidence of “objective intent”:
  - Labeling claims
  - Advertising matter
  - Oral or written statements by manufacturers, sponsors, or their representatives
  - Design or composition of the article
  - Circumstances surrounding distribution
  - Web sites, social media, medical pamphlets
  - Knowledge of circumstances that it is used by health care providers (“HCPs”) for another purpose

Drugs versus other FDA-Regulated Product Categories

Drugs versus other FDA-Regulated Product Categories

- Determines the applicable FDA regulatory framework(s)
  - Drug or device, or both?
  - Drug or cosmetic, or both?
  - Etc.

Statutory Definition of "Device"
21 U.S.C. § 321(h)

- "An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is —
  - recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
  - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

Device vs. Drug

- Key distinction between drugs and devices is the primary intended purpose
  - In effect, a question of the product's characteristics, mechanism of action, and intended use
- CDER and CDRH have entered into intercenter agreement concerning jurisdictional issues

Statutory Definition of "Cosmetic" 21 U.S.C. § 321(i)

- "Articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and articles intended for use as a component of any such articles; except that such term shall not include soap."
- E.g., skin moisturizer, perfume, lipstick, nail polish, eye and facial makeup, cleansing shampoo, hair color, and deodorant

Cosmetic vs. Drug

- Thus, whether a product is a drug or cosmetic (or both) will hinge on the product's intended use
  - Intended to treat, diagnose, or cure, or to affect the structure or function of the body?
  - Intended to cleanse, beautify, promote attractiveness, or alter the appearance?

Statutory Definition of "Food"
21 U.S.C. § 321(f)

- "Articles used for food or drink for man or other animals"
- "Chewing gum"
- "Articles used for components of any such article"

Food vs. Drug

- Statutory definition of “drug” includes articles intended to affect the structure or function of the body but expressly excludes food
- However, FDA considers putative ‘food’ products marketed with drug claims (i.e., for the diagnosis, cure, mitigation, treatment, or prevention of disease) to be drugs
  - E.g., Warning Letter for Cheerios claim to “lower . . . Cholesterol 4% in 6 weeks”

Statutory Definition of "Dietary Supplement" 21 U.S.C. § 321(ff)

(1) "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in . . . (A), (B), (C), (D), or (E)"

(2) "labeled as a dietary supplement" and either "intended for ingestion" or "not represented for use as a conventional food or as a sole item of a meal or the diet"

(3) Can include an article that is "approved as a new drug" or "licensed as a biologic" if previously "marketed as a dietary supplement or as a food"

Dietary Supplement vs. Drug

- Distinction between a drug and dietary supplement is based on intended use
- Products that qualify as dietary supplements are permitted to be marketed with health claims, qualified health claims, or a subset of structure-function claims (as distinct from disease claims) that would otherwise render the products drugs under the FDCA
  - Permitted structure-function claims should generally be limited to descriptions of natural functions of the body, and avoid reference to specific diseases or conditions
  - Health claims: express or implied characterizations of a relationship between a nutrient and a disease or health-related condition

Statutory Definition of "Tobacco Product" 21 U.S.C. § 321(rr)

- "Any product made or derived from tobacco or containing nicotine from any source that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product)."
- "The term 'tobacco product' does not mean an article that is a drug . . . , a device . . . , or a combination product . . ."
- "A tobacco product shall not be marketed in combination with any other [FDA-regulated] article or product . . . (including a drug, biologic, food, cosmetic, medical device, or a dietary supplement)"

Tobacco Product vs. Drug

- If a product made or derived from tobacco or containing nicotine otherwise meets the definition of a drug (i.e., has an intended use that renders the product a drug), it is regulated as a drug
  - E.g., Nicorette or other nicotine products marketed with smoking cessation claims
- However, conventionally-marketed tobacco products (i.e., not marketed for therapeutic purposes) are not drugs or medical devices
  - *Sottera, Inc. v. FDA*

What is a New Drug?

Statutory Definition of "New Drug" 21 U.S.C. § 321(p)

- "The term 'new drug' means—
  - (1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug [i] is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . "; or
  - (2) ". . . as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions"

Statutory Scheme

- The FDCA prohibits the introduction into interstate commerce of any adulterated or misbranded drug or any drug in violation of 21 U.S.C. §355 (21 U.S.C. § 355)
- In turn, 21 U.S.C. § 355 provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless approval of an application [i.e., a New Drug Application or Abbreviated New Drug Application] is effective with respect to such drug"

Statutory Framework

- The FDCA prohibits the introduction into interstate commerce of any adulterated or misbranded drug or any drug in violation of 21 U.S.C. §355 (21 U.S.C. § 355)
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Evolution of Premarket Review

- Federal Food, Drug, and Cosmetic Act of 1938
  - Established premarket review of New Drug Applications
  - New drugs evaluated for safety; required submission of safety data before marketing
- Drug Amendments of 1962 / Kefauver-Harris Act
  - Premarket notification replaced by premarket approval, based on demonstration of safety *and* efficacy
    - Previously, FDA could exercise authority over therapeutic claims pursuant to its misbranding authority
  - Drug Efficacy Study Implementation (DESI) review

Exceptions to Premarket Review Requirement

- GRAS & GRAE (“GRASE”) products excluded from the definition of “new drug”
- Grandfathered (pre-1938)
- DESI Review (pre-1962)

DESI Drugs

- Framework for FDA's review of post-Kefauver-Harris Act drugs
  - DESI drugs are those subject to FDA-approved NDA between 1938 and 1962
  - Permitted to remain on the market while FDA reviews efficacy
    - FDA will classify the drug as either effective, lacking substantial evidence of effectiveness, or requiring further study
      - If If classified as effective for one or more labeled indication, product can be marketed for those indications, applicant must submit a supplement to the original pre-1962 application
      - If classified as lacking substantial evidence of effectiveness, FDA will provide notice of an opportunity for a hearing
    - Drugs marketed as identical, similar, or related to a DESI drug subject to same framework

Marketed Unapproved Drugs

- Enforcement priorities for lack of premarket approval:
  - Drugs with potential safety risks
  - Drugs that lack evidence of effectiveness
  - Health fraud drugs (i.e., promoted as effective but which have not been scientifically proven safe and effective for such purposes)
  - Drugs that present direct challenges to the new drug approval or OTC monograph systems
    - E.g., unapproved drugs that compete directly with new drugs, or that are marketed in violation of a final OTC monograph
  - Unapproved drugs that are also violative of the FDCA in other ways
    - E.g., cGMP violations
  - Drugs that are reformulated to evade an FDA enforcement action

Legal Standard for Approval of New Drugs

Legal Standard for Approval of New Drugs

- Substantial evidence of safety and effectiveness under the conditions of use prescribed, recommended, or suggested in the labeling
- Methods used in, and facilities and controls used for, the manufacture, processing and packaging are adequate to preserve its identify, strength, quality and purity
- Labeling is not false or misleading in any particular

Substantial Evidence of Effectiveness

- FDA will deny an application if it lacks "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling"

Adequate and Well-Controlled Studies

- FDA has generally interpreted substantial evidence to require two adequate and well-controlled clinical investigations
  - However, FDA can approve based on evidence from other than two clinical investigations
  - E.g., accelerated approval framework
- Strength of evidence and methods of assessment in each trial assessed by FDA
  - Statistically significant result or high posterior probability of effectiveness
  - Statistical approaches should be specified in advance
  - Methods should be well-defined and reliable based on appropriate endpoints

Safety Evaluation

- FDA will deny and application if the application fails to contain “adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling” (21 U.S.C. § 355(d))
- FDA will weigh the risks and benefits of the drug in assessing the application
  - Specifically, FDA is required to implement a “structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks” (21 U.S.C. § 355(d))

New Drug Approval Pathways

New Drug Approval Pathways

- Investigational New Drug Application (“IND”)
  - Not an approval pathway
- 505(b)(1) New Drug Application (“NDA”)
- 505(b)(2) NDA
- Abbreviated New Drug Application (“ANDA”)
- New Animal Drug Applications (“NADAs”) and Abbreviated NADAs (“ANADAs”)
- Biologics and Biosimilars (Biologics License Application (“BLA”) and 351(k) biosimilars applications)
- Emergency Use Authorization (“EUA”)
- Animal Rule Approval
- Limited Population for Antibacterial and Antifungal Drugs

IND

- IND application must be submitted and allowed by FDA to proceed before human clinical trials may begin in the U.S.
  - IND automatically becomes effective 30 days after receipt by FDA unless FDA raises concerns or questions
- IND application will contain the results of preclinical tests (e.g., in vitro or in vivo animal testing), together with manufacturing information, analytical data, and any other available clinical data or literature
- IND application will describe plans for human clinical trials, and clinical trial and other information is submitted to IND

IND

- Investigational new drugs for which an IND is in effect are exempt from otherwise applicable approval requirements
  - May be shipped lawfully for the purpose of conducting clinical investigations
- Sponsor or investigator may not represent in a promotional context that an investigational new drug is safe or effective for the indication for which it is investigational
- Other reporting and labeling requirements
  - E.g., IND safety reporting requirements

Clinical Trials

- Phase 1
  - Generally involve a small number of healthy volunteers or disease-affected patients who are initially exposed to a single dose and then multiple doses of the product candidate
- Phase 2
  - Involve studies in disease-affected patients to evaluate proof of concept and/or determine the dose required to produce the desired benefits
- Phase 3
  - Generally involve a large number of patients at multiple sites and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit/risk relationship of the product and provide an adequate basis for product labeling

505(b)(1) NDA – 21 U.S.C. § 355(b)(1)

- New Drug Application must contain, among other things
  - Full reports of investigations of the drug (to assess whether safe and effective for intended use)
  - Manufacturing and processing descriptions and data
  - Labeling specimens
  - Patent number(s) and expiration date(s)
  - User fee
- Patent and Non-Patent Exclusivity
  - E.g., patent extension, orphan drug exclusivity, new chemical entity exclusivity, new clinical investigation exclusivity

505(b)(2) NDA – 21 U.S.C. § 355(b)(2)

- NDA pathway that allows applicants to reference and rely upon information and data from studies not conducted by the applicant and for which the applicant has not obtained a right of reference for use from the person for whom the investigations were conducted
  - E.g., published literature or approved NDAs
- Designed to be a shorter, less onerous application that a full NDA

505(b)(2) NDA

- Examples circumstances in which a 505(b)(2) may be used:
  - Modification to indication or dosage form of listed drug
  - Seeking approval of drug historically marketed as unapproved new drug
- 505(b)(2) NDAs automatically considered to rely upon approval for pharmaceutically equivalent approved drugs
- Remains subject to certain user fees, potential patent and non-patent exclusivities

ANDA

- Abbreviated approval pathway for generic drugs
  - Created by The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act")
- Applicant must demonstrate bioequivalence to the Reference Listed Drug ("RLD")
- Product must generally have the same route of administration, dosage form, strength, labeling and intended use as the RLD
- Complex patent provisions and potential to trigger litigation (e.g., paragraph IV certification)
  - Hatch-Waxman also established a framework whereby pioneer drug applicants must include in their NDAs information about patents for the drug products
  - Approved Drug Products With Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book, identifies drug products that have been approved by FDA, along with patent and exclusivity information related to approved drug products

ANDA

- ANDA, absent limited exceptions, must contain information to show:
  - The conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a listed drug (i.e., the RLD)
  - The active ingredient is the same as the RLD
  - The route of administration, dosage form, and strength are the same as the RLD
  - Bioequivalence to the RLD
  - The proposed labeling is the same as that of the RLD
- Must contain user fee and relevant patent certifications

Emergency Use Authorization ("EUA")

- FDA may, under delegated authority from the Secretary of HHS, allow for emergency use of a product that does not otherwise comply with the FDA premarket approval framework
  - Specifically, FDA may authorize emergency use of a product upon a declaration by the Secretary of HHS that the circumstances exist to justify the authorization (e.g., declaration of emergency declared by DHS, DOD, HHS, or other material threat pursuant to the PHSA sufficient to affect national security or health and security of U.S. citizens).
- FDA may then authorize the unapproved product or unapproved use, provided that:
  - (1) the chemical, biological, radiological, or nuclear threat agents ("CBRN") that are referred to in the EUA declaration can cause serious or life-threatening diseases or conditions;
  - (2) based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the disease or condition attributable to the CBRN and that the product's known and potential benefits outweigh its known and potential risks; and
  - (3) there is no adequate, approved, and available alternative to the product
- Products subject to an EUA must still comply with the conditions of the EUA, including labeling and marketing requirements
- EUAs are limited to the period of time the EUA declaration is in effect

Animal Rule Approval

- Allows for the approval of drugs and licensure of biological products **when human efficacy studies are not ethical** and field trials to study the effectiveness of drugs/biologics are not feasible
- Intended for drugs/biologics developed to reduce or prevent serious or life-threatening conditions caused by **exposure to lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances**; and critical for the protection of public health and national security
- Efficacy is based on adequate and well-controlled **studies in animal models** of the human disease or condition of interest, and safety is evaluated under the preexisting requirements for drugs/biologics
- The regulations are found at 21 C.F.R. §§ 314.600-650 for drugs; 21 C.F.R. §§ 601.90-95 for biologics; effective July 1, 2002
- The Center for Drug Evaluation and Research (“CDER”) has approved twelve products (e.g., for soman nerve agent poisoning, cyanide poisoning, smallpox, etc.) under the Animal Rule
- The Center for Biologics Evaluation and Research (“CBER”) has approved three products (for botulism and anthrax) under the Animal Rule

Limited Population Pathway for Antibacterial and Antifungal Drugs ("LPAD")

- Approval pathway to treat serious and life-threatening infections in a limited population of patients with unmet needs
  - Must meet drug approval standards
  - Separate written request by applicant
- Permits approval even though data is not sufficient to conclude a favorable risk-benefit analysis in a broader population
- Prominent labeling for "Limited Population"
- Pre-review of promotional materials
- Only two approved by FDA (for specific type of TB and lung disease)
- Since December 2016 – 21st Century Cures Act

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