Section III. The New Drug Approval Process: Basic Concepts

FDLI - Introduction to Drug Law and Regulation
November 9, 2020

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Overview of Section III, Basic Concepts

- What is a Drug?
- What is a New Drug?
- Legal standard for approval of New Drugs
- New Drug approval pathways

Statutory Definition of "Drug"
21 USC § 321(g)(1)

- Articles recognized in an Official Compendia
- Intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals
- Intended to affect the structure or any function of the body of man or animal
- Any component of items 1-3 above
- Excludes properly-labeled food and dietary supplement

Food – 21 USC § 321(f)
(Also FDC Act Section 201(f))

- Articles used for food or drink for man or other animals
- Chewing gum
- Components of food or drink

Dietary Supplement – 21 USC § 321(ff)

- A product intended to supplement the diet, containing:
  - Vitamin, mineral, herb or other botanical, or amino acid
  - Dietary substance to supplement the diet by increasing the total dietary intake
  - A concentrate, metabolite, constituent, extract or combination of the above
- Intended for ingestion **(not topical)**
- Not represented for use as a conventional food, or as a sole item of a meal or the diet
- Labeled as a dietary supplement
- Can include an article that is also approved as a new drug if previously marketed as a dietary supplement or food
- Subset of “food” category

Cosmetic - 21 USC § 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
- E.g., skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, cleansing shampoos, permanent waves, hair colors, and deodorants, as well as any substance intended for use as a component of a cosmetic product
- Exception: soap

Device – 21 USC § 321(h)

- An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, which is:
- Recognized in an official compendia
- Intended for use in diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in man or animal, or
- Intended to affect structure or function of body of man or animal and which does not achieve its primary purpose through chemical action within or on the body and is not dependent upon being metabolized for the achievement of its primary intended purpose

Biologics – 42 USC § 262

- Defined in the Public Health Service Act (PHSA)
- "A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide) 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."
- Usually included in the FDC Act as a subset of "drugs"
- Differ from most chemically synthesized drugs (with a known structure) in that most biologics are complex mixtures that are not easily identified or characterized.

Animal Drugs

- Included under definition of “drug”
- A new animal drug is any drug intended for use for animals other than man,
  21 USC § 321(v)

Tobacco Product – 21 USC § 321(rr)

- Any product made or derived from tobacco, intended for human consumption, including components, parts, accessories
- Excludes drugs, devices, and combination products, and tobacco marketed in combination with any other FDA-regulated article
- Includes e-cigarettes, waterpipe (hookah)

Combination Product - 21 CFR § 3.2(e)

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity
- Or if packaged together in a single package or as a unit
- Or if, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological product
- Primary mode of action determines regulatory category

Intended Use – 21 CFR § 201.128

- How a product is intended to be used determines how it will be regulated by FDA
- Definition: “the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article.”
- Express or implied statements

Intended Use

- The FDA determines your “objective intent” by:
- Labeling claims.
- Advertising matter.
- Oral or written statements by manufacturers, sponsors or their representatives.
- Circumstances surrounding distribution.
- Web sites, social media, medical pamphlets.
- With notice, knowledge of circumstances that it is used by HCPs for another purpose.

Intended Use - Proposed Rule

- Sept. 23, 2020: Proposed Rule to change the definition
- FDA: To better reflect our longstanding approach
- The FDA determines your product's “objective intent” by “any relevant source”
- Added: “the design or composition of the article”
- With notice, knowledge of circumstances that it is used by HCPs for another purpose.
- Proposed Rule: **HCP use is not enough, standing alone**

Real-world Application

- FDA website: A botanical product intended for use in treating a disease would generally be regulated as a drug; a botanical product taken by mouth, labeled as a dietary supplement, and intended for use to affect the structure or function of the body would generally be regulated as a dietary supplement; a raw or dried botanical intended for use as an ingredient to flavor food would generally be regulated as a food or as a food additive; and a lotion containing botanical ingredients and intended for use in moisturizing the skin would generally be regulated as a cosmetic.
- Drug vs. Cosmetic: Facial moisturizer with sunscreen, Lipstick with skin protectant
- Drug vs. Device: Wound dressing or ointment/gel for diabetic foot ulcers, minor cuts and burns
- Drug vs. Dietary Supplement: Omega-3 Fatty acids for cardiovascular health vs. Lovaza for lowering high triglycerides

Polling Question
How will FDA Regulate a “Shampoo”?

- A) As a Cosmetic
- B) As a Drug
- C) As a Medical Device
- D) Any of the above, depending on the manufacturer’s “intended use” for the product

Regulatory definitions

- Drug product - 21 CFR § 314.3
- Drug substance – “
- Listed drug – “
- New drug substance - 21 CFR § 310.3(g), (h)
- Related drug – 21 CFR § 310.3(k)

What is a New Drug?

- A drug that is not generally recognized, among qualified experts to evaluate safety and effectiveness, as safe and effective for use under the conditions prescribed (labeled indications)
  - Experts generally agree, based on published AWC studies, on safety and efficacy for the intended use
- Not used to a material extent or for a material time
- 21 USC § 321(p)
- Not OTC Monograph drugs

Regulatory Scheme

- No person may introduce into interstate commerce a “new drug” unless that drug product is subject to an approved New Drug Application (NDA)
- 21 U.S.C. § 331(d), § 355(a)
- Prior approval by FDA before marketing

Historical NDAs

- Federal Food, Drug, and Cosmetic Act of 1938
  - Required all new drugs to be safe
  - Required submission of safety data before marketing
- Kefauver-Harris Amendments (1962)
  - Required all new drugs to be both safe and effective
  - FDA required to review all new drugs approved between 1938 and 1962 as safe to determine if "effective"

Exceptions to New Drug Definition

- GRAS & GRAE (GRASE)
- Grandfathered (pre-1938 & pre-1962)
- Drug Efficacy Study Implementation (“DESI”) Review (pre-1962)
- Drugs Not Reviewed Yet, or Never an NDA, Are Known as “DESI 2”

DESI Drugs

- Subject to FDA-Approved Safety-Only NDA
- Remained on the Market While FDA Reviewed for Efficacy
- All Identical, Similar or Related (ISR) Drugs Could Also Remain on the Market
- Upon FDA's Final Determination of "Effective", all Drugs Had to File NDAs or ANDAs, per Federal Register Notice
- Upon FDA's Final Determination of "Less than Effective", all Drugs were to Voluntarily Leave the Market or Request a Hearing (NOOH)
- FDA Takes Enforcement Action Against Drugs that Did Not Leave Market or Request Hearing, But Few Resources
- Enforcement Discretion for 11 Pending DESI Notices and NOOH

DESI II Drugs

- No FDA Preapproval, No NDA
- Must be Identical to Pre-1962 Marketed Drug in:
  - Ingredient - Dosage Form
  - Labeling Indications - Formulation

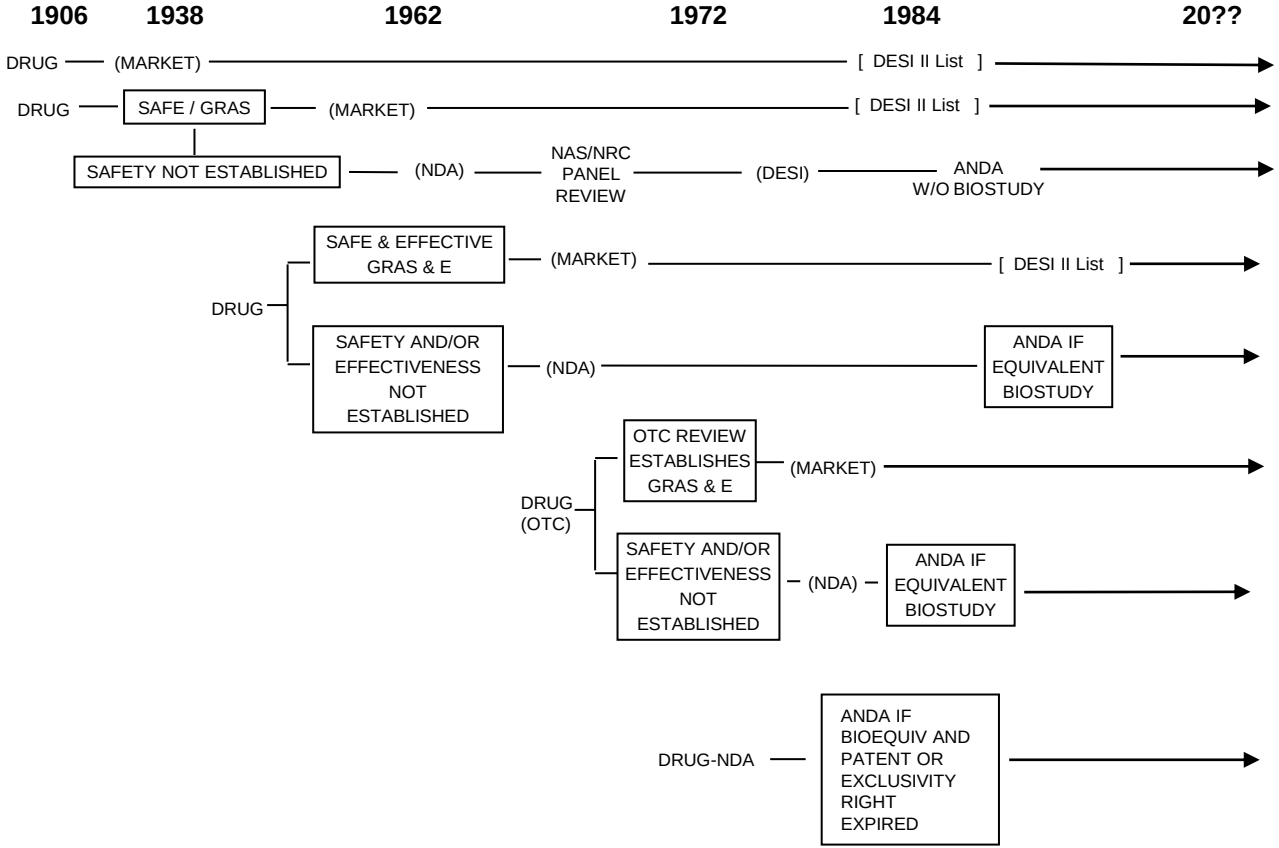
(Weiss List)

- 1986-2006: Some Regulatory Risk Under CPG Enforcement Discretion for Drugs Marketed Without NDAs/ANDAs
- 2006-Present: High Regulatory Risk Under Final Guidance on Marketed Unapproved Drugs

Final Guidance on Marketed Unapproved Drugs

- Obtain NDA or ANDA Approval to Remain on Market
- Enforcement Priorities
  - Potential Safety Risks - Health Fraud Drugs
  - Lack Effectiveness
  - Direct Challenge to NDA Approval or OTC Monograph Systems
  - Otherwise Violative, e.g., cGMPs
- Potential Short Grace Periods to Cease Manufacturing and Cease Distribution
- No New Market Entrants after Sept. 2011
  [Compliance Policy Guide 7132c.02 (2006), revised in 2011]

Drug Marketing/FDA Approval Process



Polling Question

Which item is NOT an exception to the FDA's New Drug Definition?

- A) Grandfathered Drug
- B) Listed Drug
- C) DESI Drug
- D) GRASE

Legal Standard for Approval of New Drugs

- Substantial evidence of safety and effectiveness
- Manufacturing complies with current Good Manufacturing Practices (cGMPs) (21 C.F.R. Part 210 - 211)
- Labeling is not false or misleading

Effectiveness – Substantial Evidence

- New drug approval requires “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”
- 21 U.S.C. § 355(d)

Adequate and Well-Controlled Studies

- Substantial evidence typically requires two adequate and well-controlled studies
- By experts qualified by scientific training and experience
- FDA can approve a drug on the strength of only one clinical trial, plus confirmatory evidence; 21 U.S.C. § 355(d)
- Statistically and Clinically significant
- E.g., compared against placebo; randomization and blinding of patients and investigators; pre-described objective, method of analysis, patient population, and study design via protocol, 21 CFR § 314.126

Safety – Balancing Risk and Benefit

- Demonstrate “by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions of use prescribed, recommended, or suggested” in the proposed labeling; FDCA 21 U.S.C. § 355(d)
- Safety assessment involves a case-by-case balancing of the risks and benefits of a drug
- Sliding scale: significant risks may be accepted if the drug is intended to treat a serious or life-threatening disease; only minimal risks if non-serious condition
- Via a “structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of risks and benefits”

Polling Question

All New Drugs are Approved on the Basis of 2 Adequate and Well-Controlled Studies

- A) True
- B) False
- C) The Speaker didn’t cover this

New Drug Approval Pathways

- IND
- 505(b)(1) NDA (“full” NDA)
- 505(b)(2) NDA
- ANDA
  - Post-1984 Approval process (Hatch-Waxman Act)
  - Pre-1984: the Paper NDA Policy
    - Me-Too Drugs Established Safety and Efficacy via Published Literature, Public Data
- Animal NADAs and ANADAs
- Biologics and Biosimilars (BLA and 351(k))
- Animal Rule Approval
- Limited Population for Antibacterial and Antifungal Drugs

Investigational New Drug Application

- Allows for premarket clinical testing
  - Phase 1, Phase 2 and Phase 3 testing
- Allows a person to ship in interstate commerce a drug product to be used in clinical investigations that otherwise would be barred as an unapproved new drug

IND – 21 USC § 355(i)

- "The Secretary shall promulgate regulations for exempting . . . drugs intended solely for investigational use . . . ."
- Clinical investigation may begin 30 days after sponsor submits information to FDA
- The label must bear the phrase, "Caution: New Drug - Limited By Federal (Or United States) Law To Investigational Use.“
- 21 CFR part 312

505(b)(1) NEW DRUG APPLICATION (NDA) – 21 USC § 355(b)(1)

- FDA Must Preapprove (Office of New Drugs, divisions based on therapeutic area)
  - New Ingredient (new chemical entity)
  - New Labeling Indication
- Supported by Animal and Clinical Data
- Market Protection: Patents, Patent Extension and Market Exclusivity due to Orphan Drug, New Chemical Entity, New Clinical or Pediatric Studies

505(b)(1) NDA Includes

- Full reports of investigations to establish S&E (pioneer, originator)
- Components
- Composition
- Description of manufacturing and packaging
- Labeling
- Risk Evaluation and Mitigation Strategies, if necessary
- Patent number(s) and expiration date(s)
- Financial disclosure
- 2021 User fee: $2,875,842 for clinical data

505(b)(2) NDA – 21 USC § 355(b)(2)

- Used for chemical entity that has known therapeutic effects
  - New dosage form
  - Expanded indication / subpopulation
- Can reference scientific data available to FDA from published literature or approved NDA's
- Relies on data not conducted by or for the applicant, and for which it has no right of reference
- Data required will be based on unanswered questions raised by the product change (Animal Tox - Clinical Data)
- Usually Shorter, Less Expensive R&D Program
- Viewed as a hybrid between a full NDA and an ANDA

505(b)(2) New Drug Application

- Preapproval
- Must refer to a Listed Drug
- Pre-clinical data (not likely)
- Clinical studies
  - Phase I (not likely)
  - Phase II (probably)
  - Phase III (possibly)
- Bioequivalence “Bridging” Study to Listed Drug
- Must file patent certification to Listed Drug’s patents

505(b)(2) New Drug Application

- User fee: $1,437,921 if no clinical data required (PK only)
- Patent protection (possible)
- Market exclusivity
  - 3 years clinical study
  - 6 months pediatric

Generic Drugs (ANDA)

- Created by The Drug Price Competition And Patent Term Restoration Act Of 1984 ("The Waxman-Hatch Act").
- Allows the copying of an approved or “reference listed drug” (RLD)
- Relies on known S&E data of RLD
- List is published in FDA's Approved Drug Products With Therapeutic Equivalence Evaluations, better known as "The Orange Book".
  - Provides a monthly listing of all new drug approvals, and a daily listing of patents protecting the RLDs
- Complex Patent Certification Requirements
  - Wait to market until patent expires, or challenge validity of RLD patent(s)

Generic Drugs – Abbreviated New Drug Application (ANDA)

Basic Requirements - 21 U.S.C. § 355(j) [505(j)]

- Must refer to an approved or "reference listed drug" (RLD)
- Conditions of use must be identical
- Identical active ingredient
- Identical route of administration, dosage form & strength
  - Pharmaceutical equivalence (PE)
- Bioequivalent (BE) to the listed drug (unless eligible for waiver)
  - reaches systemic circulation at the same rate and to the same relative extent
- Labeling must be the same as the RLD (but for minor differences due to different manufacturer)

505(j) Abbreviated New Drug Application

- Preapproval (Office of Generic Drugs)
- Can Change Strength, Dosage Form, or Formulation by Suitability Petition Request – but limited since most changes trigger need for pediatric data
- User fee: $196,868
- No FDA patent protection or market exclusivity (except for the first-to-file application that challenges the RLD patent, could obtain 180-day exclusivity)
- PE + BE = TE (therapeutic equivalence – automatic substitution at pharmacy)

NDA vs. ANDA Requirements

NDA Requirements	ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	6. Bioequivalence
7. Clinical Studies	
8. Bioavailability	

Polling Question

Which Application does NOT need to include Patent-related Information?

- A) IND
- B) 505(b)(1) NDA
- C) 505(b)(2) NDA
- D) ANDA

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 established 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 CFR §§ 314.600-650 for drugs; 21 CFR §§ 601.90-95 for biologics; effective July 1, 2002
- CDER has approved 11 (e.g., for nerve agent, cyanide, radiation poisoning)
- CBER has approved 3 (for botulism and anthrax)

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 in a broader population
- Prominent labeling for “Limited Population”
- Only 2 approved by FDA (for specific type of TB and lung disease)
- Since Dec. 2016 – 21st Century Cures Act

Questions?

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