The New Drug Approval Process: Basic Concepts

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FDLI

What is a Drug?

21 USC § 321(g)(1): Drugs are Articles . . .

- Recognized in USP or other compendia
- Intended to diagnose, cure, mitigate, treat or prevent disease
- Intended to affect structure or function of the body (other than food)
- Intended as component of these
- Exceptions for certain foods and supplements

The Key Principle - Intended Use

21 CFR § 201.128

- Objective intent of persons responsible for labeling of product
- Intent determined by, e.g.:
  - Labeling claims
  - Advertising/promotion
  - Oral or written statements
  - Circumstances surrounding distribution
  - The design or composition of the product

Intended Use - 21 CFR § 201.128

- Knowledge of actual use of a product for purposes for which it is not labeled or advertised is also evidence of intended use
  - However, recent rulemaking clarifies that knowledge that an approved drug is prescribed/used off label alone is not enough to show that a firm intends that unapproved new (off label) use

Distinguishing Drugs from Other FDA Regulated Products

Drug vs. Food

- 21 USC § 321(f): Foods are articles used for food or drink, chewing gum, and components of these
- 21 USC § 321(g)(1): Drugs are (among other things) articles other than food intended to affect structure/function of body

Drug vs. Food

Nutrilab, Inc. v. Schweiker, 713 F.2d 335 (1983)

- Tablets and capsules with a protein derived from raw kidney beans, sold as “starch blockers.”
- Block body’s digestion of starch as a weight loss aid
- Tablets/capsules not taken primarily for taste, aroma or nutritive value, but are intended to affect structure/function of the body → drug
- Key takeaways
  - Intended function rather than source is key
  - Nutritive value is a key concept

Drug vs. Food - Summary

Food intended to affect the structure/function of the body, based on its nutritive value

- remains a food (but recall Starch Blockers, where ingredient's effect was not based on nutritive value)

Food intended to diagnose, cure, mitigate, treat or prevent disease

- becomes a drug
- unless the claim is an acceptable "health claim"
  - Acceptable health claims are identified in FDA regulations and, for claims supported by less robust science, on FDA's website
  - e.g., a food high in calcium may be promoted with a claim linking calcium intake and reduced risk of osteoporosis without turning the food into a drug

Drug vs. Dietary Supplement

21 USC § 321(ff): Dietary Supplement is a product (other than tobacco) intended to supplement the diet

- Must contain:
  - vitamin, mineral, herb/botanical, amino acid, or dietary substance for use by man to supplement the diet by increasing total dietary intake, OR
  - A concentrate, metabolite, constituent or extract of the above
- Must be intended for ingestion
- Cannot be represented as a conventional food
- Structure-function claims need not be based on “nutritive value”
- Like conventional foods, can be promoted with certain health claims

Drug vs. Dietary Supplement

Dietary Supplements must be intended for ingestion

- *U.S. v. Ten Cartons of Ener-B Nasal Gel,* 888 F.Supp. 381 (1995)
- Vitamin B12 gel applied inside nose, absorbed directly into bloodstream, bypassing GI tract
- Held: not a supplement because not ingested (not a food for same reason). Product is a drug
- Topical vitamin patches now widely advertised – analysis and result should be the same

Drug vs. Dietary Supplement

- DS cannot contain an “article” approved or authorized for investigation as new drug prior to marketing as a food or supplement
- FDA interprets provision broadly to prohibit use of a drug ingredient in a supplement
  - Product spiked with a drug ingredient is not a supplement, even if labeled as a supplement
    - e.g., 2018 action against Rhino male enhancement products, which contained the active ingredients in the Rx drugs Viagra and Cialis

Food & Dietary Supplement Examples

Coffee (naturally containing 135 mg caffeine per serving)

- *food*

“Energy Drink” (with 250 mg added caffeine)

- *food*

A tablet with 500 mg caffeine labeled “supports mental alertness when experiencing occasional fatigue”

- *dietary supplement*

A tablet with 500 mg caffeine labeled “for relief of fatigue associated with long covid”

- *drug*

Drug vs. Biologic

42 USC § 262(i) (Section 351 of Public Health Services Act)

- Both drugs and biologics are therapeutic products intended to cure, treat, prevent disease or other condition
- Distinction turns on nature of product
  - Definition: virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or any analogous product
  - Basic rule of thumb: biologics are derived from living organisms

Distinguishing drugs from biologics

- Biologics are typically made by or from living cells -- human, plant, animal, or microorganism
  - Drug is typically manufactured through chemical synthesis
- Can be difficult to fully characterize a complex biologic by lab tests on the finished product, and some of the components of a finished biologic may be unknown
  - Drugs generally have well-defined chemical structures, and a finished drug can usually be analyzed to determine all its various components
- Even small changes to a biologic's manufacturing process, formulation or packaging may potentially affect the product's structural, functional and clinical properties
  - Drug manufacturer can change process or ingredient(s) and typically finished product testing can show the product is the same
- Biologics tend to be composed of larger molecules than drugs

Biologic Examples

- vaccines
- blood and blood products for transfusion and/or manufacturing into other products
- allergenic extracts, which are used for both diagnosis and treatment (for example, allergy shots)
- human cells and tissues used for transplantation (for example, tendons, ligaments and bone)
- gene therapies
- cellular therapies
- tests to screen potential blood donors for infectious agents such as HIV

Drug vs. Medical Device

21 USC § 321(h)

- Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, including component parts and accessories
- That meets the definition of a drug (e.g., intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease or intended to affect structure/function of the body)
  - Range from simple (tongue depressor or toothbrush) to complex (respirator)

Drug vs. Medical Device

- Key issue is mechanism of action
- Device definition excludes:
  - Products that achieve their primary intended purpose through chemical action within or on the body
  - Products that are dependent upon being metabolized for the achievement of their primary intended purpose

Drug vs. Combination Product

21 CFR § 3.2(e) – therapeutic and diagnostic products that combine drugs, devices, and/or biological products to varying degrees

- physically combined (nicotine patch, asthma inhaler)
- packaged together (Surgical tray with surgical instruments, drapes, and lidocaine or alcohol swabs)
- packaged and distributed separately but labeled for use only with each other (Photosensitizing drug and activating laser/light source)

Drug vs. Combination Product

21 USC § 353(g) - FDA center with primary jurisdiction (lead center) is based the “primary mode of action” (PMOA) of the combination product

- The PMOA is “the single mode of action . . . expected to make the greatest contribution to the overall intended therapeutic effects of the combination product”
- For drug/device combos, often resulted in CDER assignment - viewed as a more difficult path than CDRH

Drug vs. Combination Product

21st Century Cures Act –

- FDA "shall not determine" that the PMOA is "that of a drug or biological product solely because the combination product has any chemical action within or on the human body"
  - Chemical action alone is insufficient to trigger CDER/CBER review, but Cures Act does not define what is sufficient
- Formal process to appeal PMOA determinations
- Mechanism for sponsor-FDA agreement on study(s) to establish relevance of chemical action to the PMOA

FDA Feedback on Classification of a Human Medical Product

Pre-Request for Designation Process –

- In place for some time; now described in detail in 2018 Guidance
- informal, non-binding feedback regarding the classification of a human medical product as a drug, device, biological product, or combination product, and/or
- whether CBER, CDER, or CDRH will regulate the product if non-combination product, or which center will have primary jurisdiction if it is a combination product
- Goal – respond in 60 days
- Opportunity for consultation if sponsor disagrees with feedback

FDA Feedback on Classification of a Human Medical Product

Formal Request for Designation – 21 CFR Part 3 and 2017 Guidance

- formal, binding determination
- same two topics (classification and center assignment)
- Goal – respond in 60 days
- Sponsor may request reconsideration
- Content prescribed by regulation; strict page limit
  - Not so with informal Pre-Request for Designation

Drug v. Cosmetic

21 USC § 321(i)

- Cosmetics are articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the body for cleansing, beautifying, promoting attractiveness, or altering appearance
- Excludes soap

Drug/Cosmetic Combinations

Products with dual intended uses may be both drugs and cosmetics

- Examples:
  - anti-dandruff shampoos (cosmetic due to cleansing; drug due to treatment of dandruff)
  - antiperspirant/deodorant products
  - moisturizers with sunscreen
- Must meet requirements for both drugs and cosmetics

Wrinkle and anti-aging products

- Cosmetic = temporary, superficial effect linked closely to appearance
- Drug = more permanent, structural change; impact on living processes of skin; more than superficial
- Examples of “drug” claims, per FDA:
  - Reduces deep wrinkles
  - Stimulates skin’s collagen building network, rebuild collagen
  - Stimulates the renewal of skin cells, Promotes cell proliferation/cell regeneration
  - Helps correct the effects of sun damage on the skin
  - Reduces inflammation, anti-inflammatory
  - Improves/stimulates circulation
  - Claims about psoriasis, eczema, dermatitis, or acne

Drug vs. Tobacco Product

21 USC § 321(rr)

Tobacco product = 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

- Excludes raw material
- Includes cigarettes, cigarette tobacco, roll-your-own-tobacco, and smokeless tobacco

Drug vs. Tobacco Product

Definition excludes items that meet the definition of tobacco product but also fall within the definition of drug, medical device, or combination product

- 21 CFR § 1100.5 – Exclusion from Tobacco Regulation
  - tobacco products “marketed for therapeutic purposes” are subject to regulation as drugs, devices, or combination products
  - products for cure or treatment of nicotine addiction (e.g., smoking cessation), relapse prevention, or relief of nicotine withdrawal symptoms are drugs

Drug vs. Animal Drug

21 USC § 321(v)

- Distinction is target – a drug intended for use for animals other than man
  - Pets (called companion animals)
  - Food producing animals (e.g., dairy cows, beef cattle)
- Regulated by the Center for Veterinary Medicine
- New animal drugs must be reviewed by FDA for safety and effectiveness and obtain legal marketing status before they can be marketed

“New” Drugs

What is a “New” Drug?

21 USC § 201(p): All drugs “new” drugs except drugs that are:

- GRAS/E = 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/suggested in the labeling and
- Have been used for a material time and to a material extent under the labeled conditions
- FDA has taken the position that it is very unlikely that any currently marketed product satisfies these two conditions
- New drugs require FDA approval before marketing

GRAS/E

Construed very narrowly by FDA and the courts. Criteria:

- the particular drug product must have been subjected to adequate & well-controlled clinical investigations that establish the product as safe and effective
- those investigations must have been published in the scientific literature available to qualified experts
- experts must generally agree, based on those published studies, that the product is safe and effective for its intended uses
- the general acceptance of a product as GRAS/E must be supported by the same quality and quantity of scientific and/or clinical data necessary to support the approval of a New Drug Application

Grandfathered Drugs
Exempt from New Drug Status

- Marketed prior to 6/25/38 & no change in formulation, dosage, strength, route of administration, intended patient population, indications, & other conditions of use
- Marketed prior to 10/10/62 and
  - Used or sold commercially in US at the time the 1962 amendments took effect
  - Not a “new” drug as defined at that time
  - Not covered by an effective application AND
  - Composition and labeling have not changed
- Construed narrowly by courts
- FDA says few, if any, drugs on market are entitled to grandfather status - any unapproved drug first marketed (or changed) after 1962 is a new drug & on the market illegally

“New” Factors

21 CFR § 310.3(h) states that a drug may be considered a “new” drug because of:

- Inclusion of a component not previously for drug use (active or inactive)
- Combination not previously for drug use (even if the individual substances are not new drugs)
- New intended use/indication (even if the substance is not a new drug when for a different use)
- New dosage, method of administration, or duration of administration
- Essentially any change can trigger “new” drug status

Who Decides?

- No mechanism for administrative determination of new drug status prior to marketing
  - "not new drug" letters FDA once issued have been revoked (21 CFR § 310.100)
  - Up to company to decide whether to market as "old" drug
  - Penalties if FDA determines company is marketing a new drug without FDA approval
- Company's burden to prove a drug is not subject to new drug requirements (21 CFR § 314.200(e))
  - Requires extensive historical documentation of formulation, labeling, and marketing

Approval Standards for New Drugs

General Standards

21 USC § 355(d)

- Substantial evidence of effectiveness under the conditions prescribed, recommended or suggested in labeling
- Adequate tests showing safety under the conditions prescribed, recommended or suggested in labeling
- Manufacturing, processing and packing is adequate to assure identity, strength, quality and purity

Substantial Evidence of Effectiveness

21 USC § 355(d) (2019 Draft Guidance)

- adequate and well-controlled investigations
- that qualified experts would agree are adequate to show effectiveness
- generally two studies are required
  - but FDA may accept one adequate and well controlled investigation, along with confirmatory evidence

When is 1 study + Confirmatory Evidence Enough?

- 2019 Guidance addresses; recommends consultation w/ FDA in advance & provides examples where approach may be adequate
- Factors FDA will consider:
  - persuasiveness of the single trial
  - the robustness of the confirmatory evidence
  - the seriousness of the disease
  - the size of the patient population
  - Whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation.

Adequate and well-controlled study

Goal: control other influences so study evaluates effect of drug

Defined at 21 CFR § 314.126

- Clear protocol describing study objectives and methods of analysis
- Comparison against a control (e.g., placebo, alternative treatment)
- Careful selection of subjects

Adequate and well-controlled study

Defined at 21 CFR § 314.126 – cont.

- Procedures to minimize bias (e.g., blinding and random assignment of subjects to treatment and control groups)
- Reliable means of assessing effectiveness
  - Objective – analytical measures used to assess changes in cholesterol or blood pressure, for example
  - Subjective – measures of pain or sleep quality – validated questionnaires/scales required
- Valid methods of statistical analysis

Adequate and well-controlled study

- FDA has issued many disease-specific guidances that aid in clinical trial design
- Sponsors can obtain Agency feedback on clinical study questions

Adequate Tests of Safety

Preclinical studies – using cell cultures and animals

- Purpose: to develop adequate data to assess whether it is reasonably safe to proceed with human trials of the drug
- Evaluate pharmacology (absorption, distribution, metabolism, excretion), toxicity, reproductive toxicity, carcinogenicity, etc.

Adequate Tests of Safety

Clinical studies

- Early studies – focus on how drug is absorbed, distributed, metabolized, and excreted (“ADME”)
- Routine safety assessment (blood, urine, etc.) and monitoring for adverse events and side effects
- Special assessments such as potential to interact with other drugs, absorption/metabolism in special populations (e.g., pregnant, subjects with impaired kidney or liver function)

Risk Benefit Assessment

- Draft Guidance (2021)
- Starting premises
  - all drugs present risk (potential for adverse effects)
  - Uncertainties may exist – concerning both benefits and risks
- Approval only if benefits outweigh risks

Risk Benefit Assessment

Factors, beyond the safety and efficacy data

- alternative therapies available for the condition
- severity of condition
  - e.g., more risk acceptable for a serious condition or one with no alternative therapies
- Extent of uncertainties
- Public health considerations – in some cases, FDA considers risks to non-patients and risks associated with off label use
  - e.g., opioids – FDA considers the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others

Tools to Mitigate Risk

- Labeling – to inform prescribers and sometimes patients of risks and steps to monitor or address
  - e.g., periodic blood tests to evaluate of liver function
- Risk Evaluation and Mitigation Strategy (REMS) – used for specific drugs when additional measures are necessary for risk/benefit assessment to be favorable
  - e.g., prescriber training, patient registries, restricted distribution
  - 2019 Guidance explains how FDA decides if a REMS is needed
- Post-marketing study requirements - to evaluate potential safety issues (2019 draft guidance)

Assessment not Static

- Risk/benefit assessment continues after approval
- Post approval information bearing on risks
  - Adverse event reports
  - Agency evaluation of administratie and insurance claims databases (Sentinel Initiative)
  - Results of post-marketing studies
  - approval of alternate therapies with different benefits and risks

Approval Pathways for New Drugs

Full NDA - 505(b)(1) NDA

Used for Pioneer Drugs

- Clinical safety and efficacy data
- Chemistry, manufacturing, and controls (CMC) data
- Nonclinical pharmacology and toxicology
- Human pharmacokinetics and bioavailability
- Pediatric assessment
- Proposed Labeling
- Case report forms and tabulations

Full NDA - 505(b)(1) NDA

- May be eligible for various types of exclusivity (generally, time during which FDA may not approve another competing product)
- Must provide patent information in NDA
- Approval generally not delayed by patent or exclusivity rights of other drugs

505(b)(2) NDA

Used for Pioneer Drugs

- Content is same as full NDA except –
  - The NDA is based at least in part on “investigations … [that] were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use”
- Sometimes used for products quite similar to already approved drugs, but that are not eligible for approval as generic drugs

505(b)(2) NDA

- NDA will be a 505(b)(2) application if any of the specific info necessary for approval is obtained from another source, even if the sponsor also conducted its own clinical studies
- 505(b)(2) applicant can rely on
  - Published literature
  - FDA's prior safety and effectiveness determination for one or more already approved drugs
    - To do this, sponsor must cite the prior approved drug(s)

505(b)(2) NDA

Examples of changes from already approved drugs that may be pursued through a 505(b)(2) application:

- Dosage form – change from tablet to liquid
- Strength – change to a lower or higher strength
- Route of administration – change from oral dosage form to transdermal patch
- Change of active ingredient – change to a different salt or to an esterified form of an active
- Dosing regimen – change from immediate release to extended release
- Prescription to OTC switch

505(b)(2) NDA

- May be eligible for various types of exclusivity
- Must provide patent information in NDA
- Approval may be delayed by patent or exclusivity rights of the already approved drug(s) on which the application relies

Abbreviated New Drug Application (ANDA)

Used for Generic Drugs - exact or close copies of already approved drugs

- Identical in active ingredients, dosage form, strength, route of administration, conditions of use (some changes in inactive ingredients are permitted)
- 21 CFR 314.93 - Suitability Petition may be submitted seeking FDA permission to file an ANDA despite certain changes from the already approved drug

ANDA

Data required:

- Chemistry, Manufacturing, and Controls data
- Labeling
- No preclinical or clinical data required, instead. . .
- Bioequivalence data
  - Data showing the active ingredient becomes available in the body at the same rate and to the same extent as from the copied pioneer drug
  - establishes a link to the copied drug, allowing FDA to rely on its previous conclusion that the copied drug is safe and effective

ANDA

- May be eligible for exclusivity
  - Different types of exclusivity than those available to Pioneer drugs approved in an NDA
- Approval delayed by patent or exclusivity rights of the copied drug

Non-Traditional Approval Pathways

Emergency Use Authorization (EUA)

21 USC § 360bbb-3 and Jan. 2017 guidance

- Expedited authorization of medical products to address public health emergencies
- Allows FDA to authorize emergency use of medical products for certain emergency circumstances involving chemical, biological, radiological, and nuclear (CBRN) agents after the HHS Secretary has made a declaration of emergency or threat justifying emergency use
  - During an emergency and in advance of emergency to support preparedness planning

Emergency Use Authorization (EUA)

- May apply to drugs, devices, or biological products
- EUA is temporary and ceases when emergency is resolved
- FDA may revise or revoke EUA
- Private sponsor can request declaration of an emergency, but most are from government sponsors (HHS or DoD)

Emergency Use Authorization (EUA)

Criteria for issuance of EUA

- The CBRN agent must be capable of causing a serious or life threatening illness
- “Reasonable to believe” that product “may be effective“ based on totality of scientific evidence available
  - Lower standard than substantial evidence of effectiveness

Emergency Use Authorization (EUA)

Criteria, cont.

- Favorable risk benefit profile - known and potential benefits must outweigh known and potential risks of the product, taking into account the threat level
  - e.g., greater risk and/or uncertainty may be acceptable during an ongoing emergency compared to during preparedness planning
- No adequate, approved, and available alternative for diagnosing, preventing, or treating the disease or condition
- Other criteria HHS Secretary prescribes by regulation

Emergency Use Authorization (EUA)

FDA may impose conditions appropriate to protect public health, e.g.

- Info for practitioners/dispensers re: status, risks, contraindications, etc.
- Info for patients re: status, risks, options
- Monitoring/reporting adverse events
- Limits on distribution/administration

The “Animal Rule”

21 CFR § 314.600 et seq. and 2015 guidance

Evidence from adequate and well controlled animal studies may be sufficient to show efficacy if:

- Drug for treatment of serious or life-threatening conditions caused by exposure to biological, chemical, radiological or nuclear substances, i.e., lethal or permanently disabling toxic substances
- Human efficacy trials unethical and field trials after an accidental or deliberate exposure are not feasible
- Not available for drugs that can be approved under typical efficacy standards

The “Animal Rule”

Scope

- threat agents for deliberate exposure (e.g., nerve agent, anthrax)
- threats from accidental exposure (e.g., infectious pathogens, industrial chemicals)

Human data still required, e.g.,

- absorption, distribution, metabolism, and excretion must be characterized in animals and humans, as routine
- safety must be evaluated in typical manner, including human studies

The “Animal Rule”

Four criteria:

- reasonably well-understood mechanisms – both the toxicity of the substance and the therapeutic effect of the product
- Two positive animal studies in different species
  - FDA may approve if the effect is shown in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans

The “Animal Rule”

Four criteria, cont.

- animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity
- Available data allows selection of an effective dose in humans (e.g., PK, PD)

The “Animal Rule”

Three additional requirements

- Postmarketing study to verify clinical benefit, if circumstances allow feasible/ethical study (i.e., if drug is used in an emergency)
  - A plan for conducting study must be included with the NDA
- Information provided to patients explaining limits of testing
- Restrictions on distribution, if needed (e.g., restricting distribution to facilities or health care practitioners with special training, requiring specified types of follow up, or imposing record keeping requirements)

LPAD Pathway

- Limited Population Pathway for Antibacterial & Antifungal Drugs
- 21 USC § 356(h) – added in 2016 through 21st Century Cures Act; 2020 Guidance
- Purpose – facilitate development/approval of certain antibacterial and antifungal drugs
- Benefit – streamlined approach to clinical development
- Sponsor must request approval under LPAD Pathway
- Consultation with FDA early in development program encouraged

LPAD Pathway – Applicability

- Must treat, diagnose, or prevent a serious and life-threatening infection in a limited population of patients with unmet medical needs
  - Serious, life threatening, and unmet medical needs -- terms are defined in separate 2014 guidance (Expedited Programs for Serious Conditions – Drugs and Biologics) and 21 CFR §§ 312.300, 312.81
- Limited population
  - group of patients that is limited in a way that is clinically relevant to healthcare providers and that can be defined in labeling so that a healthcare provider can identify the patients
  - Not the same as a rare condition
  - Example from Guidance: drug for prevention in mechanically ventilated patients with no other options is a potential LPAD candidate, while a drug for prevention of a rare infection in the general population is not

LPAD Pathway – Approval Standards

Drug must meet same approval standards, however . . .

- studies may be smaller or shorter, or FDA may require fewer clinical trials
- A smaller number of patients exposed to the proposed dose for the proposed duration of therapy (the safety database) may be adequate
- risk/benefit assessment still required, but balance may come out differently when the focus is a limited population with no other treatment options
  - risk may be acceptable in patients with serious conditions that do not have other treatment options
- Separate 2017 guidance addresses possible streamlined development programs and clinical trial designs for these products

LPAD Pathway – Conditions of Approval

- These products must have specific labeling to inform practitioners and patients that the drug was approved under the LPAD pathway
- Promotional materials must be submitted to FDA at least 30 days before dissemination
- “Limited Population” must appear prominently in all labeling and advertising

Thank You.

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