Introduction to FDA Review and Approval of Biological Products

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AGENDA

- **Basic Principles**
- **Pathways to Market**
- **Combination Products**
- **General Principles of Premarket Approval for Drugs and Biologics**
- **Market Exclusivities and Intellectual Property**

Background on Biologics

- What is a biologic?
  - Simple definition:
    - A medicine derived from living organisms
  - The FDA definition:
    - A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product
    - That is applicable to the prevention, treatment or cure of a disease or condition of humans (Public Health Service Act (PHSA) § 351(i))

Background on Biologics

- Made by genetically engineering living cells
  - Cells become miniature factories producing the desired molecule (e.g., proteins)
- Complex structure
  - Elaborate folding
  - Several forms of the active molecule may be present
  - Analytical methods may not detect variations
  - Difficult to characterize
- “The product is the process”
  - Living systems can be very sensitive to minor changes in manufacturing process
  - Small changes can significantly affect finished product

Key Principle: Intended Use

- Key concept in determining regulatory status of most FDA-regulated products
- Refers to the objective intent of the persons legally responsible for the labeling of product
- Objective intent may be shown by:
  - labeling claims
  - advertising matter
  - oral or written statements
  - circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised

21 C.F.R. 201.128

Biological Product vs. Drug

Biological Product (PHSA § 351(i))	Drug (Federal Food, Drug, and Cosmetic Act (FDCA) § 201(g))
▪ A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product ▪ That is applicable to the prevention, treatment or cure of a disease or condition of humans	▪ Articles that are recognized in the United States Pharmacopoeia, Homeopathic Pharmacopoeia, or National Formulary ▪ Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals ▪ Articles intended to affect the structure or function of the body of man or other animals ▪ Articles intended for use as a component of any articles above ▪ Not food

Biological Product vs. Medical Device

Biological Product (PHSA § 351(i))	Medical Device (FDCA § 201(h))
▪ A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product ▪ That is applicable to the prevention, treatment or cure of a disease or condition of humans	An instrument, apparatus, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is: ▪ recognized in an official compendium, ▪ intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease or intended to affect the structure or any function of the body, ▪ does not achieve its primary intended purposes through chemical action within or on the body, and ▪ is not dependent upon being metabolized for the achievement of its primary intended purposes

Biological Product vs. Veterinary Biologic

Biological Product (PHSA) § 351(i))	Veterinary Biological Product (9 C.F.R. § 101.2)
▪ A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product ▪ That is applicable to the prevention, treatment or cure of a disease or condition of humans	▪ All viruses, serums, toxins (excluding substances that are selectively toxic to microorganisms, e.g., antibiotics), or analogous products at any stage of production, shipment, distribution, or sale ▪ Which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response

Biological Product vs. Cosmetic

Biological Product (PHSA § 351(i))	Cosmetic (FDCA § 201(i))
▪ A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product ▪ That is applicable to the prevention, treatment or cure of a disease or condition of humans	▪ Articles that are 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 that are intended for use as a component of any such articles ▪ Does not include soap

Biological Product vs. Food, Dietary Supplement

Biological Product (PHSA) § 351(i))	Food (FDCA § 201 (f))	Dietary Supplement (FDCA § 201(ff))
▪ A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product ▪ That is applicable to the prevention, treatment or cure of a disease or condition of humans	▪ Articles used for food or drink for man or other animals ▪ Chewing gum, and ▪ Articles used for components of any such article.	▪ Product (other than tobacco) intended to supplement the diet that contains one or more of the following dietary ingredients: vitamin; mineral; herb/botanical; amino acid; substance used to increase total dietary intake; a concentrate, metabolite, constituent, extract, or combination ▪ intended for ingestion – subset of food ▪ not represented for use as a conventional food or as a sole item of a meal or the diet

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Marketing Authorization: Biologics

- Biologic License Application (BLA)
- Contents of BLA include
  - Pre-clinical data
  - Clinical data
  - Chemistry, Mfg, Controls
  - Manufacturing information
  - Human PK/BA data
  - Description of product
  - Proposed labeling

FDCA § 351(a)

Marketing Authorization: Biosimilars

- Abbreviated licensure pathway for biological products that are "biosimilar" to or "interchangeable" with reference products (RPs) already licensed by FDA ("Section 351(k) application")
- A "biosimilar" is a biological product that is highly similar to and has no clinically meaningful differences from an RP
- An "interchangeable" biosimilar is one expected to produce the same clinical result as the RP in any given patient

FDCA § 351(k)

Marketing Authorization: Biosimilars

- Section 351(k) application requires information demonstrating:
  - Biological product is biosimilar to the RP based on analytical, animal, and possibly clinical studies
  - Same mechanism(s) of action as RP, if known
  - Condition(s) of use previously approved for RP
  - Same route of administration, dosage form and strength as RP
  - Approved manufacturing facility
  - Publicly available information regarding determination that RP is safe, pure and potent
- Additional information regarding the RP as required by FDA
- Contents of application are product-dependent

New Drug Application (NDA)

- A traditional NDA contains the full slate of clinical data
- Substantive standards for review of NDAs
  - Substantial evidence of **effectiveness** and adequate tests of **safety** under the conditions prescribed, recommended, or suggested in labeling
  - **Manufacturing, processing, and packing** is adequate to preserve identity, strength, quality, and purity
  - Proposed **labeling** must comply with statutory and regulatory requirements

FDCA § 505(b)(1), (d)

Abbreviated NDAs (ANDAs)

- ANDAs
  - Used when the new drug is identical in active ingredient, dosage form, strength, route of administration, labeling, and intended use, to a previously approved drug (a/k/a listed drug)
  - No safety and efficacy studies required
  - Adequate manufacturing and controls

FDCA § 505(j); 21 C.F.R. § 314

Abbreviated NDAs (ANDAs)

- ANDAs
  - Generic must be “bioequivalent” to listed drug
  - Bioequivalence means
    - Same rate of absorption
    - Same extent of absorption
  - Difficulties in measuring bioequivalence for non-systemically absorbed products (e.g., topical or other locally acting medicines)

505(b)(2) Application

- 505(b)(2) applications
  - Considered an NDA, not an ANDA
  - Used when product contains a modification to an approved drug such that the new product is not identical to the approved product (making ANDA pathway inapplicable)
    - New indication
    - Strength
    - Dosage form
    - Route of administration
    - Change of active ingredient in a combination product

505(b)(2) Application

- 505(b)(2) applications
  - Must contain full reports of investigations of safety/efficacy
  - Some of the information comes from studies not conducted by/for the applicant and for which the applicant does not have a right of reference
- 505(b)(2) applicant can rely on:
  - Published literature
  - Unpublished data in FDA's files that FDA claims is no longer legally protected
  - FDA’s prior safety and effectiveness determination
  - Original research

Device Applications/Notifications

- Pre-Market Approval (PMA) for Class III devices
  - Clinical data showing "reasonable assurance" that the device is safe and effective for its intended use (21 USC § 360j(e))
- Premarket notification 510(k)
  - Device is "substantially equivalent" to a predicate device (21 C.F.R. § 807.93)
- "510(k)-exempt"
  - Grandfathered/"pre-amendments"
  - Class I, unless on reserved list
  - Class II, 510(k) exempt by regulation

Approval Standards: PMA

- "Reasonable assurance" that the device is safe and effective for its intended use
  - Established by "valid scientific evidence," which may derive from
    - Well-controlled investigations
    - Partially controlled studies
    - Studies and objective trials without matched controls
    - Well-documented case histories
    - Reports of significant human experience

Clearance Standards: 510(k)

- Substantial Equivalence
  - Device has same intended use as predicate

    AND EITHER

  - Device has same technological characteristics as the predicate

    OR

  - Device has different technological characteristics but
    - Does not raise different questions of safety and effectiveness than the predicate, and
    - Is at least as safe and effective as the predicate

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Combination Products

- Comprises two or more FDA-regulated components:
  - Drug, device, biologic
- Packaged together or intended for concurrent use:
  - Physically, chemically, or otherwise combined or mixed,
  - Packaged in a single package or as a unit, or
  - Packaged separately but intended for use only with another approved product
- Combination product examples:
  - Device coated or impregnated with a drug or biologic
  - Prefilled syringes, pen injectors, auto-injectors
  - Metered dose inhalers, transdermal patches

21 C.F.R. § 3.2(e)

Primary Mode of Action

- Primary Mode of Action (PMOA) is the "single mode of action of a combination product that provides the most important therapeutic action of the combination product"
- The "most important therapeutic action" is the "mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product"

FDCA § 503(g); 21 C.F.R. § 3.2(m)

FDA Office of Combination Products

- FDA Office of Combination Products (OCP)
  - Determines PMOA
  - Designates a “Lead Center”
    - Center for Biologics Evaluation and Research (CBER)
    - Center for Drug Evaluation and Research (CDER)
    - Center for Devices and Radiological Health (CDRH)

Requests for Designation

- If the classification of a product is unclear or in dispute, a sponsor can submit a Request for Designation (RFD) to OCP to obtain a formal classification determination
  - Once OCP determines the RFD is complete for filing, FDA reviews the RFD
  - The sponsor recommends a classification in the RFD, and should explain the basis for the recommendation
  - Generally, OCP will respond to the sponsor in writing within 60 days of the RFD filing, identifying the classification of the product as a drug, device, biological product, or combination product
  - If FDA does not provide a written response within 60 days, the sponsor's recommendation is considered to be the final determination

  21 C.F.R. § 3.7

Intercenter Agreements

- After the FDCA was amended to include combination products, CBER, CDER, and CDRH entered into three Intercenter Agreements (ICAs)
  - Common objective of the ICAs: explain how categories of combination and single-entity medical products were classified
  - Provide guidance on product jurisdiction
  - Initially represented major jurisdictional statements issued by FDA
    - However, less useful since adoption of PMOA rule and as new products develop and new uses develop for existing products

21st Century Cures

- The 21st Century Cures Act included several provisions to enhance combination product innovation, including provisions that:
  - Allow sponsors to request substantive rationale for FDA designation
  - Establish voluntary Combination Product Review Plan
  - Require FDA to apply a risk-based approach to combination products consisting of previously approved drug or device constituent part
  - Expressly apply Hatch-Waxman concepts to certain combination product applications

Combination Products with Biological PMOA

- Biological product with implantable delivery device*
- Cellular transplant for diabetes
- Biological hemostatic agent with reconstitution and delivery devices
- Fibrin sealant & delivery catheter
- Interferon & injector for treatment of hepatitis C
- Injectable protein with delivery device for orthopedic use
- Drug/biologic embolization agent
- Autologous cellular product & delivery device
- Radiolabeled antibody with delivery device
- Autologous cell therapy & delivery device to treat cardiovascular disease
- Autologous cells & scaffold for orthopedic use
- Blood-derived protein & delivery device/dressing for wound management
- Autologous cells & scaffold for organ replacement
- Pegylated interferon & ribavarin to treat chronic hepatitis C
- Interferon & drug to treat chronic hepatitis C

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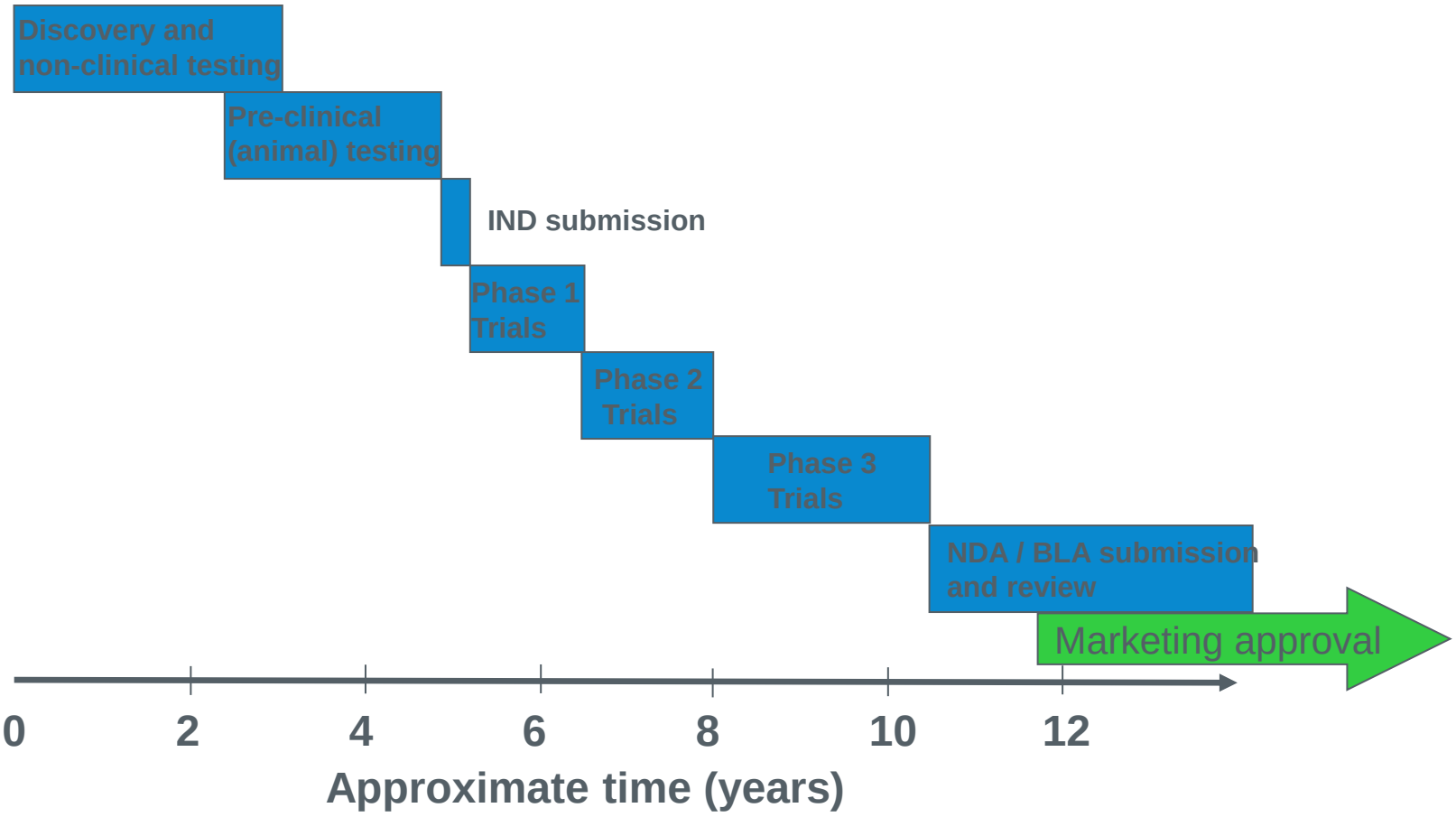
Drug/Biologic Development

Overview and approximate timeline of the new drug / biologic development and approval process



Non-clinical testing

- For new drugs and biologics, FDA and ICH guidance documents prescribe a relatively standard battery of preclinical toxicology, carcinogenicity/genotoxicity, and other tests prior to introducing a compound into human subjects
  - In vitro testing
  - In vivo (animal) testing
- Testing intended to support an FDA submission is subject to Good Laboratory Practices (GLP) regulations (21 C.F.R. Part 58)
  - Quality assurance
  - Documentation requirements
  - Sample maintenance
  - Animal welfare

What is an IND?

- Before FDA will allow a drug/biologic to be tested on human subjects, the sponsor normally must have an IND in effect
  - Formal notice of company's intent to begin trials in humans
  - Based on preliminary (animal, in vitro, early human) data
  - Evidence that product is "reasonably safe" for proposed studies on humans
  - FDA has 30 days to object before IND becomes effective
- Sponsor can contract obligations to a contract research organization (CRO), though sponsor generally remains ultimately responsible

21 C.F.R. Part 312

Drug/Biologic Clinical Studies: Classic Model

- Phase I
  - Initial testing generally in healthy human subjects
  - The primary purpose of the trials is safety (not efficacy)
  - The total number of subjects is generally less than 50
- Phase II
  - Testing in patients with the target disease or condition
  - Intended to obtain preliminary data on effectiveness and to obtain additional information on safety
  - Used to establish the dosing range for pivotal trials
  - The total number of subjects is generally less than 100

Drug/Biologic Clinical Studies: Classic Model (cont'd)

- Phase III
  - Testing in patients with the given disease or condition
  - Intended to gather the information about effectiveness and safety that is needed to support the marketing application
  - The sample size must be large enough to provide an adequate basis for extrapolating the results to the general population
  - The total number of subjects is generally several hundred people
- Phase IV (post-marketing)
  - FDA may require that the sponsor conduct Phase IV studies as a condition of approval or sponsor may conduct on its own accord
  - Studies conducted after marketing approval
  - Usually to confirm safety

Substantial Evidence Standard for Drugs

- "Substantial evidence" of safety and effectiveness
  - Consists of **adequate and well-controlled investigations** by experts with the scientific training and expertise to evaluate the safety and effectiveness of the drug involved. 21 C.F.R. § 202.1(e)(4)(ii)(b)
- "Adequate & well-controlled" 21 C.F.R. § 314.126
  - Randomization
  - Blinding
  - Valid comparison against control
  - Clear statement of objectives and methods of analysis
  - Well-defined and reliable methods of assessing response

Safe, Pure, and Potent Standard for Biologics

- Biological product must be “safe, pure, and potent”
- Comparable to substantial evidence standard
- Safety
  - The relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered
- Purity
  - Relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product
- Potency
  - Interpreted to include effectiveness
  - Proof of effectiveness comprised of controlled clinical investigations defined in the adequate and well-controlled studies provision for drugs

21 C.F.R. § 600.2

Balancing Risk and Benefit

- Risk/Benefit analysis
  - Policy
    - Determine the benefit
    - Determine the risk
    - Weigh the effectiveness of the product against the risks
      - Do the benefits outweigh the risks?
  - Considerations
    - Seriousness of the disease
    - Adequacy of existing therapy
    - Adverse events
    - Any other safety data

Expedited Review Programs: Background

- Four types of expedited programs:
  - Fast Track
  - Breakthrough Therapy
  - Accelerated Approval
  - Priority Review
- All are intended to expedite the development and review of new drugs and biologics that
  - Address an unmet medical need
  - Treat a serious or life-threatening condition
  - Are for conditions not otherwise addressed by available therapies
- Note that a drug or biologic may qualify for more than one program

Important Concepts for Expedited Programs

- **Unmet Medical Need**
  - An immediate need for a defined population
  - A longer-term need for society (e.g., resistance to antibacterial drugs)
- **Serious Condition**
  - Substantial impact on day-to-day functioning
  - Product must be intended to treat a serious condition
- **Available Therapy**
  - Another therapy approved or licensed in the U.S. for the same indication
  - Relevant to current U.S. standard of care for the indication

Fast Track Designation

- **Eligibility**
  - Drugs intended to treat a serious condition where nonclinical or clinical data demonstrate the potential to address an unmet medical need; or
  - Drugs designated as “qualified infectious disease products” (QIDPs)
- **Features**
  - More frequent FDA-sponsor meetings
  - Rolling review
- **Timing**
  - Request with an IND application, or at pre-BLA or pre-NDA meeting
  - FDA will respond within 60 calendar days

FDCA § 506(b)

Breakthrough Therapy Designation

- **Eligibility**
  - Drugs intended to treat a serious condition where preliminary clinical evidence indicates the drug may demonstrate substantial improvement on a clinically significant endpoint as compared to available therapies
- **Features**
  - Fast Track features plus:
    - Early and intensive guidance from FDA on drug development (e.g., efficient clinical trial design)
    - Cross-disciplinary FDA team of senior reviewers
- **Timing**
  - Submit with the IND or no later than end-of-Phase II meeting
  - FDA will respond within 60 calendar days

FDCA § 506(a)

Accelerated Approval Process

- **Eligibility**
  - Drugs intended to treat a serious condition that provide a meaningful advantage over other therapies and demonstrate an effect on:
    - A surrogate endpoint; or
    - An intermediate clinical endpoint
- **Features**
  - Approval based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit

Accelerated Approval Process (cont'd)

- **Conditions**
  - FDA pre-review of all promotional materials
  - Confirmatory trials
  - More flexibility for FDA to withdraw approval
- **Timing**
  - Initiate discussions with FDA as soon as possible, so as to reach agreement on the use of a planned endpoint and design of confirmatory trials
  - No deadline for FDA to respond to request

FDCA § 506(c); 21 C.F.R. §§ 314 Subpart H and 601 Subpart E

Priority Review Designation

- **Eligibility**
  - Drugs that treat a serious condition and would provide a significant improvement in safety or effectiveness over available therapies
  - Labeling supplements based on pediatric studies under FDCA § 505A
  - QIDPs
  - Applications or supplements submitted with priority review vouchers
- **Features**
  - Shorter clock for review of marketing application (6-8 months rather than 10-12)

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Regulatory Exclusivity

- Exclusivity applicable only to biological products:
  - Reference Product Exclusivity
  - Interchangeable Exclusivity

- Exclusivity applicable to drugs and biological products:
  - Orphan Exclusivity
  - Pediatric Exclusivity

Reference Product Exclusivity

- Biosimilar application may not be:
  - Submitted until 4 years following approval of the RP
  - Approved until 12 years following approval of the RP
- Exclusivity period runs from date of “first licensure”
  - In most instances, this is the initial date the particular product at issue was licensed in the U.S.
  - Some exceptions from “first licensure” in section 351(k)(7)(C) of the PHS Act
- First licensure does not include licensure for a BLA from the same sponsor as the RP:
  - For new indication, new route of administration, dosing schedule, delivery systems, delivery device, or strength; or
  - For a structural change that does not result in a change to safety, purity or potency

Interchangeable Exclusivity

- Exclusivity periods are available for interchangeable products
- The first biological product approved as interchangeable is entitled to a period of exclusivity during which no other product may be deemed interchangeable
- Exclusivity period ends on the earliest of:
  - One year after first commercial marketing
  - 18 months after approval if no expedited litigation
  - 18 months after final court decision if expedited litigation is brought
  - 42 months after approval if expedited litigation is pending

Orphan Exclusivity

- 7 years of marketing exclusivity following approval, which means FDA will not approve another application for the same drug/biologic and same indication, except if:
  - Sponsor of orphan product application cannot assure availability of sufficient quantities of the drug
  - Subsequent drug is clinically superior
- When are two biologics "the same"?
  - Existing regulations for determining sameness of macromolecules are often inadequate for biologics
  - Specific FDA guidance on interpreting sameness for monoclonal antibodies and gene therapy products
  - Determinations must be made on a case-by-case basis and therefore the outcomes can be very uncertain
- "Clinically superior" means that a product provides significant therapeutic advantage over the orphan product

Pediatric Exclusivity

- 6 months of additional exclusivity that attaches to all concurrently applicable exclusivities, *e.g.*,
  - Reference Product exclusivity for biologics
  - Orphan drug exclusivity for drugs and biologics
  - 5-year NCE exclusivity for drugs
- Based on the satisfactory completion of pediatric studies conducted in response to a Written Request from FDA
  - "Fair response" standard
- Only available if pediatric exclusivity determination is made at least 9 months prior to expiration of drug's existing exclusivity
- No requirement that the applicant obtain approval of pediatric labeling

Patent Exclusivity

- **Patents** are a property right granted by the United States Patent and Trademark Office anytime during the development of a drug and can encompass a wide range of claims.
- **Regulatory Exclusivity** refers to certain delays and prohibitions on approval of competitor drugs available under the statute that attach upon approval of a drug or of certain supplements.
- Periods of exclusivity and patent terms may or may not run concurrently.
- Biologics Price Competition and Innovation Act of 2009 (BPCIA) Patent Enforcement Scheme for Biologics
  - Section 351(l) of the PHS Act (42 U.S.C. § 262(l))
  - Mandatory exchange of information by biosimilars applicant ("patent dance")
  - Identification of relevant patents to be litigated
  - Penalties for failure to comply with timetables

Trade Secrets

- A trade secret:
  - is information that has either actual or potential independent economic value by virtue of not being generally known,
  - has value to others who cannot legitimately obtain the information, and
  - is subject to reasonable efforts to maintain its secrecy.
- Trade secret information is often shared with FDA in support of an application, but can be protected from public disclosure.
  - The Freedom of Information Act (FOIA) and FDA regulations generally require disclosure of FDA records unless the information falls under one of the FOIA exemptions
    - Exemption #4: Trade secrets and confidential business information
  - FDA publishes the “Action Package” upon approval of a BLA, which generally includes review and decision documents related to the application
    - Any information exempt from disclosure, such as trade secret and confidential commercial information, will be redacted before posting

Questions

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