Morgan Lewis

THE LIFE SCIENCES GROWTH SERIES

FDA AND IP PRIMER FOR EARLY-STAGE LIFE SCIENCES COMPANIES

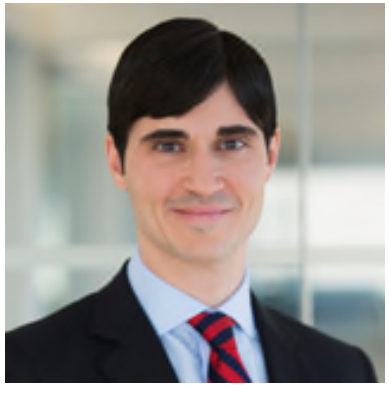
Stephen Altieri, Ph.D. | Benjamin Pensak | Kathleen Sanzo

February 12, 2019

Overview of Presentation

- Intellectual Property: Stephen Altieri, Ph.D., Partner, Boston
- FDA/Regulatory: Kathy Sanzo, Partner, Washington D.C.
- Commercial Agreements: Ben Pensak, Partner, San Francisco

Biography



Stephen L. Altieri, Ph.D.
Boston, MA
T +1.617.951.8525
F +1.617.951.8736

Stephen Altieri, Ph.D., focuses his practice on patent counseling, procurement, and licensing in the life sciences sector. Throughout his career, Steve has represented clients of all sizes, including emerging companies as well as public companies and universities. He creates and develops US and international intellectual property rights that are aligned with client business objectives. Steve also handles post-grant proceedings, including inter partes reviews and reexaminations, as well as patent litigations.

Previously, Stephen was an associate at another international law firm, where his subject area focus was on life sciences, including biologics, diagnostics, oncology, immunotherapies and small molecule drugs.

Stephen, a Fulbright Fellow, received his Ph.D. from Yale University from the Department of Molecular Biophysics and Biochemistry. His doctoral research examined mechanisms of ion channel activation, particularly the structural and molecular basis of gating in cyclic nucleotide-gated ion channels. After finishing at Yale, Stephen received his J.D. from Boston College Law School, *magna cum laude* and Order of the Coif.

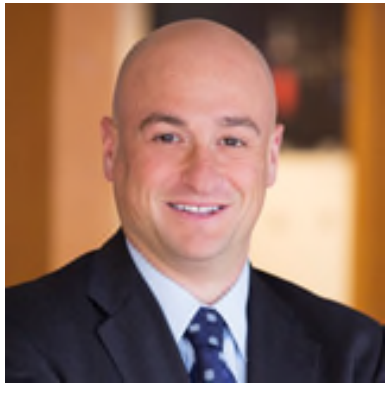
Stephen also serves as co-chair of the Massachusetts Biotechnology Council's Entrepreneur University.

Biography

Kathleen M. Sanzo
Washington, D.C.
T +1.202.739.5209
F +1.202.739.3001

Kathleen M. Sanzo centers her practice on regulatory and compliance issues connected to products regulated by the US Food and Drug Administration (FDA). She leads and counsels clients on matters relating to prescription, OTC drug, and biotechnology product development and clinical testing; food, dietary supplement, and cosmetic product manufacture, approval, marketing, and distribution, including inspection and resulting deficiencies; and product promotion and labeling issues including Warning Letters; and compliance and crises management issues; As the FDA practice leader, Kathleen represents clients in the pharmaceuticals and biotechnology, food and dietary supplements, consumer products, consumer protection safety, advertising, cosmetics, drugs, and medical industries.

Biography



Benjamin H. Pensak
San Francisco, CA
T +1.415.442.1368
F +1.415.442.1001

Benjamin H. Pensak counsels clients on technology transactions and related corporate matters, primarily in the life sciences industry. Ben represents international and US-based public and private companies and institutions, and his clients include biotechnology, pharmaceuticals, medical device, diagnostics, and medical informatics companies. Ben advises clients regarding negotiating and structuring acquisitions, divestitures, joint ventures, corporate partnering, licensing, and other complex collaborations. He also drafts and negotiates day-to-day technical contractual arrangements. He is the deputy leader of the firm's life sciences transactions practice.

In his transactional work, Ben handles arrangements related to discovery, development, manufacture and supply, marketing, and outsourcing for life sciences companies and other innovative and developed technology companies. He also works with research organizations and institutions. Recognized by Chambers USA, Ben is hailed as having "an extremely high legal and life sciences IQ . . . . He is quick on his feet and is an excellent technical drafter."

Contracting considerations

- The goal of a life sciences company is to obtain and maintain regulatory approval for its product(s).
  - Obtaining and maintaining approvals requires compliance with regulatory requirements and the funds necessary to do so.
  - Raising the funds necessary to do so usually requires investment return/commercial prospects.
  - Funders usually require proprietary intellectual property that distinguishes and protects a product's market position.
- Contracts should be structured to protect and ensure the ability to satisfy regulatory requirements and a company's IP strategy.
- Even if the initial product developer does not anticipate obtaining and maintaining an approval itself, anticipating an outlicense or acquisition, contracts should be structured with the same objectives to facilitate the exit strategy.

INTELLECTUAL PROPERTY

STEPHEN ALTIERI PH.D.

Types of IP Protection

- **Patents**
  - Utility Patents: any Process, Machine, Manufacture, or Composition of Matter, or any New and Useful Improvement Thereof
  - Design Patents and Plant Patents
- **Trademarks**
  - Words, Symbols, Logos, Designs, or Slogans that Identify and Distinguish Products or Services
- **Copyright**
  - Original Works of Authorship, Fixed in a Tangible Medium of Expression, Includes Software (Source or Compiled)
- **Trade Secrets**
  - Information that is Confidential and Provides a Business Advantage
  - Formulas, Methods, Devices, Manufacturing Specifications, New Inventions for which a Patent Application has Not Yet Been Filed
  - Unlike Patents, Does Not Give One the Ability to Exclude (e.g. Prevent "Design Around")

Scope and Duration of Patents

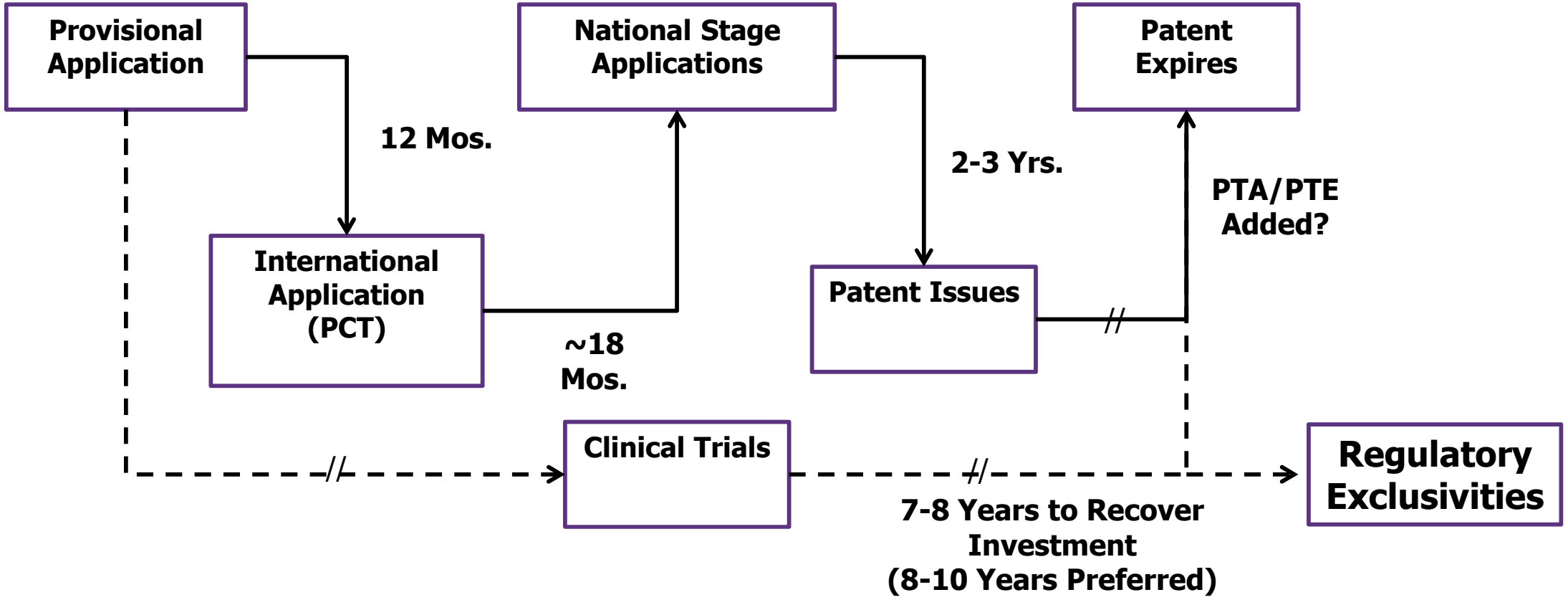
- Patents Must Have Adequate Scope
- Dual Purpose:
  - Protect Products Being Marketed (e.g. Avoid Copying – Generics)
    - Narrower Claim Scope is Typically Sufficient
  - Keep Competitors Out of Company's Therapeutic/Indication Space
    - Broader Claim Scope is Typically Needed
- Claim Scope - Inverse Relationship with Validity:
  - Broader Claims Cover More Subject Matter but are Typically More Susceptible to Invalidity Challenges
  - Narrower Claims Cover Less Subject Matter but are Typically More Resilient to Invalidity Challenges
- "Gold Standard" = Composition of Matter Claims Covering Product with ~8-10 Years of Patent Term (i.e., Patent Issuance to Expiration) Post-Launch

Scope and Duration of Intellectual Property

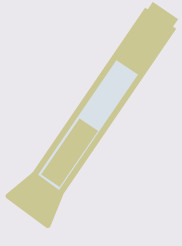
- Patent Term is 20 Years from Non-Provisional Filing
  - Patent Term Adjustment (PTA): Extra Term from USPTO Delays
  - Patent Term Extension (PTE): Extra Term from US FDA Delays (Max. 5 Years)
- Estate Building:
  - Primary Protection Subject Matter (Typically First Filings):
    - Compositions of Matter
    - Methods of Use
  - Secondary Protection Subject Matter (Life Cycle Management):
    - Combination Therapies
    - Formulations and Routes of Administration
    - Dose or Dosing Regimens
    - Additional Methods of Use Specific to Patient Subpopulations
    - Methods of Manufacturing, Key Chemical Intermediates or Biocatalysts

Scope and Duration of Intellectual Property

Patents Should Endure Long Enough to Take Advantage of Market Exclusivity



Categories of Patent Protection
(Non-Exhaustive)

Composition of Matter	Formulation	Method of Making	Method of Use	Delivery Device
• Patents pertaining to the specific reference product gene and protein sequences • The most readily discoverable and referenced patent for biologics	• Patents pertaining to the mixture the protein is presented within • There are various formulations, e.g., liquid, powder for reconstitution, etc.	• Patents pertaining to the process used to create the product • Specific to each individual biosimilar manufacturer's process	• Patents pertaining to how the product is administered • Can be related to strength, indication, dosage schedule, administration type, etc.	• Patents pertaining to the delivery device of the product • Delivery devices are created to best administer the product and then patented as proprietary
				

Claim Examples: Dosing Amounts

US Patent No. 9,278,094

A method for treating relapsing or recurrent major depressive disorder (MDD), comprising

administering a therapeutically effective low dose amount of naltrexone to a human patient in need thereof, wherein:

the low dose amount of naltrexone is about 1 mg,

administered once or twice daily for at least three weeks; and

the patient is undergoing treatment for MDD comprising at least one dopaminergic agent.

- Naltrexone was approved by the FDA in 1994 for Alcohol Withdrawal (25-50 mg), Prior Art Reported ng Doses for Depression

Claim Examples: Dosing Amounts/Regimens

US Patent No. 10,183,056

A method of treating acute radiation syndrome (ARS) in a human patient, the method comprising

> administering to the human patient not more than a single dose of an effective amount of a composition comprising entolimod,
>
> wherein the effective amount is about 0.4 to about 0.6 µg/kg, and wherein the entolimod comprises the amino acid sequence of SEQ ID NO: 1.

- Entolimod in Clinical Trials for ARS
- This Patent to Expire 2035 (Original Composition Patents Expire 2024)

Claim Examples: Combinations Therapies

EP Patent No. 2451459

A therapeutically effective amount of inositol trispyrophosphate (ITPP) for use in partial vascular normalization of a tumor in a cancer patient prior to the administration of an effective amount of a chemotherapeutic agent,

> wherein the chemotherapeutic agent is: a microtubule-targeting agent selected from colchicine, docetaxel, paclitaxel, vinblastine, vincristine, vindesine, and vinorelbine; a DNA-intercalating agent selected from cisplatin, daunorubicin, doxorubicin, or epirubicin; or a nucleoside metabolic inhibitor selected from cytarabine, fludarabine, fluorouracil, gemcitabine, mercaptopurine, or pentostatin.

- This Claim Also Has Regimen-Like Features
- ITPP Patented as a Composition > 10 Years Before this Filing
- Clinical Trial: ITPP + Fluorouracil

Claim Examples: Combinations Therapies

US Patent No. 9,278,094

A method for treating relapsing or recurrent major depressive disorder (MDD), comprising

> administering a therapeutically effective low dose amount of naltrexone to a human patient in need thereof, wherein:
>
> the low dose amount of naltrexone is about 1 mg,
>
> administered once or twice daily for at least three weeks; and
>
> the patient is undergoing treatment for MDD comprising at least one dopaminergic agent.

- "Split Infringement" Issue . .

Claim Examples: Formulations

US Patent No. 9,744,221

A pH-dependent modified-release formulation comprising a beta-lactamase,

wherein the formulation releases the beta-lactamase in the gastrointestinal (GI) tract, and

wherein the formulation comprises at least one pH-dependent modified-release pellet with each pellet comprising:

about 10-20% by weight beta-lactamase; about 10-20% by weight sucrose sphere; about 20-30% by weight hydroxypropylcellulose; about 10-20% by weight a first enteric polymer; about 20-30% by weight a second enteric polymer; about 1-10% by weight triethyl citrate; and about 1-2% by weight buffer salt; and

wherein the formulation releases the beta-lactamase at a pH of greater than 6.7.

- Clinical-Stage Beta Lactamase (Prior Patents On Compositions and Methods of Treatment Granted), Term to 2035

Claim Examples: Manufacturing

US Patent No. 9,119,840

A method for activating and expanding T cells in a cell suspension, comprising reacting the cell suspension with a superagonistic monoclonal antibody specific for CD28,

> wherein the cell suspension is prepared from a body fluid taken from a B-cell chronic lymphocytic leukemia (B-CLL) patient.

Freedom to Operate

- PATENTABILITY ≠ FREEDOM-TO-OPERATE
- FTO is a Legal Analysis Based on a Search and Evaluation of Patents and Applications in Relevant Countries to Determine if a Commercial Product, Use or Manufacture Could Infringe the Rights of a Third party
- FTO Helps to Avoid/Anticipate Conflicts with Third Parties Regarding Their Patent Portfolio
- Lack of FTO could lead to
  - Loss in Transaction Values,
  - Litigation, and
  - Injunctions and Damages

Patent Term Extension (PTE)

- (Sometimes referred to as Patent Term Restoration as well)
- PTE is a mechanism for the patent owner to claw back some, but not all, of the patent term lost to the premarket regulatory approval process (from IND filing to NDA approval, for example)
- PTE is added to the end of the patent term, when many pharmaceutical products are at their peak earning power
- One PTE per "pharmaceutical product" (PP) in the US
  - Multiple patents to: compound, method of treatment, method of making
  - Company picks one for PTE
  - Pick the one with the fewest litigation issues
    - Narrow, specific claims with a short file history ("picture claims")
- One PTE per patent
  - If patent has claims to two different indications, or two different compounds, Company has to pick which gets the PTE award
    - Thus, "single compound" or "single method" are best
    - So we need to be thoughtful on strategies of combination patents

Patent Term Extension (PTE)

- In General, there's a
  - Testing Phase, and there's an
  - Approval Phase
- Testing Phase runs from the filing of the IND to the submission of the NDA
  - You get 50% back on the time lost during the Testing Phase.
- Approval Phase runs from the submission of the NDA to the approval of the NDA.
  - You get 100% back on the time lost during the Approval Phase.
- **Clock starts only once the patent is issued.** If the IND is filed, and the patent has not issued yet, the PTE clock does not start.
  - **So, want to have your "picture claims" issued before IND filed**
- You can get time deducted if you are slow in responding to the FDA during this regulatory process. **Important to keep a diligence log**.

Patent Term Extension (PTE)

- Maximum PTE: 5 years
  - The testing + approval calculation is capped at 5 years.
  - But you don't want to wait too long before you get a patent, as it can be less
- PTE cannot push the patent term beyond 14 years from the date of product approval

- **Take homes/best practices/good ideas/things to consider:**
  - Have at least one, and maybe more, "picture claim" patents
    - Single claims or close to it
    - Be careful about breadth beyond what you are doing: breadth generally means more vulnerability to litigation attack (claim interpretation issues, written description, prior art, indefiniteness, etc.)

IP Contracting

- Understand your IP strategy
- Which type(s) of IP protection are being employing (e.g., trade secret or patent)?
  - Trade secret will require attention to confidentiality to retain protection
  - Patent will require that appropriate data is being generated and made available to support patent filings
  - Decision making around PTE (aligned interests?)
- Ensure that freedom to operate is not being lost or do so with eyes open
  - Are licenses necessary and appropriate? Options?
  - "hereby" v. "shall" assign(s)
  - Assistance
- Allocation of responsibilities
  - Prosecution and maintenance
  - Enforcement and defense
  - Step-in, review, or other rights for non-lead
  - Cost allocation

FDA/REGULATORY

KATHY SANZO

Drug Development Realities

- Generally takes about $1.2B to develop a drug
- More than 50% of drug candidates fail
- General regulatory review times have increased from 15 months to 25 months
- Some industry analysts believe stress of the necessary financial and time investment is leading to many incremental developments rather than significant innovations

What FDA Regulatory Issues Should Be Considered in Initial Phases of Development?

- What is the optimal FDA regulatory pathway?
  - Is it a drug, a device, a biologic, or a combination product?
- What are the preclinical and clinical requirements for the chosen pathway?
  - Pre-IND meeting with FDA will assist to identify
- Can the proposed studies satisfy multiple regulatory authorities?
- Do you have the right scientific, medical, statistical, regulatory, and manufacturing resources/partners (in-house or consultants) and advisors on board?

What is the Optimal FDA Regulatory Pathway

- Is your product a drug, a device, a biologic, or a combination product?
  - Preferred pathway factors – science, time to market, $$ (to raise and to spend), market position and reimbursement
  - Not always straightforward – product jurisdictional disputes within FDA may affect ultimate classification
  - Not always known (e.g., no predicates for first in class device, stem cell products, etc.)
- Are there expedited review programs or designations that are available and that would affect the pathway?
- Is the intended indication or disease area eligible for a voucher (e.g., pediatric or tropical disease, countermeasure drugs)

Jurisdictional Assessments

- CDER
  - Drugs
  - Therapeutic biological products (transferred from CBER in 2003) including:
    - Monoclonal antibodies for *in vivo* use
    - Most proteins for therapeutic use
- CBER
  - Stem cells
  - Biologics
  - Certain devices, including:
    - Devices involved in the collection, processing, testing, manufacture and administration of licensed blood, and cellular products
- CDRH
  - Devices
  - IVDs
- Office of Combination Products
  - Combination products

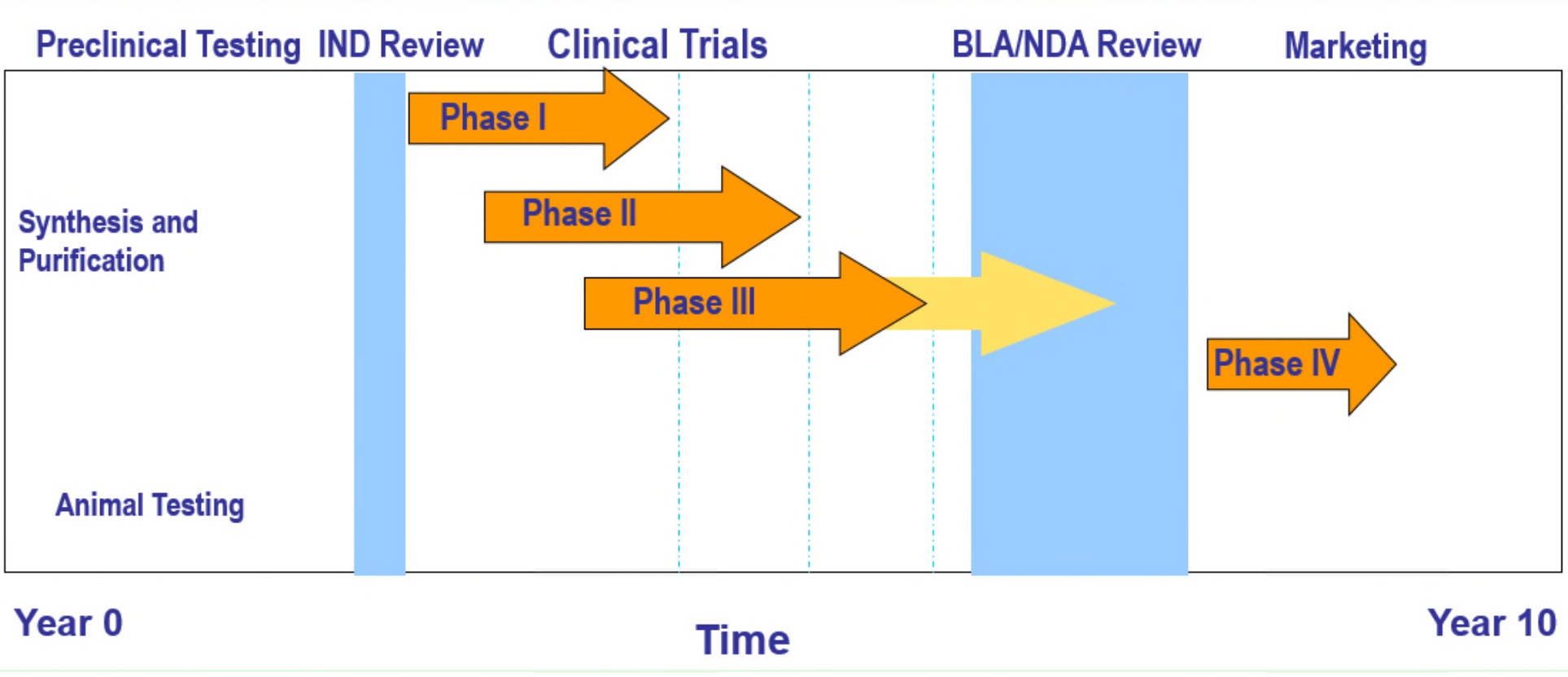
Types of Expedited Approval Pathways

- Accelerated Approval
- Fast Track Designation
- Priority Review
- Breakthrough Therapy Designation
- Regenerative Advanced Therapy Designation

Others to Mention

- Antimicrobials for Limited Populations (21st Century Cures Act)

Drug Development Timeline



PRE-CLINICAL PHASE DEVELOPMENT

Preclinical Phase Development–Meeting with FDA

- Draft request for pre-IND meeting, which can reduce the time to market by
  - Identifying and avoiding unnecessary studies / minimizing costs
  - Ensuring that necessary studies are designed to provide useful information
  - Gaining FDA support for a proposed strategy / allowing early interactions
  - Minimizing potential for clinical hold
  - Providing opportunity to discuss expedited pathways, orphan drug, special protocol assessments
  - Obtaining regulatory insight
  - Clearly defining endpoints and goals of the development program

Preclinical Phase Requirements

- At the preclinical phase, FDA will generally ask that sponsors:
  - Develop a pharmacological profile of the drug;
  - Determine the acute toxicity of the drug in at least two species of animals;
  - Conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies;
  - Assess carcinogenic potential (but may be done in clinical phase);
  - Assess dose/toxicity; and
  - Provide identification and control of the raw material, and new drug substance or biologic, and drug product, in CMC information.

Selection of Preclinical Tests

- Selection of preclinical tests and protocol development concerning the drug's toxic and pharmacologic effects will be required, including
  - *In vitro* and *in vivo* laboratory animal testing
  - Genotoxicity screening
  - Drug absorption and metabolism
  - Toxicity of the drug's metabolites
  - Excretion of the drug and its metabolites
  - Development of Master Services Agreements
- GLPs apply – 21 CFR Part 58

Some Critical Aspects of GLP Compliance

- Establishing a GLP Compliance Program, including among outside testing organizations
- Creating Quality Assurance Unit to inspect and audit laboratory studies and pertinent data
- Establishing written protocols and SOPs
- Ensuring contractual agreements require GLP conformance and allow for Company auditing and CAPA monitoring
- Responding to FDA 483 observations

CLINICAL PHASE DEVELOPMENT

Investigational New Drug Applications (IND)

- The IND application must contain information in three broad areas:
  - Animal Pharmacology and Toxicology Studies
    - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans
    - Any previous experience with the drug in humans (often foreign use)
  - CMC Information
    - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product
  - Clinical Protocols and Investigator Information
- IND must be submitted to FDA and the clinical study cannot be initiated for at least 30 days; most companies will not start a trial until they have heard from FDA, to avoid a clinical hold on the trial, and negative press

Clinical Development – Phase I

- The initial introduction of an investigational new drug into humans
  - in patients, or
  - in healthy volunteer subjects
- The total number of subjects generally in the range of 20 to 80
- The goal is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, scientifically valid, Phase II studies
- Also evaluate:
  - drug metabolism,
  - structure-activity relationships, and
  - the mechanism of action in humans

Clinical Development – Phase II

- Early well-controlled, closely monitored, clinical studies conducted to:
  - obtain preliminary data on the effectiveness of the drug for intended uses
  - determine the common short-term side effects and risks associated with the drug
- Conducted in a relatively small number of patients, usually involving several hundred people
- Must be registered with clinicaltrials.gov
- Company may need an expanded access policy
- CMC data continues to be refined

Clinical Development – Phase III

- Expanded controlled and uncontrolled trials (2 or more)
  - Provides adequate data to allow risk-benefit assessment
- Usually includes several hundred to thousands of people, especially for chronic indications, and many sites; expanded access issues continue
- Clinical trial monitoring is critical and sites should be prepared for BIMO inspections
- Manufacture of product/CMC issues become critical; CMOs are preparing for Pre-approval Inspection
- Pediatric waiver or studies being developed
- NDA/BLA and resources are being assembled

Emerging Clinical Trial Issues

- Role of Adaptive Design in Clinical Trials and FDA's comfort level with it
  - Adaptive design uses results accumulated in the trial to modify the trial's course or the next trial in accordance with pre-specified rules.
  - AD may require additional statistical and related analyses
  - AD will require additional contacts/meetings with FDA (Type C or EOPII meeting); special protocol agreements not likely available able for AD trial
  - AD will likely require DSMB to monitor results, provide guidance to sponsor
  - See FDA guidelines FDA Adaptive Design Guideline
- Clinical trial strategies for rare diseases—see FDA Guideline on Drug Development in Rare Diseases
- Role of NIH funding and/or sites (and NIH Rules) on product development

Emerging Clinical Trial Issues

- FDA's use of real world evidence and Patient Experience Data to assist in design of study protocols; resulting need for strategy/contacts with patient advocacy groups
- Increasing difficulty in subject recruiting and how it affects study design and timelines
- Potential effects of right to try laws on recruiting and sponsor profile
- Incorporation of diagnostics in identifying study populations and potentially patients—development of the diagnostic as a companion diagnostic and affect on development plans and timeline, as well as need for expertise in device development

Regulatory Contracting

- Understand your regulatory needs
  - Submittable data
  - Compliant systems
- Ensure that your counterparty is contractually obligated appropriately
  - Compliance with law
  - No debarred, etc., individuals
  - Appropriate record keeping requirements
- Audit rights
  - Direct
  - By a regulatory authority
  - Limitations and effect
- Assistance
  - Consultation
  - Further development
  - Cost allocation
  - Non-lead rights

Our Global Reach

Africa
Asia Pacific
Europe
Latin America
Middle East
North America

Our Locations

Almaty
Astana
Beijing*
Boston
Brussels
Century City
Chicago
Dallas
Dubai
Frankfurt
Hartford
Hong Kong*
Houston
London
Los Angeles
Miami
Moscow
New York
Orange County
Paris
Philadelphia
Pittsburgh
Princeton
San Francisco
Shanghai*
Silicon Valley
Singapore
Tokyo
Washington, DC
Wilmington

Morgan Lewis

*Our Beijing and Shanghai offices operate as representative offices of Morgan, Lewis & Bockius LLP. In Hong Kong, Morgan Lewis operates through Morgan, Lewis & Bockius, which is a separate Hong Kong general partnership registered with The Law Society of Hong Kong as a registered foreign law firm operating in Association with Luk & Partners.

THANK YOU

Morgan Lewis