Clinical Trials of

Special Products

Module 3 Topic 7

Outline

- Introduction to Vaccines
- Clinical Development of Vaccines
  - Herpes Zoster Vaccine Example
- Opportunities for Adaptive Design Strategy
- Issues and Challenges in Adaptive Designs
  - Illustrated with Examples

What Are Vaccines?

- Biological products
- Typically for prophylaxis, not treatment
- Use antigen or attenuated live virus to trigger immune responses for disease protection
- Administered as a single dose or series with a potential booster dose
- Highly complex immunologic milieu
  - Array of humoral and cellular immune responses

Examples of Vaccines

Pediatric vaccines

- Polio
- Measles, mumps, rubella (MMR)
- Chickenpox (Varivax®)
- Hepatitis B
- Diphtheria, tetanus, pertussis
- Rotavirus (infant gastroenteritis, RotaTeq®)
- Invasive pneumococcal disease (Prevnar®)

Examples of Vaccines

Adolescents and Adult vaccines

- HPV (cervical cancer, Gardasil®)
- Meningitis (Menactra®)
- Influenza
- Invasive pneumococcal disease (Pneumovax 23®)
- Herpes zoster (shingles, Zostavax®)

Benefits of Vaccines

- Direct benefit
  - Efficacy in clinical trials
  - Risk benefit at individual level
- Indirect benefit
  - Herd immunity by reducing exposure and transmission
  - Public health implications

Types of Immunity

- Humoral (antibody-mediated) immunity
  - B lymphocytes,
  - Plasma cells
  - Immunoglobulins (Ig)
    - IgG, IgM, IgA, IgD and IgE
- Cell-mediated immunity (CMI)
  - T lymphocytes
  - Cytokine/Interleukins

Functions of Immunoglobulins

- Serve as antibodies
- Neutralize viruses and bacterial toxins
  - IgG accounts for ~80% of total immunoglobulin pool
- Bind antigen
- Prevent or clear first infection

Functions of T-cells (CMI)

- T lymphocytes (helper cells) stimulate B cells to produce antibodies
- T suppressor (regulatory) cells play an inhibitory role and control the level and quality of the immune response (CD4)
- Cytotoxic T-cells recognize and destroy infected cells (CD8)

Evaluation of New Vaccines - Safety

- Assess local (injection-site) and systemic adverse experiences
- Need a large database, particularly because of giving vaccines to healthy subjects
- Choice of safety parameters depend on type of disease, population, and route of administration
- Need large-scale post licensure study for additional safety monitoring

Evaluation of New Vaccines - Immunogenicity

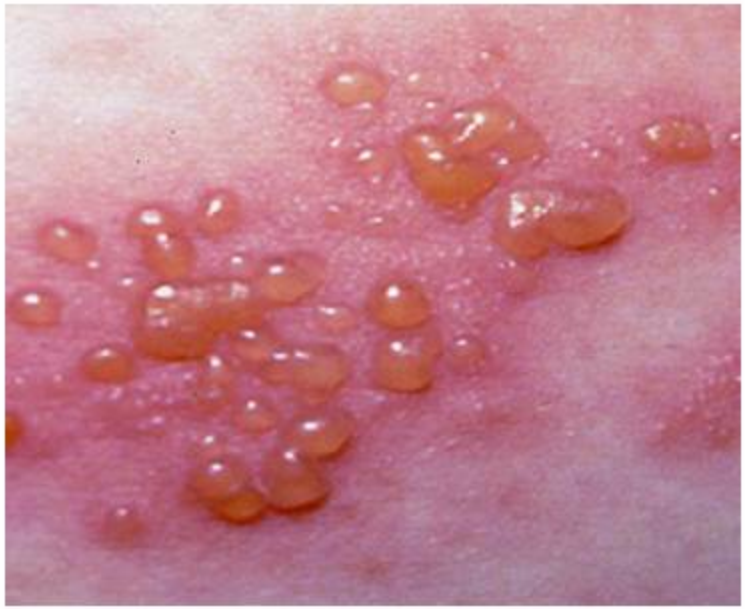
- Important in understanding the biology
- Humoral immunity
  - Antibody responses
  - Priming, first defense
- Cell-mediated immunity
  - T-cell responses
  - Prevent virus reactivation, kill infected cells
- Identify immune markers that correlates with disease protection

Variability/Stability of Vaccines

- Vaccines are biological products that have more variability in than chemical compound
  - Need to demonstrate consistency of manufacturing
- Many vaccines contains attenuated live viruses and will lose potency over time
  - E.g., chickenpox vaccine, zoster vaccine
- Need to establish a range of potency for manufacturing and product shelf-life
  - Study the safety at the high potency
  - Establish efficacy at near-expiry potencies

Herpes Zoster Is a Consequence of Varicella-Zoster Virus (VZV) Reactivation

Reactivation of varicella-zoster virus (VZV) that has remained dormant within dorsal root ganglia, often for decades after the patient's initial exposure to the virus in the form of varicella (chickenpox), results in herpes zoster (shingles).



Phases of Clinical Trials

- Phase I
  - Healthy subjects
  - PK/PD of drugs
  - Modeling and simulations
  - Dose ranging for safety and immunogenicity of vaccines
  - Biomarker/assay development

Phase I Study for Dose Ranging

- Assess the immune responses of 8 dose levels
  - Potencies = 0 (placebo), 2000, 8000, 17000, 19000, 34000, and 67000 PFUs
  - Evaluate both antibody and T-cell responses
  - N ~40 per group
- Results suggested potencies above 17000 PFUs elicit immune responses
  - Some plateau between 34,000 and 67,000 PFUs
  - No safety concern

Phases of Clinical Trials

- Phase II
  - Target population
  - Dose ranging and dose selection for safety and efficacy (or immunogenicity for vaccines)
    - Minimum effective dose
    - Optimal dose
  - Proof of concept (POC) study of efficacy
  - Hypothesis generating

Phase II Study for Dose Selection

- Assess the immune responses of 2 dose levels
  - Potencies = 0 (placebo), 34000, and 50000 PFUs
  - Evaluate T-cell responses
  - N =398 total (1:3:3 ratio)
- Results showed similar immune responses of two selected potencies
  - 1.9 fold higher than placebo ($p<0.001$)
  - Confirmed the plateau observed in phase I study

Phase II/III Dose-Selection Trial

- Dose selection based on immune responses at phase II
- Efficacy outcome followed at both phases for the selected dose and control
  - Analysis combines data from phases II and III
- Overall type I error depends on
  - The number of doses at phase II
  - Correlation between immune marker and disease outcome
  - Sample size at different phases
- Type I error can be controlled using closed testing procedure and/or use of exact test for efficacy comparison

Phases of Clinical Trials

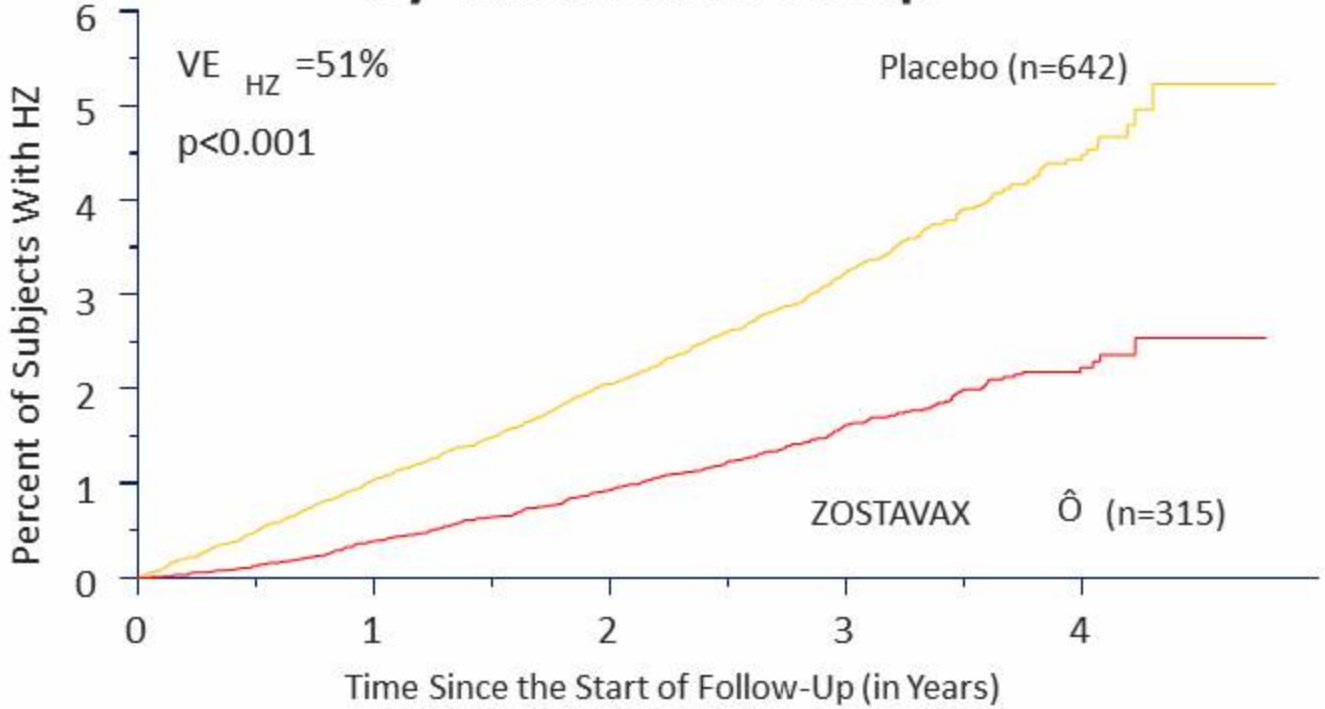
- Phase III
  - Confirmatory trial of efficacy and safety
  - Demonstration of consistency of the manufacturing process for vaccines
  - Large scale in size
  - Last stage before submission for licensure

Phase III Study for Efficacy and Safety: The Shingles Prevention Study (SPS) (Oxman *et al.*, NEJM 2005)

- N = 38,546 subjects ≥60 years of age randomized 1:1 to receive ZOSTAVAX® or placebo
- Single dose of vaccine with potency ranging from 18,700 to 60,000 PFU (median 24,600 PFU)
  - To bracket end-expiry potency
- Average of 3.1 years of HZ surveillance and ≥6-month follow-up of HZ pain after HZ rash onset
- Conducted by Dept. of Veteran Affairs (VA) in collaboration with the National Institutes of Health (NIH) and Merck & Co., Inc.

ZOSTAVAX® Efficacy: HZ Incidence

Estimate of the Cumulative Incidence of HZ Over Time by Vaccination Group



Number of subjects at risk

ZOSTAVAX	Ô	19254	18994	18626	9942	1906
Placebo		19247	18915	18422	9806	1856

v211p4ACMkm_t2hz_mittv4 Dec. 1, 2005

Key Efficacy Endpoints of SPS

- HZ incidence
- HZ pain burden of illness (BOI)
  - Composite of incidence, severity, and duration of pain
- Post-herpetic neuralgia (PHN)
  - Clinically significant pain persisting for or present after 90 days of HZ rash onset
- Success requires 95% CI lower bound for vaccine efficacy >25%

Phases of Clinical Trials

- Phase IV
  - Post-marketing studies to collect additional data on safety, efficacy or immunogenicity
  - Supports marketing or regulatory commitments
  - Expansion to different populations
  - Studying the efficacy in large number of subjects in a real life situation
  - Studying safety in large number of subjects in a real life situation

Medical Device Trials

Medical Devices

An instrument, implant, in vitro reagent, or other similar or related article, which is:

- Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, in man or animals, or
- Intended to affect the structure or any function of the body of man or animals, and which does not have chemical action within or on the body and which is not dependent upon being metabolized for producing its effects.

As per (21 U.S.C. 321(h)) U.S Food & Drug Administration

Medical Devices

1. Specific devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals
2. Specific substances intended to affect the structure or any function of the human body. At present, the substances notified are mechanical contraceptives (e.g. Condoms, IUDs, tubal rings) and disinfectants.
3. Substances used for in vitro diagnosis.

Medical Device Rules, 2017, CDSCO

Classification

- In accordance with the Federal Food, Drug, and Cosmetic Act, FDA places all medical devices into one of three regulatory classes.

- Classification is based on the level of control necessary to ensure safety and effectiveness of the device.

Class I

- Class I devices are subject only to general controls. Typically present the lowest potential for harm and are simpler in designs.
- Most are exempted from 510(k) PREMARKET NOTIFICATION
- In some cases exempted from QSR compliance
- Clinical studies are not generally required for marketing clearance. (e.g. Elastic bandage, examination gloves, hand held surgical instruments.)

Class II

- General controls are insufficient to provide reasonable assurance of safety and effectiveness.
- Carry moderate risk to patients.
- Special controls (e.g. special labelling requirements, mandatory performance standards, post marketing surveillance) are available to mitigate risk.
- Most of them require PREMARKETNOTIFICATION via 510(k) process (e.g. Powered wheelchairs, infusion pump, surgical drapes.)

Class III

- Carry potential risk of illness or injury Clinical study required to demonstrate safety and effectiveness prior to marketing approval.
- Most require PRE MARKET APPROVAL unless marketed prior to 1976.
- To be used in supporting human life or for a use which is of substantial importance in preventing impairment of human health. (e.g. Artificial heart valves, silicone gel filled breast implants, implanted cerebellar stimulator, coronary stents.)

Classification in India

- As per Medical Device Rules 2017, classification is based on the level of risk involved in their use.
- CLASS A - LOW RISK (Thermometer, Tongue depressor)
- CLASS B - LOW-MODERATE RISK (Suction equipment, Hypodermic needle)
- CLASS C - MODERATE-HIGH RISK(Ventilator, Bone fixation plate)
- CLASS D - HIGH RISK(Heart valves, AICD)

Pilot Phase of Device Trials

Pilot (Feasibility Study)

1) First done in humans, intended to acquire specific essential information about a device, before going to pivotal study.
2) Exploratory in nature
3) Use small number of patients (10-30)
4) Meant to give insight into the performance and safety, but can't provide definitive support to specific mechanism or therapeutic claims.

Pilot Phase of Device Trials

Objectives:

Include assessing feasibility (e.g. preliminary device performance), exploring eligibility criteria and their practical application for pivotal randomized controlled investigation, ascertaining potential harm (preliminary safety evaluations), validating a method for determining an outcome measure and evaluating the logistics of pivotal trial performance.

Pivotal Phase of Device Trials

- Definitive, confirmatory study. Conducted in a larger number of patients (100-300) to gather evidence for safety and efficacy
- For medical device which doesn't have a predicate medical device but approved outside INDIA, pivotal studies need to be carried.
- Prior to conducting a pivotal clinical investigation in Indian subjects, Central Drugs Standard Control Organization(CDSCO) may require pilot study data generated in Indian population.

Post Marketing Study

Post Marketing Clinical Investigation may not be considered necessary at the time of device approval but may be required by CDSCO for optimizing the intended use of medical device. It includes additional drug-device interaction, safety studies, investigation designed to support use under the approved condition(e.g. mortality/morbidity studies etc.)

Drug and Device Trials

Parameter	Drug Trial	Device Trial
Healthy subjects	Used in Phase 0 and Phase I	For medical devices specially those that are required as surgical implants, it's not possible to insert the device into healthy subjects
Number of subjects	In thousands	Usually in 100s
Randomization and Blinding	Commonly used	Difficult to implement
Standard tools to measure efficacy and safety	Tools such as ECG, Blood Pressure, Blood Sugar levels etc. used	Very much on per case basis.
Need for trials	In every case, even me too drugs	Not always required, depends on risk assessment

Trials on Herbal Products

Traditional Medicine

Diversity of health practices, approaches, knowledge, and beliefs incorporating plant, animal, and/or mineral-based medicines; spiritual therapies; manual techniques; and exercises, applied singly or in combination maintain well-being, as well as to treat, diagnose, or prevent illness

WHO

Categories of Herbal Drugs

- The substance is being clinically evaluated for same indication for which it is being used or as has been described in the texts.

- An extract of a plant or a compound isolated from the plant has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems- new chemical entity (NCE)

- A herbal product that has never been in use before and has not ever been mentioned in ancient literature.

Regulatory Requirements

- Traditional medicines are governed by the Drugs and Cosmetics Act (1940) and Rules (1945).
- In 1959, the Government of India amended the Drugs and Cosmetics Act to include drugs which are derived from traditional Indian medicine
- In 1993, the guidelines for the safety and efficacy of herbal medicines developed by an expert committee
- No new herbal medicines other than those authorized by the licensing authorities be allowed to be manufactured or marketed, except for those mentioned in ancient scriptures.

Clinical Trials

- The procedures laid down by the office of the DCGI for allopathic drugs should be followed for all traditional and herbal products to enter into clinical trials for any therapeutic condition.
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Trial Phases

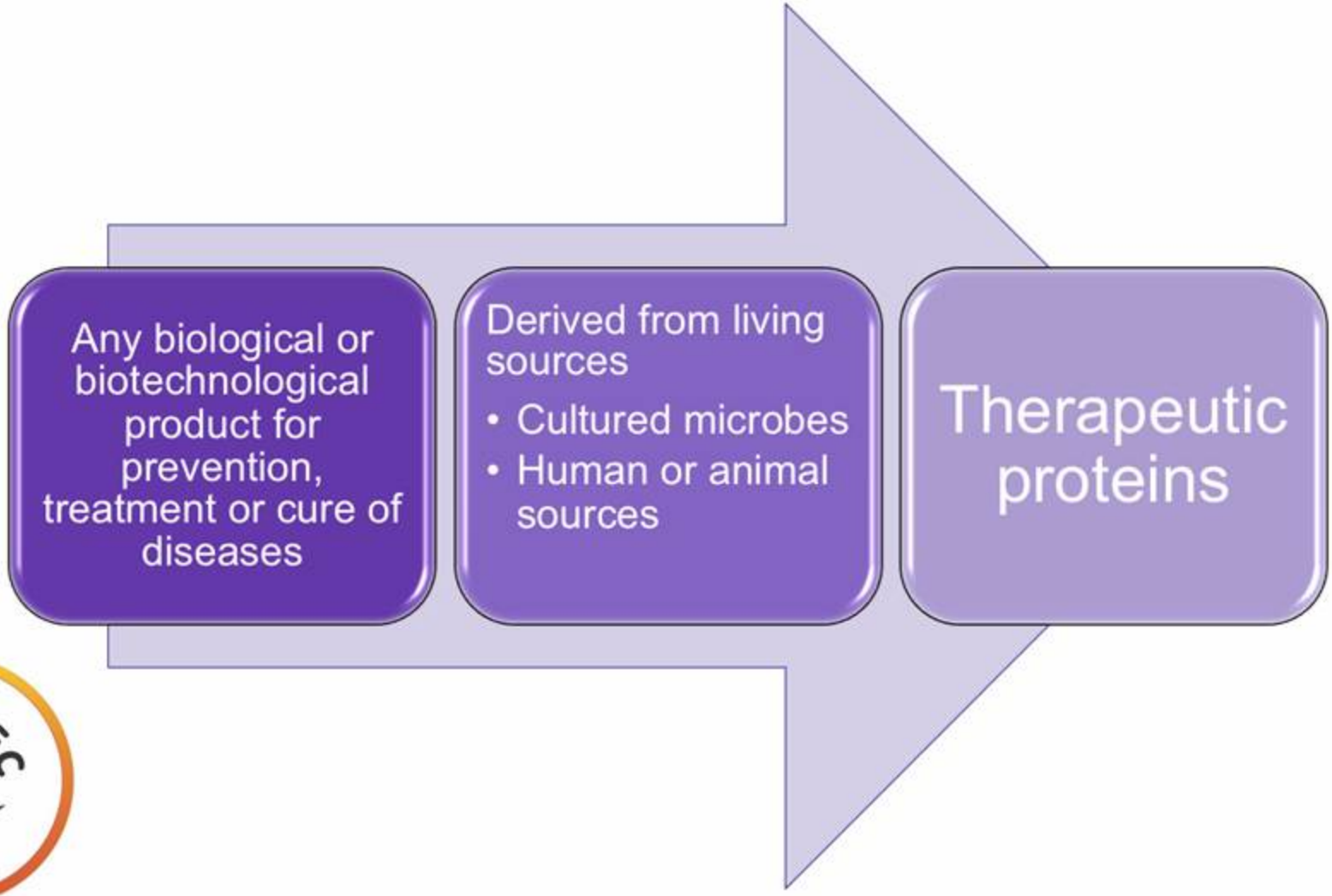
- Phase I studies may not be necessary
- Need for testing its toxicity in animals has been considerably reduced.
- Toxicity study may not be needed for phase II trial unless reports suggesting toxicity or herbal preparation is to be used for more than 3 months
- Larger multicentric phase III trial is subsequently planned based on results of phase II study.
- These trials have also got to be approved by the appropriate scientific and ethical committees of the concerned Institutes

Biosimilar Trials

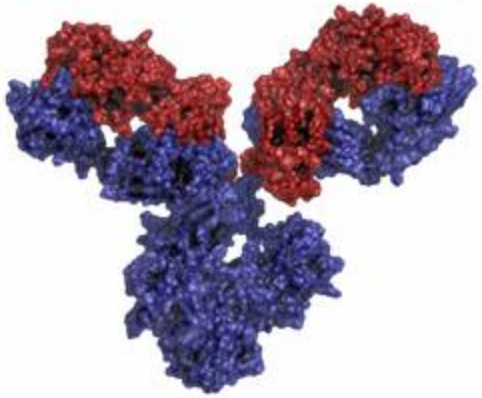
Why Biosimilars

- Biologicals have revolutionized the treatment for autoimmune, autoinflammatory, and cancer
- Biosimilars are expensive: drugs for rheumatoid arthritis cost $50,000/year[1]
- Costs have increased progressively: cost of some drugs doubled since their introduction
- Biosimilar TNFi in Norway in 2014 led to nearly a 60% annual saving
- Estimates of cost saving: >$66 billion USD over the next decade (4% of total biologics)[3]

What is a Biopharmaceutical?



The larger the better

Small Molecule	Biologics		
			
Aspirin ~ 180 Daltons	**Insulin** ~ 5,700 Daltons	**Growth hormone** ~ 22,000 Daltons	**Monoclonal antibody** ~ 150,000 Daltons

What Is a Biosimilar?

A biosimilar is a "copy" of a commercially available biopharmaceutical (reference product) that no longer is protected by patent which has:

- Undergone rigorous analytical and clinical assessment, in comparison to its reference product
- **AND**
- Been approved by a regulatory agency according to a specific pathway for biosimilar evaluation

A biosimilar is "highly similar" to its reference product in physicochemical characteristics, efficacy, and safety.

Biosimilars Are Not…

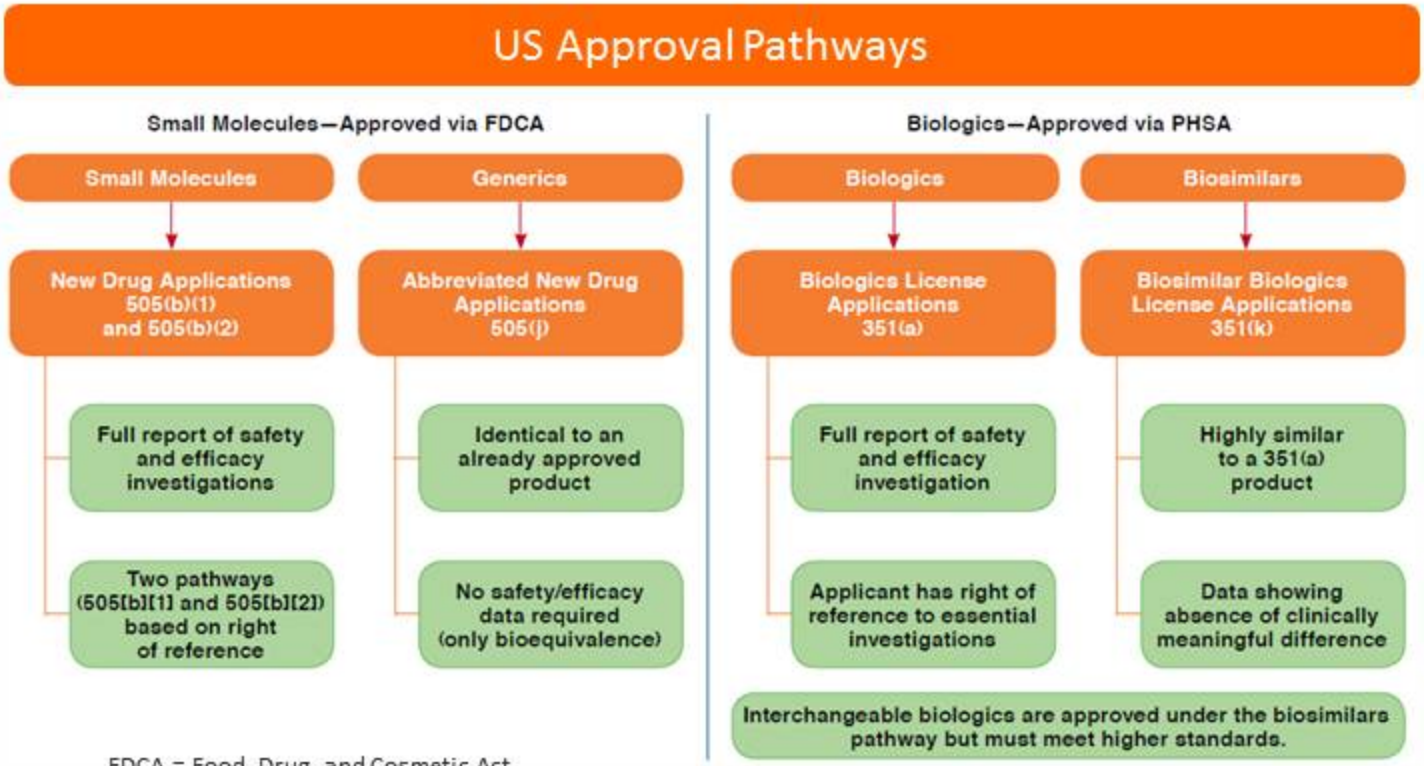
Second-Generation (or Biobetter)

- Structurally different Intended to improve performance while preserving mechanism of action
- Examples
  - Infliximab and adalimumab
  - Filgrastim and pegfilgrastim
- Not considered to bebiosimilar

Generic Drugs

- Small-molecule drugs, that are less complex than biosimilars
- Manufacturing process is several orders of magnitude less complex
- Regulated under different legislation

US Regulatory Pathways

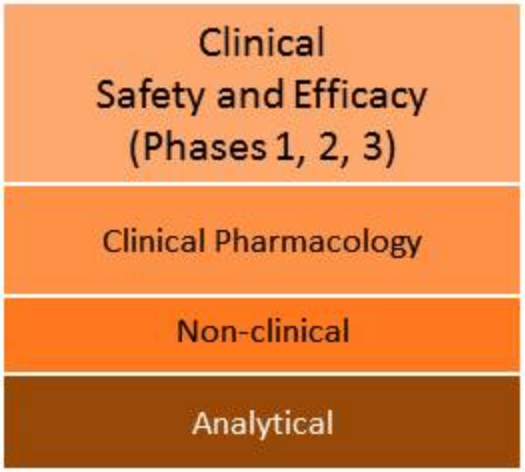


FDCA = Food, Drug, and Cosmetic Act
BPCI = Biologics Price Competition and Innovation
PHSA = Public Health Service Act

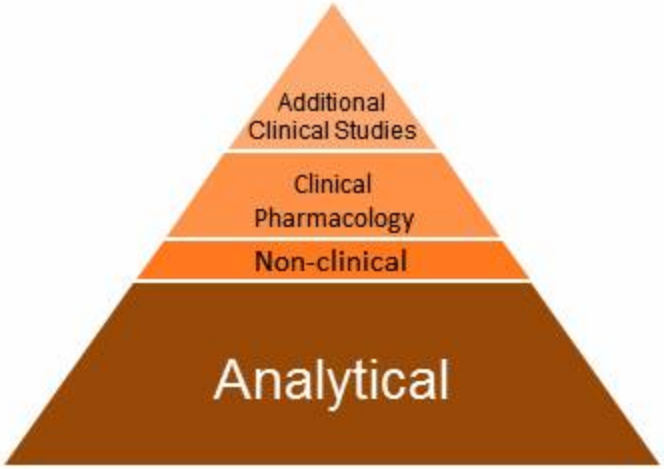
For historical reasons, some biologic products are currently approved under the FDCA. From 2020, all biologic products will be approved under the PHSA beginning in 2020.
Li EC, et al. J Manag Care Spec Pharm. 2015;21(7):532-539.

Goals of Development are Different

"Stand-alone" Development Program, 351(a)
Goal: To establish safety and efficacy of a new product

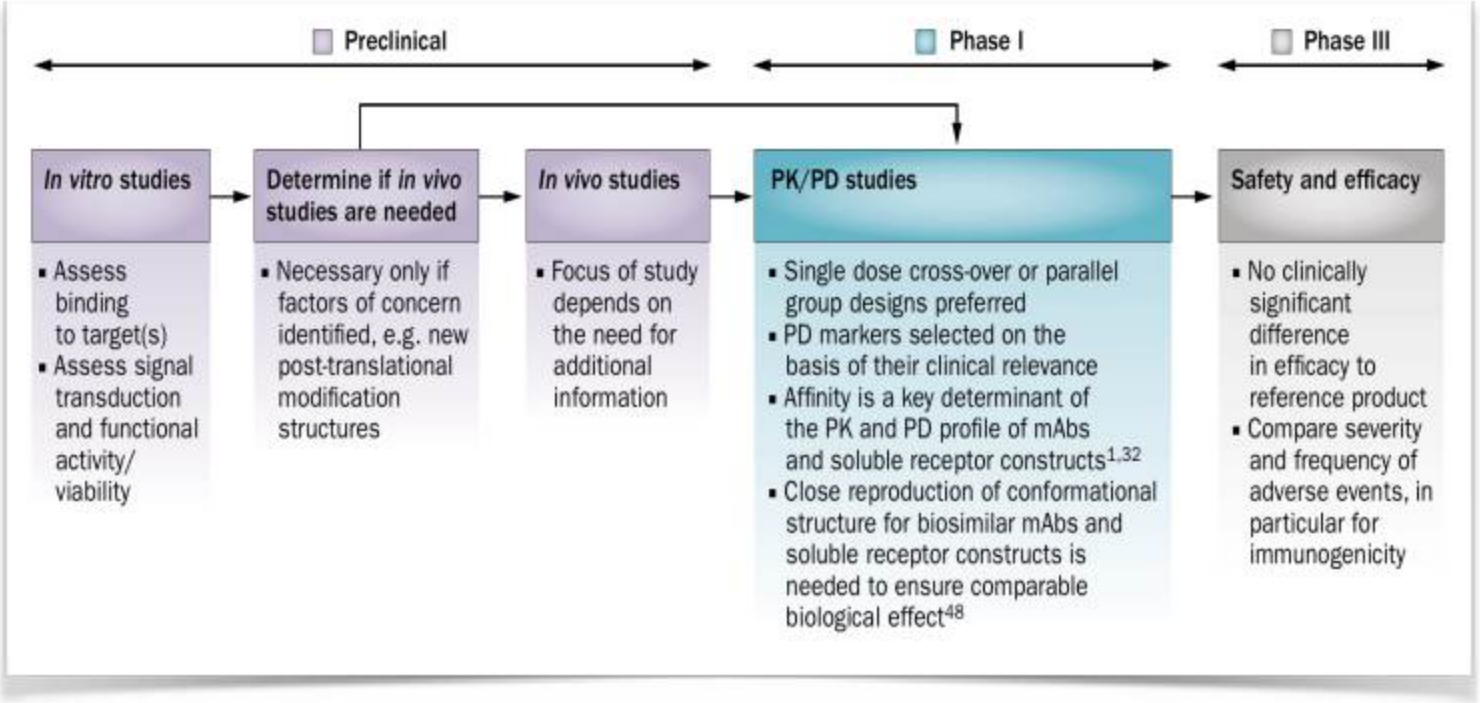


"Abbreviated" Development Program, 351(k)
Goal: To demonstrate biosimilarity (or interchangeability)



Overview of the Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the US. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM486171.pdf. Accessed February 4, 2017.

Biosimilars Development: A Stepwise Approach



PK = pharmacokinetics
PD = pharmacodynamics

Dörner T, et al. Nat Rev Rheumatol. 2015;11(12):713-724.
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What is immunogenicity?

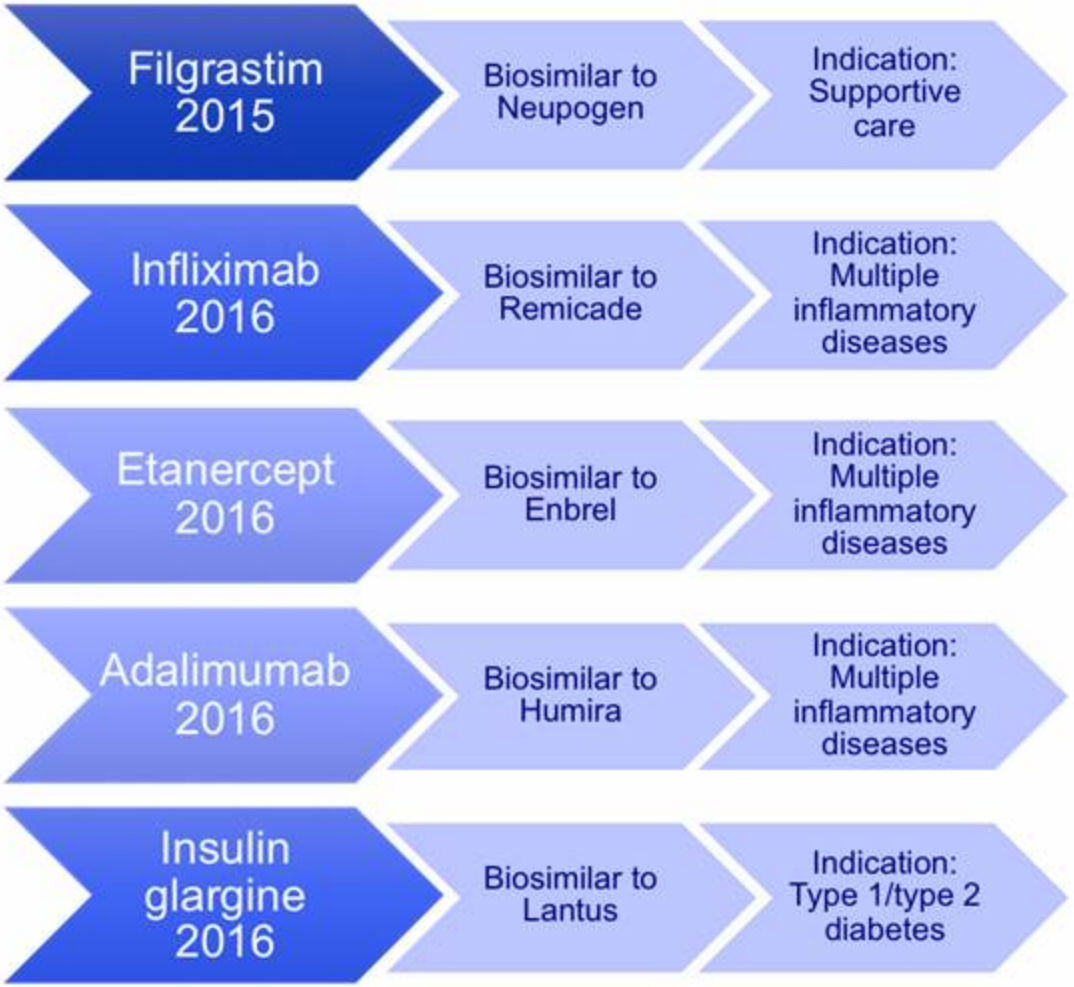
Immunogenicity is:

…the ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human or animal.

…the ability to induce a humoral and/or cell-mediated immune responses.

Woodcock J, et al. *Nat Rev Drug Discov*. 2007;6(6):437-442.

FDA-Approved Biosimilar Products

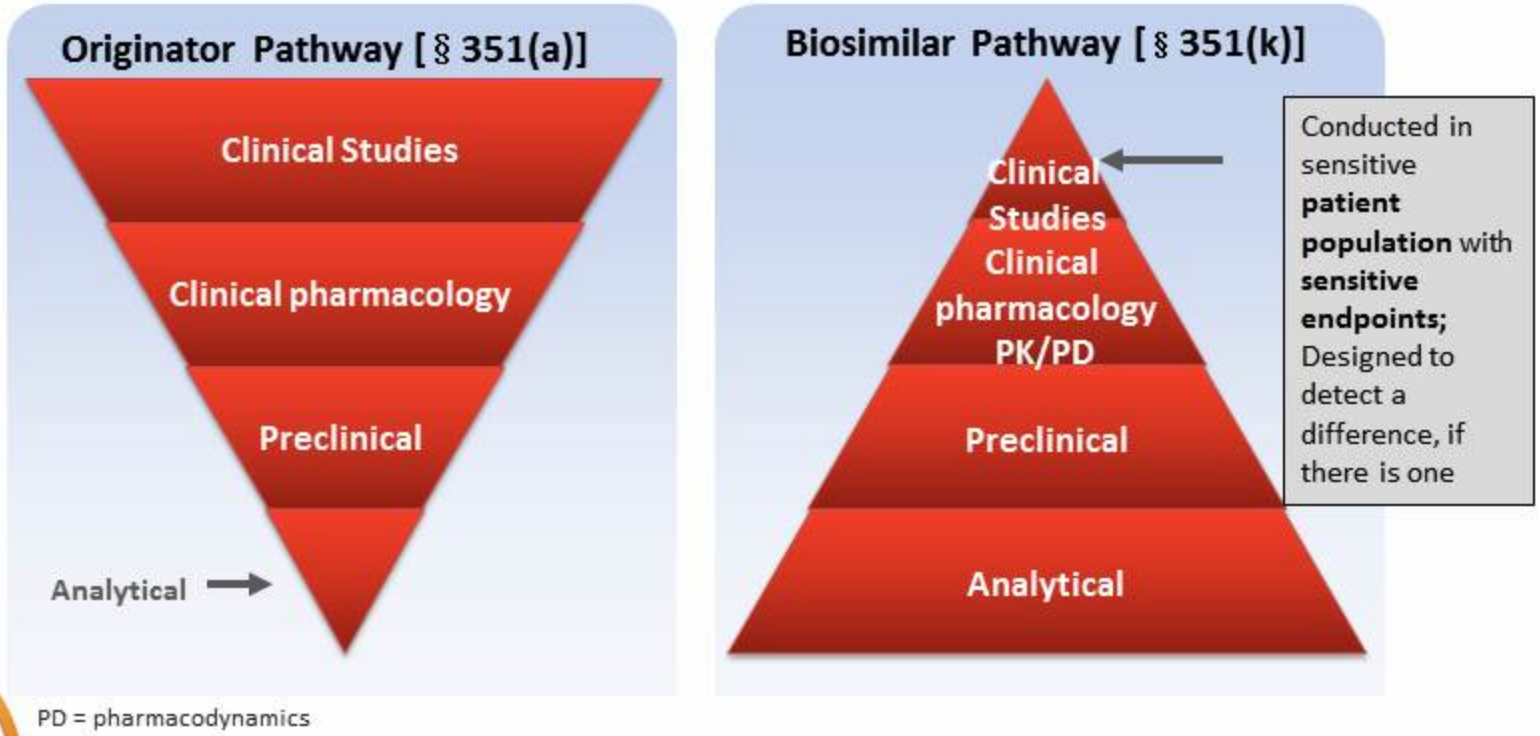


www.fda.gov

Biosimilar Pathway Represents a Paradigm Shift From Standard Originator Registration Pathway

Biosimilar Development Program Objective:

Establish Biosimilarity Based Upon Totality of Evidence, Not Reestablish Benefit



PD = pharmacodynamics

Schneider CK, et al. Nat Biotechnol. 2012;30(12):1179-1185. Kozlowski S, et al. N Engl J Med. 2011;365(5): 385-388. Macdonald J. Presented at: APEC Biotherapeutics Workshop; September 25, 2013; Seoul, Republic of Korea. Oral Presentation. McCamish M. Presented at: EMA Workshop on Biosimilars; October 31, 2013; London, UK. Oral Presentation. FDA. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm291197.htm . Accessed July 2016.

Comparative Clinical Studies

The goal of comparative clinical studies is to assess whether the biosimilar is different than the reference, not to demonstrate safety and efficacy.