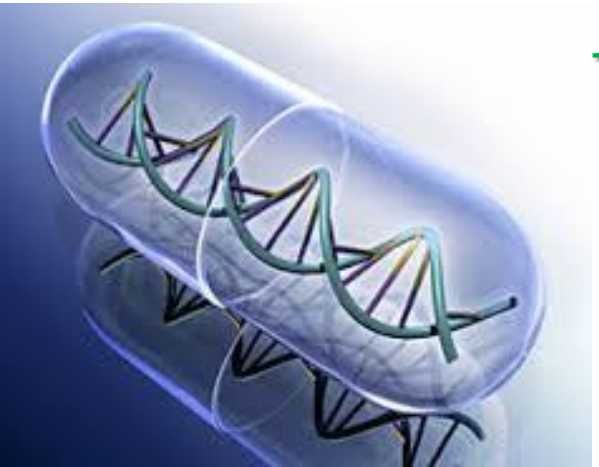
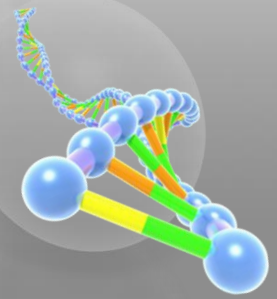
Comparative Study of Regulatory Requirements for Biologics Filing in United States and European Union



Mr. Shashi Kumar Yadav
Assistant Professor
Sri Indu Institute of Pharmacy
Hyderabad

Outline

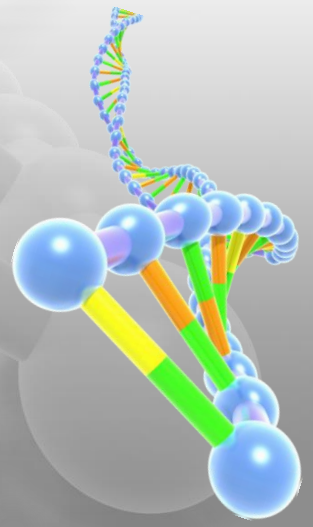
- Introduction
- Regulatory requirements for biologics in the US
  - What are biologics
  - Preclinical Studies for Biologics in US
  - Clinical Studies for Biologics in US
  - The Biologics License Application (BLA) in US
- Regulatory requirements for the development of Biologics in EU
  - Marketing authorization process
  - Preclinical Studies for Biologics
  - Clinical Studies for Biologics
  - The Marketing Authorization Application(MAA)
- Conclusion



Introduction

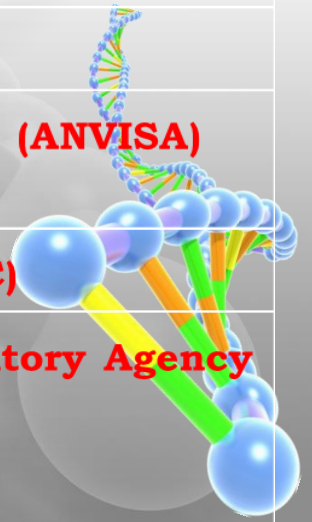
- **Regulatory Affairs in the Pharmaceutical industry may be defined as "The interface between the pharmaceutical company and the regulatory agencies across the world".**

- **Each and every country has its own regulatory body.**



Introduction

S.NO	Country	Regulatory Body
1	India	Central Drug Standard Control Organization (CDSCO)
2	USA	Food and Drug Administration (FDA)
3	Europe	European Medicines Evaluation Agency (EMEA)
4	Australia	Therapeutic Goods Administration (TGA)
5	Japan	Ministry of Health, Labor and Welfare (MHLW)
6	Canada	Health Canada
7	Brazil	Agencia Nacional de Vigilancia Sanitaria (ANVISA)
8	South Africa	Medicines Control Council (MCC)
9	UK	Medicines and Health care Products Regulatory Agency (MHRA)



Introduction

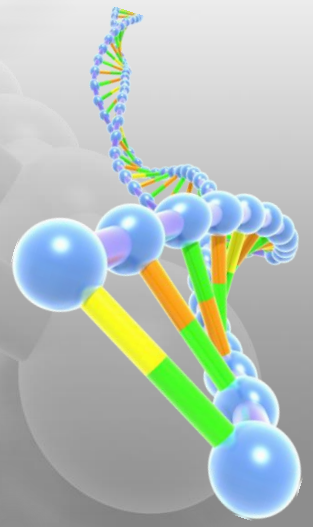
US FDA:

- The FDA regulates biopharmaceuticals as drugs under the Federal Food, Drug, and Cosmetic Act.
- FDA is a part of the Department of Health and Human Services.
- Currently the Public Health Service Act authorizes the FDA to ensure the safety, purity, and potency of biologics.
- The FDA approves biologics for marketing under section 351 of the Act.

Introduction

What Does the FDA Regulate?

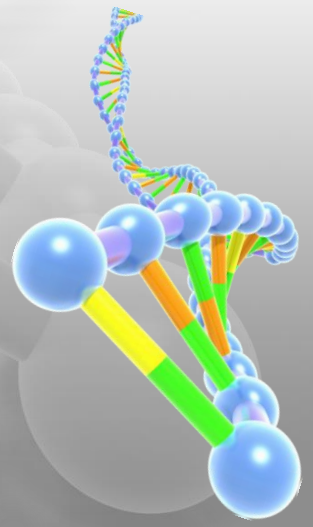
- Food (with Agriculture Department)
- Drugs
- Biologics
- Medical Devices
- Cosmetics
- Anything That Produces Dangerous Radiation



Introduction

FDA is comprised of several Offices and Centers

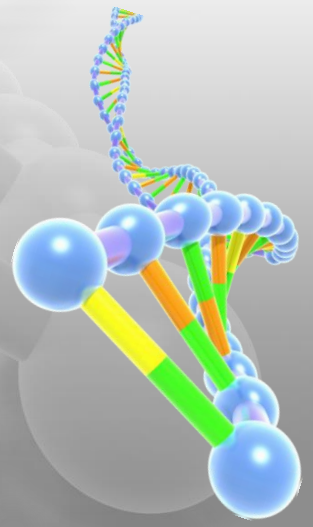
- **Office of the Commissioner (OC)**
- **Office of Regulatory Affairs (ORA)**
- **Center for Devices and Radiological Health (CDRH)**
- **Center for Drug Evaluation and Research (CDER)**
- **Center for Biologics Evaluation and Research (CBER)**
- **Center for Food Safety and Applied Nutrition (CFSAN)**
- **Center for Veterinary Medicine (CVM)**
- **National Center for Toxicological Research (NCTR)**



Introduction

- **Three FDA Centers deal with medical products:**
  - **Center for Drug Evaluation and Research (CDER)**
  - **Center for Devices and Radiological Health (CDRH)**
  - **Center for Biologics Evaluation and Research (CBER)**

Compounds characterized as biologics are reviewed by CBER

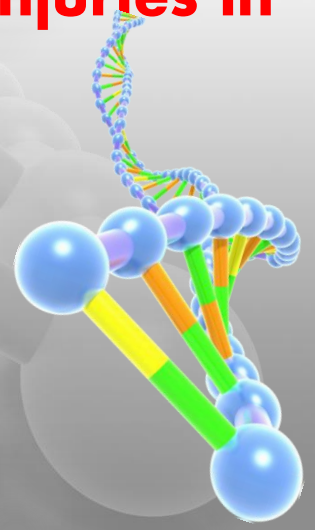


Regulatory requirements for the development of Biologics in the United States

- What are BIOLOGICS

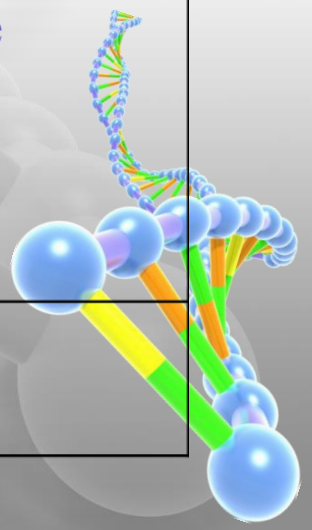
- **"Biological Products or biologics" were defined as**

"Any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product applicable to the prevention, treatment, or cure of a disease or injuries in man."



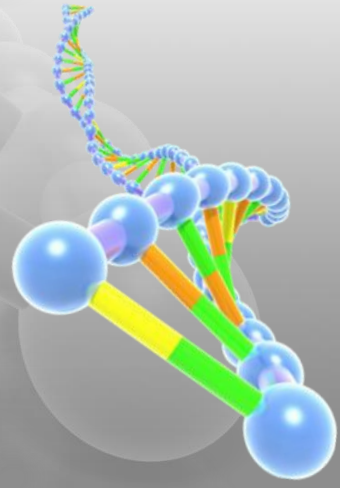
Differentiation

Properties	Biologic drugs	Chemical drugs
Size	Large	Small
Structure	Complex	Simple
Stability	Unstable	Stable
Modification	Many options	Well defined
Manufacturing	Unique line of living cells impossible to ensure identical copy	Predictable chemical process identical copy can be made
Characterization	Impossible to characterise	Easy to characterise



Preclinical Studies for Biologics in US

- **For biologics, the FDA has adopted the ICH S6 guidance and FDAs GLP regulations typically apply.**
- **In May 2012, the FDA adopted the addendum to that ICH guidance.**



Preclinical Studies for Biologics in US

Species selection:

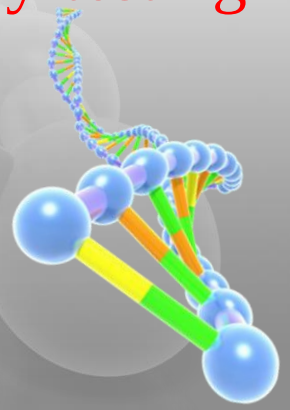
- Many biologics cannot be tested in commonly used animal species, such as rats and dogs, because of their biological activity and species or tissue-specific activity.
  - **In vitro binding assays and**
  - **Functional tests, to identify a "relevant species,"**
- In some cases, the chimpanzee is the only relevant species

Preclinical Studies for Biologics in US

Immunogenicity:

- Many biologics elicit immune responses, which can affect preclinical study results.
  - neutralizing or prolonging the biologic's activity,
  - forming immune complexes, or
  - cross-reacting with endogenous substances.

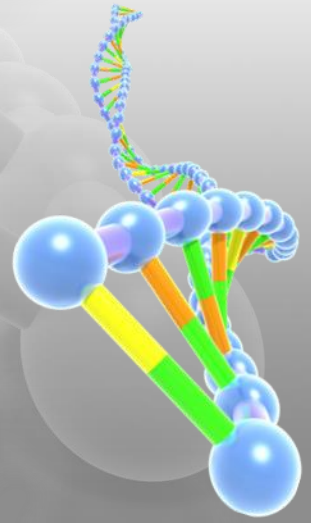
- Sponsors should obtain necessary samples for antibody testing during repeat-dose toxicity studies.



Preclinical Studies for Biologics in US

Study design:

1) Primary pharmacodynamics studies
    In vitro binding assay
    In vivo studies
2) Secondary pharmacodynamics studies
3) Safety pharmacodynamics studies

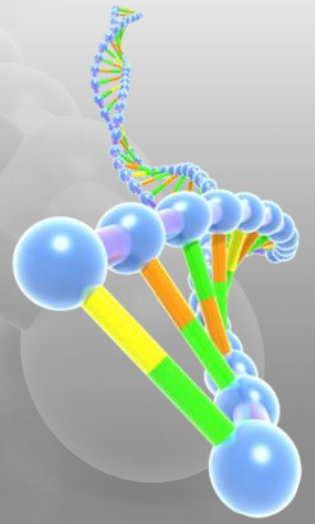


FDA Review and Decision-Making

- FDA inaction in 30 days triggers the study under the IND to "proceed"

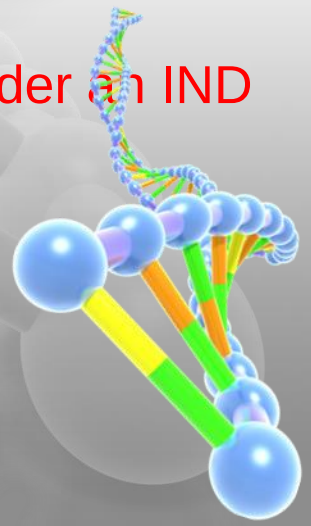
or

- FDA issuance of "clinical hold"



"Clinical Hold" (21 C.F.R. § 312.42)

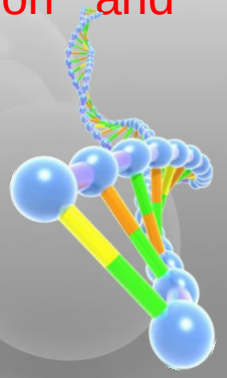
- A clinical hold is an order issued by FDA to the sponsor of an IND to delay or to suspend a clinical investigation
- Partial or complete clinical hold
  - Partial
    - A delay or suspension of only part of the clinical work requested under the IND
  - Complete
    - A delay or suspension of all clinical work requested under an IND



Clinical Studies for Biologics in US

The Investigational New Drug Application:

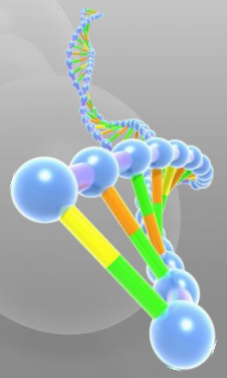
- The sponsor will submit the INDA to the FDA to perform clinical testing of a biologic in the United States
- An IND generally goes into effect 30 days after the FDA receives it.
- The IND must contain
  - information from preclinical studies.
  - the product's pharmacologic effects and mechanism of action and information on its ADME.
  - Chemistry, Manufacturing, and Control (CMC) information.



Clinical Studies for Biologics in US

Study Design Considerations:

- As with new drugs, clinical development of biologics typically involves three phases, Phase I, Phase II and Phase III.
- This programs must include an assessment of immunogenicity.
- With respect to immunogenicity, these studies should assess subjects' antibody development, both directly after administration and at least 28 days thereafter.



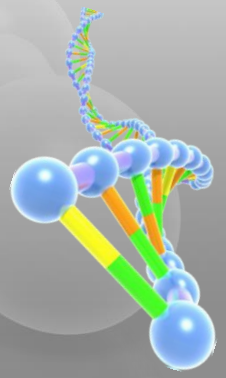
Clinical Studies for Biologics in US

Study Design Considerations:

Phase I studies

- the “initial introduction” of the biologic to f humans
- to assess the product’s metabolism, pharmacology, and safety at escalating doses.
- Determine Maximum Tolerated Dose (MTD)

- Unlike Phase I trials for drugs, Phase I studies of biologics frequently involve administration to patients rather than healthy volunteers.

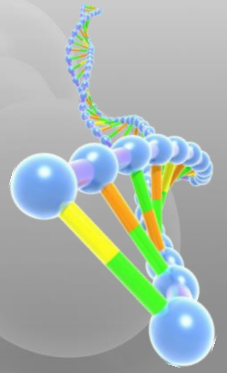


Clinical Studies for Biologics in US

- Phase II trials
- Begin if Phase 1 studies do not reveal unacceptable toxicity

- Phase II trials are controlled studies that evaluate safety and short-term adverse events

- Biologics sponsors often combine phase II studies with phase I or phase III studies.

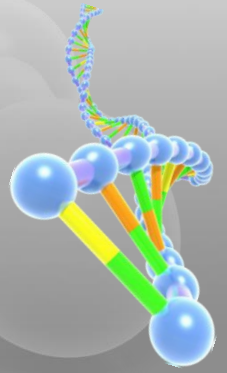


Clinical Studies for Biologics in US

Phase III studies

- Begin if preliminary evidence of effectiveness is shown during phase II.
- Phase III studies are randomized, controlled, and performed at multiple study centers.

- Gather more information about safety and effectiveness in a defined population.



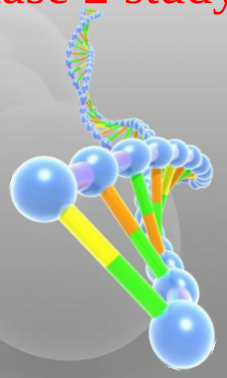
Clinical Studies for Biologics in US

Meetings with the FDA Before and During the Clinical Trial Period:

- Sponsors can obtain several types of pre-approval meetings with the FDA.
- 21 C.F.R. 312.82 describes two types of such meetings.

- First, the sponsor can seek a pre-IND meeting
  - to reach agreement with the FDA on the design of preclinical studies.

- Second, the sponsor may meet with the FDA to reach agreement on phase 2 study design.

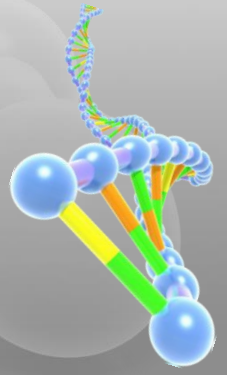


The Biologics License Application (BLA) in US

A BLA is used rather than a NDA though the official FDA form is designated 356h and is identical.

Under 21 C.F.R. § 601.2, the BLA must contain,

- nonclinical and clinical data,
- a "full description of manufacturing methods,
- stability data,
- proposed labeling,
- enclosures, and containers;



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CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

32. Typed Name and Title of Respons ble Official or Agent signing this form	33. Date *(mm/dd/yyyy)*

34. Telephone Number *(Include country code if applicable and area code)*	35. FAX Number *(Include country code if applicable and area code)*	36. Email Address

37. Address

Address 1 *(Street address, P.O. box, company name c/o)*	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	
City	State/Province/Region
Country United States of America	ZIP or Postal Code

38. Signature of Applicant's Responsible Official Sign	39. Signature of Authorized U.S. Agent Sign

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: December 31, 2013
See PRA Statement on page 3.

1. Date of Submission *(mm/dd/yyyy)*

APPLICANT INFORMATION

2. Name of Applicant

3. Telephone Number *(Include country code if applicable and area code)*

4. Facsimile (FAX) Number *(Include country code if applicable and area code)*

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

U.S. License Number if previous issued

6. Authorized U.S. Agent Name, Address, Telephone and FAX Number *(If applicable)*

U.S. Agent Name

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State

ZIP or Postal Code

Telephone Number *(Include area code)*

FAX Number *(Include area code)*

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number

8. Supplement Number *(If applicable)*

9. Established Name *(e.g., proper name, USP/USAN name)*

10. Proprietary Name *(Trade Name) (If any)*

11. Chemical/Biochemical/Blood Product Name *(If any)*

12. Dosage Form | 13. Strengths | 14. Route of Administration

15. Proposed Indication for Use

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

Contin. Page for #15

APPLICATION INFORMATION

16. Application Type *(Select one)*
☐ New Drug Application (NDA) ☐ Biologics License Application (BLA)
☐ Abbreviated New Drug Application (ANDA)

17. If an NDA, identify the type ☐ 505 (b)(1) ☐ 505 (b)(2)

18. If a BLA, identify the type ☐ 351 (a) ☐ 351 (k)

19. If a 351(k), identify the biological reference product that is the basis for the submission.
Name of Biologic: _____ Holder of Licensed Application: _____

20. If an ANDA, or 505(b)(2), identify the listed drug product that is the basis for the submission.
Name of Drug: _____ Application Number of Relied Upon Product: _____
Indicate Patent Certification: ☐ P1 ☐ P2 ☐ P3 ☐ P4 ☐ Section viii - MOU ☐ Statement of no relevant patents

21. Submission *(Select one)* ☐ Original ☐ Labeling Supplement ☐ CMC Supplement ☐ Efficacy Supplement ☐ Annual Report
☐ Product Correspondence ☐ REMS Supplement ☐ Post Marketing Requirements or Commitments ☐ Periodic Safety Report
☐ Other *(Specify)*: _____

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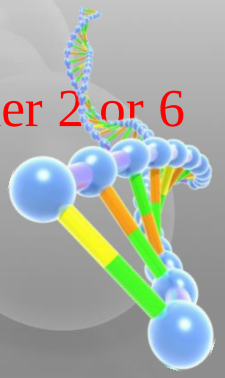
The Biologics License Application (BLA) in US

Biologics License Application review process:

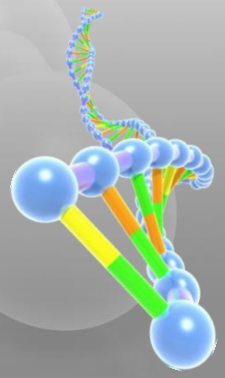
- After a sponsor submits a BLA, the FDA assembles a review team and then decides, within the first 60 days after submission, whether it can
  - "file" the application or
  - a refuse-to-file decision
- After the agency completes its review of the BLA, it will issue
  - an approval letter, or
  - a complete response letter (CRL), which states that the agency cannot approve the BLA in its current form.
- An applicant may file a "resubmission" to address the deficiencies.
- The review timeline for a resubmission depends on its content but is either 2 or 6 months from receipt.



The Biologics License Application (BLA) in US

Approval Standard :

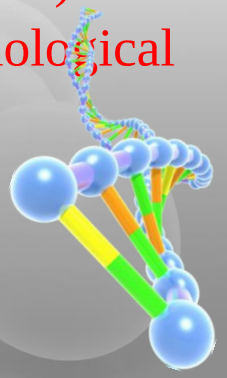
- The FDA must approve a BLA if it shows that the proposed product is “safe, pure, and potent” and the facilities where the product made, processed, packed, or held comply with good manufacturing practice (GMP).



Regulatory requirements for the development of Biologics in EU

EUROPEAN UNION

- European Medicines Agency, an EU regulatory agency for the evaluation of medicinal products.
- In EU Directive 2001/83/EC of the European Parliament Regulates marketing authorization of biologics with the essential aim of governing the production, distribution, and use of biological products for protection of public health.
- The Committee for Medicinal Products for Human Use (CHMP) for assessment of all medicinal products for human use including biological products.



MARKETING AUTHORIZATION PROCESS

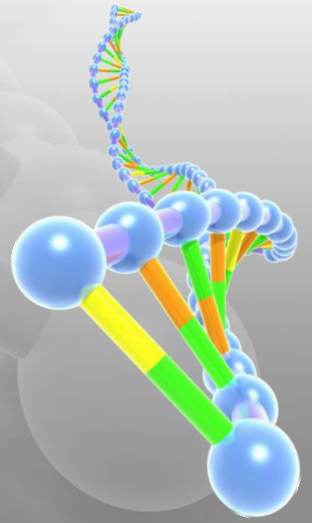
Marketing authorisations Procedure in European Union divided in to Four types.

National procedure

Centralised procedure

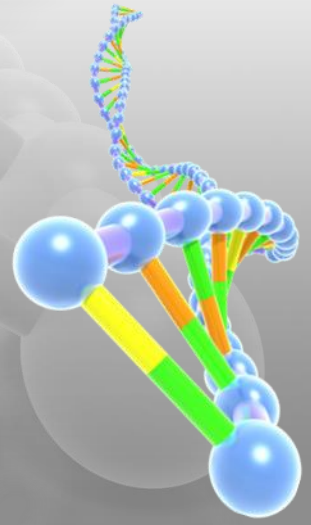
Mutual recognition procedure

Decentralised procedure



Preclinical Studies for Biologics in EU

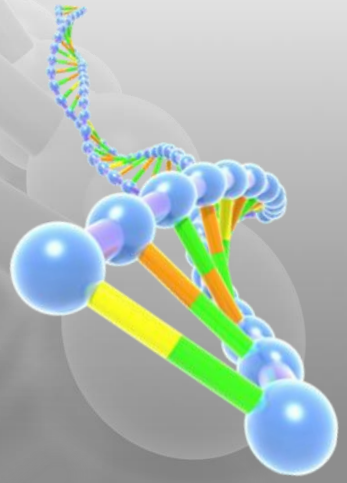
- The CHMP has adopted ICH S6 as a guideline governing preclinical testing of biologics.
- In July 2011, the CHMP adopted the addendum to this guideline, and the addendum came into effect in Europe in December 2011.



Preclinical Studies for Biologics in EU

- The addendum covers the following five topics:

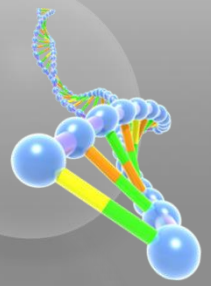
- Species selection,
- Study design,
- Immunogenicity,
- Reproductive and developmental toxicity, and
- Carcinogenicity.



Preclinical Studies for Biologics in EU

- **Species selection:**
- According to the addendum, the sponsor use in vitro assays making qualitative and quantitative cross-species comparisons of relative target binding affinities, receptor–ligand occupancy, and kinetics.

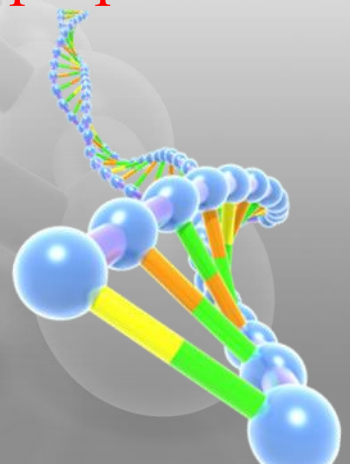
- Sponsors also should assess functional activity.
- **Immunogenicity:**
- The addendum provides more detail than ICH S6 regarding situations when the sponsor should measure antidrug antibodies (ADAs), namely when (1) there is evidence of altered PD activity, (2) there is evidence of immune-mediated reactions.



Preclinical Studies for Biologics in EU

- **Reproductive and Developmental Toxicity:**
- The addendum provides general advice on reproductive and developmental testing and then discusses more specific recommendations for fertility studies, embryo–fetal development (EFD) studies and pre- and postnatal development (PPND) studies, and the timing of studies in nonhuman primates (NHPs).

- Typical carcinogenicity bioassays are “generally inappropriate” for biologics

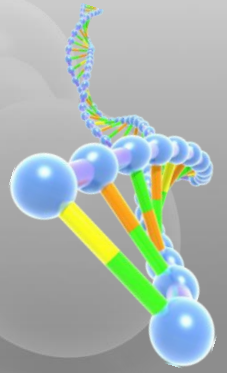


Clinical Studies for Biologics in EU

Clinical trials of biologics must comply with GCP, as described in Directive 2005 /28 /EC and the ICH E6 guideline, which the CHMP has adopted.

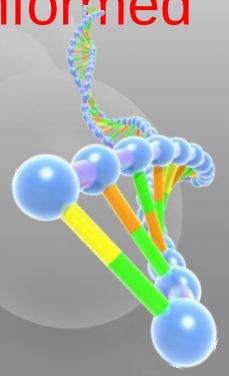
- CHMP has issued a guideline on quality requirements during the clinical trial period for investigational medicinal products (IMPs) containing biological or biotechnology-derived substances.

- The sponsor will submit the sponsor's Investigational Medicinal Product Dossier (IMPD) to the competent authority to perform clinical trials.



Clinical Studies for Biologics in EU

- The sponsor then must apply for approval from both
  - the ethics committee in the country
  - competent authorities of the Member States.
- The opinion of the ethics committee should be issued within 60 days.
- The trial may begin only if (1) the ethics committee has issued a favorable opinion and (2) no competent authority has informed the applicant for non acceptance.



Clinical Studies for Biologics in EU

Phase I studies typically investigate

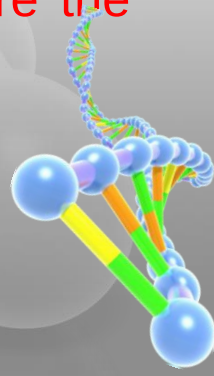
(1) initial safety and tolerability; (2) PK, (3) PD; and (4) drug activity.

Phase I studies may be conducted in healthy volunteers or certain types of patients. If the medicine has significant potential toxicity (e.g., cytotoxic products), the trial will usually be conducted In patients.

Phase II trials usually allowing for evaluation of the medicine's safety and efficacy.

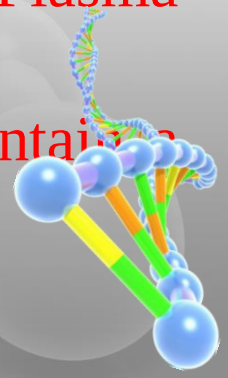
- A major goal of this phase is to determine the dose(s) for phase III trials.

Phase III typically involves therapeutic confirmatory studies and explore the dose response relationship



The Marketing Authorization Application(MAA): Contents and Approval Standard

- The approval standards for biotechnology products are the same as for drugs. Both types of products must be safe and effective and have appropriate quality.
- Many biologics fall under the scope of the centralized marketing authorization procedure, which is mandatory for medicines developed through biotechnological methods.
- Other special rules apply certain types of biological medicines. For example, for plasma-derived medicinal products, the applicant must provide an information dossier, the Plasma Master File.
- MAAs for vaccines other than for influenza need to contain a Vaccine Antigen Master File.



conclusion

- The study introduces the legal and regulatory aspects pertaining to biological products in the United States and in the European Union.

- The Drug approvals in the US, Europe are the most demanding in the world. The primary purpose of the rules governing medicinal products in US, Europe is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient’s well - being is protected.

BIBLIOGRAPHY

- Richard Guarino - New Drug Approval Process, Fifth Edition; Informa health care;2009: 219-240
- Douglas J. Pisano, David S. Mantus- FDA Regulatory Affairs: A Guide For Prescription Drugs, Medical Devices, And Biologics; CRC Press; Second Edition; 2008: 28-29,417-418
- http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073246.pdf
- http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/12/WC500136402.pdf
- www.amgen.com_pdfs_misc_Biologics_and_Biosimilars_Overview
- Steven Lee, Ph.D, ceo, A-Bio Pharma Pte Ltd-Process development and manufacturing (CMC) for biologics development-an overview-. November 26 2009
- Gary Walsh- Pharmaceutical biotechnology concepts and application; Wiley Publications; 2007:1-11.


Thank
You!