"REGULATORY ASPECTS OF BIOLOGICS IN INDIA, USA AND EUROPE"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

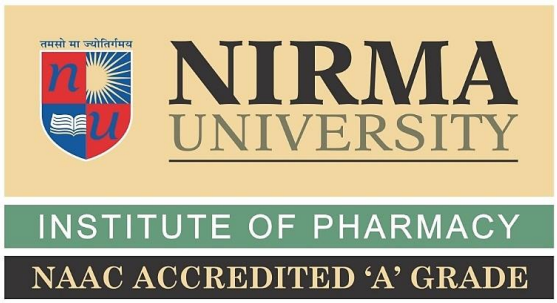
BY

KAVYA SHAH (16BPH040)

Semester VIII

UNDER THE GUIDANCE OF

DR. BHUMIKA D. PATEL



INSTITUTE OF PHARMACY
NIRMA UNIVERSITY
SARKHEJ-GANDHINAGAR HIGHWAY
AHMEDABAD-382481
GUJARAT, INDIA

MAY 2020

CERTIFICATE

This is to certify that ***"REGULATORY ASPECTS OF BIOLOGICS IN INDIA, USA AND EUROPE"*** *is the bonafide work carried out by* ***KAVYA SHAH*** *(16BPH040), B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction.*

Guide:

Dr. Bhumika D. Patel
M.Pharm, Ph.D.
Assistant Professor
Department of Pharmaceutical Chemistry
Institute of Pharmacy,
Nirma University

Dr. Hardik Bhatt
M.Pharm, Ph.D.
Head, Department of Pharmaceutical Chemistry
Institute of Pharmacy,
Nirma University

Dr. Manjunath Ghate
M.Pharm, Ph.D.
Director
Institute of Pharmacy,
Nirma University

Date: 29 / 05 / 2020

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Guide:

B.D.Patel

Dr. Bhumika D. Patel
M.Pharm, Ph.D.
Assistant Professor
Department of Pharmaceutical Chemistry
Institute of Pharmacy,
Nirma University

Dr. Hardik Bhatt
M.Pharm, Ph.D.
Head, Department of Pharmaceutical Chemistry
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Kavya Shah (16BPH040)
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Guide:

Dr. Bhumika D. Patel
M.Pharm, Ph.D.
Assistant Professor
Department of Pharmaceutical Chemistry
Institute of Pharmacy,
Nirma University

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K. D. Shah

Kavya Shah (16BPH040)
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Guide:

B. D. Patel

Dr. Bhumika D. Patel
M.Pharm, Ph.D.
Assistant Professor
Department of Pharmaceutical Chemistry
Institute of Pharmacy,
Nirma University

Date: 29/05/2020

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DECLARATION

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Kavya Shah (16BPH040),
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Date: 29/05/ 2020

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K.D.Shah

Kavya Shah (16BPH040),
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Date: 29/05/ 2020

Acknowledgement

Foremost, I would like to express my sincere gratitude to Dr. Bhumika D Patel for her continuous support and guidance throughout my project, for her patience, motivation, enthusiasm and most importantly immense knowledge, which made the process easier and smooth.

I would also like to thank Dr. Manjunath Ghate for offering us an opportunity due to which we were able to carry out this project, which has enriched our knowledge.

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K. D. Shah

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1. Abstract –

Biologics has been a category in pharmaceuticals for almost a decade now. Increased market need for biologics accounts due to various reasons like big brand name companies losing patent extensions, increased need for biologics as therapeutic interventions in chronic diseases, increased initiatives taken up by governments and rising regulatory convergence and better healthcare facilities for all nations. Hence which also demands for well-defined and structured protocols and procedures for manufacturing, approval and marketing authorization for these, this study will provide an approach for understanding these regulatory aspects of biologics in USA, Europe and India.

2. Introduction -

Biologics are products obtained from living organisms like humans, animals and microorganisms, which may or may not contain a component of it. It finds its application in diagnosis, treatment and prevention of a lot of diseases including various cancers and autoimmune diseases. Biologics mainly include antitoxins, vaccines, proteins, blood, gene therapy, blood components and tissues.(Maurya et al.) These are made up of sugars, nucleic acids or proteins or combinations of these substances. As a matter of fact biologics are an advanced therapy for many diseases like Chron's disease, Ulcerative colitis and Rheumatoid arthritis.

First time biologics were produced by recombinant technique to create replica or enhance complex peptides, proteins and naturally occurring glycoproteins. Today even more complex biologics like monoclonal antibodies have been furnished through use of DNA in cells of bacteria, yeast and mammals to provide assistance to therapeutic intervention. Biologics, biosimilars and generic drugs differ from each other on the basis of their origin, chemical method are usually involved in making of small molecules while biologics are mainly derived from living organisms.

Drug makers in developed and developing countries are more interested in investing in biologics than small molecules as it presents more profitable investment opportunities. The total global budget for 2006 stood at 93 billion dollars and grew by 69 percent to 157 billion dollars in 2011. In 2010 the biological industry was projected at $254.9 billion, with an growth of 9.5% in CAGR to $580.5 billion by 2026.

Regulatory factors have developed from the government's intention to safeguard public health by regulation of the protection and efficacy of medication, the veterinary medication, cosmetic goods, medical devices and pesticides; numerous regulatory bodies regulate specific elements of biological goods such as manufacturing, clearance, quality monitoring and authorization to market.

In India CDSCO (central drugs standard control organization), a regulatory body for the assessment of product protection, efficacy and uniformity in the region, is the

Main Product Performance Regulation Agency. Genetic Manipulation Review Committee monitors the production and preclinical evaluation of recombinant biologics. A number of biologics are under production in India because of which regulatory agencies are expected to establish an unambiguous regulatory pathway, which specifies the needs of related biologics to an licensed biological comparison to achieve comparable health, effectiveness and efficiency. (CUTS International)

In 2009 a legal outline for authorising biosimilars was established in USA via BPCI act (biologics price competition and innovation act). The BPCI was a amendment to the Act for Public Safety to create an abbreviated for biologics clearance process. The first biosimilars approved in 2015 for the FDA had announced sale in the USA. Since then, FDA has licensed 16 biosimilars and FDA is still planning guidelines on these products and released multiple guidelines on the topic.

In Europe the regulatory body responsible regulation is EMA (European medical agency) in January 2001 EMA started considering scientific issues presented by biosimilars products, In 2003, the European Commission updated the marketing authorization standards for medicinal products and created a related category of biological medicinal products.

3. Market trends-

- Capital expenditures in biologics are rising due to the pressure of chronic illnesses, end of patent rights or exclusivity period of important biologic pharmaceuticals, and growing demand for creative drugs, which are pushing up the global market. (Poojar et al.)
- Investing in biological drugs has allowed large pharmaceutical firms, including Eli Lilly and Company, Bristol-Myers Squibb, Novartis, AstraZeneca, and GlaxoSmithKline (GSK), to capitalize in such drugs, especially in finding cure of major chronic diseases, including cancer and autoimmune diseases. The United States Food and Drug Administration

(FDA) approved three biological products in 2019; one of them is Griffols' anticoagulant treatment. (Ii)

- In the year 2006 the annual global expenditure was $93 billion and increased by 69% to $157 billion in 2011.
- In 2015, the global demand for biologics was valued at USD 276.6 billion.
- The demand for biologics was forecast at 254.9 billion dollars in 2017 and with increase of 11.9% CAGR at 625,6 billion by 2026. (Poojar et al.)
- Market share for biologics based on diseases from 2014-2025.

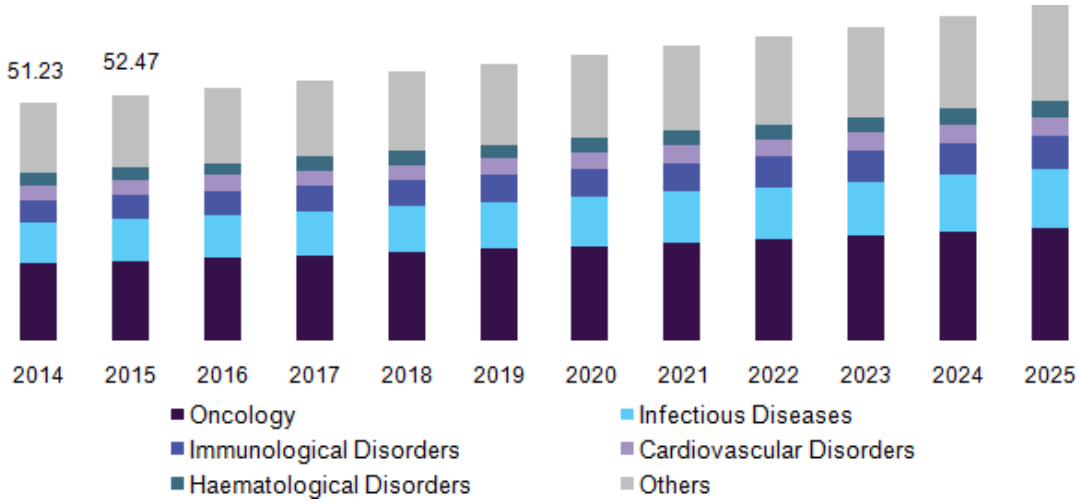

Figure 1 – Use of biologics in diseases 2014-2025

- Due to the decrease in profitability of small drug molecules, biologics are predicted to experience sustainable growth over the next few years. Pharmaceutical firms concentrate on producing multiple biopharmaceutical drugs to retain a spot on the market. (Poojar et al.)
- In Asia Pacific with CAGR, the Biologics demand has risen by 13%, led by 11.8% and 11.6%, respectively, by North America and Europe. The rise in cancer incidence and other target diseases globally is the cornerstone to the growth of the industry in all regions throughout the projected era. (Ii) (Poojar et al.)
- As of 2018, monoclonal antibodies segment dominates the market holding 39% of the global market since it is the primary medicine used for treating cancer. (Ecker et al.)

- Gene biologics expand mainly depending on drug form with a CAGR of 14.3% and followed by vaccines and cell biologics.
- Segment of implementation in the cancer field, autoimmune and infectious diseases industry of 42.2 percent and 35.9 and 14.6 percent respectively.
- Asia Pacific is expected, because of the wide prevalence of target diseases in nations such as India and China, to account for 21.4 percent of the global biological industry. (Poojar et al.)

Figure 2 – Regional analysis of biologic market 2018-2022

Figure 3 – global analysis of biologic market 2018-2022

4. ICH –

In uniting regulatory authorities and the pharmaceutical industry, the The International Council for Harmonisation (ICH) is exceptional in addressing scientific and technological issues of pharmaceuticals and establishing ICH recommendations. ICH has steadily grown since its establishment in 1990, as it has tackled increasingly global trends in the pharmaceutical industry and a growing range of regulatories have implemented these ICH recommendations. ICH's goal is to insure that worldwide harmonization ensures the production, registration and management of secure, effective and good-quality medicines in the most resource-efficient way, in accordance with high standards. (Levenson et al.)

ICH has expanded as an organisation, with 16 Leaders and 32 members, following the declaration of the operational reforms in October 2015.

4.1 ICH Quality Guidelines for biologics (Levenson et al.) –

These include

1. Q5A(R1): (Evaluation of biotechnology products for viral safety, which are derived from human or animal cell lines) The purpose of this study is to determine the viral safeness of biotechnology products extracted from labeled human or animal-based cell lines and outline data to be submitted for marketing applications / registration. This guidance intends to include an overall structure for virus detection and viral clearance evaluation studies.
2. Q5B: (Analysis of the expression construct in cells used for production of r-DNA derived protein products) It aims to explain details that is considered useful when analyzing the expression structure of protein derived from recombinant DNA.
3. Q5C: (Quality of biotechnological products, stability testing of biotechnological/biological products) The document enhances the recommendations for stability (Q1A) and also discusses particular details of stabilization test procedures that will take into consideration the unique properties of drugs in which proteins and/or polypeptides are present as the active components.
4. Q5D: (Characterization and derivation of cell substances intended for manufacturing of biotechnological/biological). This provides wider guidelines

for the growth and the processing of biotechnological / biological goods and for the preparation and characterization of human and animal cell lines as well as microbial cell lines.

5. Q5E: (Comparability evaluation of biologics in which changes regarding manufacturing process are made) The aim of this guideline is to develop guidelines for evaluating the comparability of biotechnological / biological goods prior and post improvements have been prepared in drug content or drug product manufacturing processes.

ICH Safety Guidelines for biologics (Levenson et al.) –

1. S6(R1): (Preclinical safety evaluation of biotechnology-derived pharmaceuticals) This covers the preclinical safety testing requirements for biotechnological products. It addresses the use of animal models of disease, determination of when genotoxicity assays and carcinogenicity studies should be performed and the impact of antibody formation on duration of toxicology studies.

5. Comparison table of regulatory aspects for biologics in India USA and Europe

Serial number	Parameter	India	USA	Europe
5.1	Regulatory body	• **CDSCO -** The primary product quality control authority (CDSCO) chaired by the Drug Controller General of India (DCGI) is responsible for the clearance of clinical trials and experimental medicines, the administrative body working in the Ministry of health and Family Welfare (MoHFW). Clinical trial clearance, product import permit is the duty of Biologics CDSCO, export of clinical samples for biochemical and	• **USFDA –** **(**United nations food and drug administration), It is the federal agency of united nations, which works under the department of health & human services, to safeguard and encourage public health by control and surveillance of food protection, tobacco products, dietary additives, counter-medicinal goods, vaccinations, biological medicines, transfusion of the blood, medical equipment,	**EMA –** (European medicines agency) is an agency under European Union (EU), which evaluates and supervises medicinal products. Before 2004, EMA was called as EMEA (European medicines evaluation agency). EMA operates in a decentralized manner and its primary function lies in public and animal safety security and health promotion by evaluation and control of human and veterinary use. It evaluates

		immunological analysis and permission for marketing and manufacturing. Zonal CDSCO authorize import of drugs for examination, test and analysis for research and development. • **RCGM** - It functions by department of biotechnology (DBT), ministry of science and technology. In matters of biologics RCGM will be responsible for authorizing the conduct of research and development, exchange of genetically engineered cell banks for the purpose of research and	cosmetics, electromagnetic medicines radiation emitting devices, animal food and veterinary products. The FDA has several offices and centres. • **CBER** – (The centre for biologics evaluation and research). It is one of the centre of USFDA, and is also a part of US department of health and human services, it mainly is responsible for assuring the safety, purity, potency and effectiveness of biologics and related products like vaccines, probiotics, blood products, cell,	and monitors centrally authorized products, national referrals. The scope of operations of EMA is not just restricted to medicines used for human and veterinary use but also includes biologics and advanced therapies, and herbal medicinal products. **CHMP** – (committee for medicinal products for human use), the committee was formed replacing the earlier one CPMP (committee for proprietary medicinal products). CHMP authorizes medicines in EU

		development and review of data for preclinical assessment. • **IBSC** –In addition, it has the authority to authorize on site the transfers of aforesaid species for the purpose of study. along with the analysis of applications submitted to RCGM. • **GEAC** – This Committee evaluates proposals and clearance practices for genetically modified organisms / living modified organisms of which the ultimate drug formulation includes. (Natarajan)	tissue and genetic therapy. • **CDER –** (The centre for drug evaluation and research), certain biologics like monoclonal antibodies and other therapeutic proteins are regulated by CDER.(Srilakshmi)	(European Union), it does so by Initial review of proposals for EU wide marketing authorisation, examination of changes or modifications of current marketing authorisation, consultancy. The European Commission shall change or withhold or remove from the market the authorisation of the drug. This also assesses centrally licensed drugs for EMA.

5.2	Definition	Biological product or biologics. A selection of biological products (man, animal or microorganism) are derived from a range of natural sources. Many biologics, like medicines, are meant to cure medical disorders and diseases. Disease treatment or evaluation is focused on certain biologics. Examples of biological items involve transfusion and/or other-produced vaccinations, plasma and plasma components, sources of allergy which are used for the purpose of	Biological materials are a broad commodity group that is typically large and complex molecules. These compounds are also more difficult to classify in a living environment than tiny molecular medicines by biotechnology.(Sharma)	A material generated or derived from a biological source, which requires a combination of physico-chemical-biological research, manufacturing method and control in order to classify and assess its quality.(Pashikanti et al.)

		treatment and diagnosis (e.g. allergy), human cells and replacement tissues (e.g. tendon, ligament and bone), genetic engineering, cell therapy, screening tests for prospective blood donation. (Declerck et al.)		
5.3	Registration process	One step registration process	One step registration process	Multiple registration process 1. Centralized (E.U) 2. Decentralized (at least two state member) 3. Mutual recognition (minimum two state member) National

				(1member state)
5.4	Approval timeline	12- 18 months	18 months	12 months
5.5	Exclusivity period	In India there is no further market exclusivity beyond the patent rights. (Basha et al.)	12 years (Basha et al.)	10 years (Basha et al.)
5.6	Guidelines and regulation	• Recombinant DNA safety (guidelines 1990) • Drafting preclinical & clinical data for rDNA vaccines, diagnostics and other biologics guidelines 1999 • Handbook of guidelines for IBCs, 2011 • CDSCO guidelines for industry 2008 • application for clinical trial for evaluating safety and efficacy • Conditions for permission of	**BPCI Act 2009 –** similar to Hatch-Waxman amendments to FD&C Act. Supports FDA's age-old policy of authorizing suitable dependence on what is already known about a drug, hence saves time & resources & also avoids needless replication of human or animal testing, create abbreviated approval pathway for biologics. **BLA –** (Biologics Licensing	**BWP** – (Biotechnology working party) guidelines • Production and QC of rDNA derived medicinal products • manufacturing and QC of cytokine • Production and QC of monoclonal antibodies. • Allergen products-1992 • Radiopharmaceuticals – 1990 • Validation of virus removal and inactivation procedures

		new drug approvals. • post approval changes in biological products: efficacy, safety and quality document • For new drug approval: information on quality for drugs submission: biotechnological or biologicals	Application) analogous to 505(b)(1) NDA for drugs. Earlier to 2009 abbreviated approval method did not exist for products licensed under 351 of PHSA until 2010. (Srilakshmi)	• Use of transgenic plants for production of medicines. • Products prepared from blood and plasma of living organism for medicinal use • TSE guideline • Gene therapy products **BWP at international level** – helps ICH in elaboration of international guidelines • (Q5C) Genetic stability. • (Q5B) Stability testing for biological products. • (Q5A) Viral safety of products derived from cell lines

				• (Q5D) Cell substances • (Q6B) Specifications for biotech products • (S6) Safety studies for biotech (Howie)
5.7	Scope of guideline	This refer drugs/biologics t hat include well-known proteins, developed from conventional biological methodologies such as recombinant therapeutics developed from DNA, as their active ingredient. (Basha et al.)	Therapeutic protein products. (Basha et al.)	Medicinal products comprising derived proteins obtained by biotechnological methods constituting as active constituent, immunologicals such as vaccines, blood derived products, monoclonal antibodies and etc. (Basha et al.)
5.8	Requirements for development of biologics	<u>Pre-requisites for conducting preclinical studies</u> 1. Information about the drug/biologic	<u>Preclinical studies</u> In matters of biologics the FDA follows guideline of ICH like S6 generally apply	Similar to FDA, the CHMP has implemented ICH S6 as guideline for biologic's preclinical testing.

		– this involves identification of the drug to its pharmacokinetics and dose, even includes adverse effects and utilization 2. Route of administration – this means the way in which drug will be administered in the body, commonly employed routes are oral and intravenous. 3. Absorption rate – It is the measure of the rate at which the drug moves from intestinal tract into systemic circulation. 4. Elimination rate – measure	1. Species selection –Not all biologics can be tested for their biological behavior and habitats and for their particular behaviors in widely utilized animal organisms such as rats or dogs. In-vitro attachment measurements and practical checks to classify the organisms concerned. In few cases the chimpanzee was the only relevant specie. 2. Immunogenicity - many Biological products induce immune	In July 2011, the CHMP embraced the appendix to this guideline and From December 2011 came into effect. <u>Preclinical studies</u> 1. Species selection - This addendum says that relevant species should be selected for nonclinical testing, For this additional initial study, the investigator will also assess behavioral behavior by contrasting the target-sequence homology with the qualitative and quantitative cross-species measurements of relative

		of the rate at which the drug is completely eliminated from the body. 5. Mode of administration – this is taken into consideration when there is a target of action i.e. target specific 6. Mode of action – this means the pharmacological action the drug produces. <u>Preclinical studies –</u> 1. Pharmacodynamics studies – this is the study of biochemical and physiologic effects of drugs. 2. Toxicology	responses that may influence the outcomes of preclinical studies either by Biological operation neutralizing or prolonging, immune complexing or cross contact with natural substances. 3. Study design – Primary, secondary and safety pharmacodynamics studies. 4. In vitro ("test tube") and animal research shall be performed in compliance with GLP to assess the relative toxicity of the medication or biologic over a wide range of	binding affinities and kinetics.This testing allows identification of a species model that can demonstrate potentially adverse consequences of target modulation. If two relevant species are available short-term studies should be conducted in both. 2. Study design – this suggests the sponsor to adopt PK-PD approach such as exposure response relationship, modeling or simulation, when selecting the higher dose for toxicity

		studies – this study assesses the onset of action, severity, and duration of toxic effects. 3. Immune responses in animals- after the satisfactory result from preclinical study, The Review Committee on Genetic Manipulation (RCGM) will guide the applicant to precede DCGI fro conduction of clinical trials according to CDSCO guidelines <u>Clinical trials -</u> • Protocol to be authorised by DCGI along with toxicity study report approval by	doses and to identify the potential for causing a number of adverse effects or diseases, including birth defects or cancer. Where the results warrant continued drug or biological development, The manufacturer must send the findings of the studies to the FDA as part of its investigational new drugs ('IND') application which the FDA has to approve before the clinical study proposed can start. An IND	testing. However the higher dose should higher than dose providing minimum intended pharmacologic al effect. 3. Immunogenicit y – as said by IDC S6 Nonclinical experiments will not lead to the assessment of human or humanised proteins' possible immunogenicit y in humans. In the event of altered PD behavior, sudden shifts in the body or signs of immunosuppor tive reactions, the sponsor will calculate

		DBT • License for manufacturing is needed for CT batch manufacturing (along with WHO GMP certificate) • Protocol has to be approved by institutional committee of ethics • DCGI and DSMB need to approve or authorize incase of any deviation. (Chauhan and Malik)	must contain, inter alia, preclinical data, information on chemistry, information on Manufacturing and monitoring, and a testing plan must work before these trials initiate. An IND will automatically take effect after 30 days of receiving by the FDA, if the FDA poses queries or questions about one or more planned clinical trials during the 30-day time period. <u>Clinical trials –</u> Phase – I Involves 20 to 80	antidrug antibodies. 4. Carcinogenicity –In addition the sponsor may devise a method to mitigate possible carcinogenicity, focused on an evaluation of specific evidence including the literature, class effect specifics, target biology and methods of action, in vitro knowledge and clinical data, and chronic toxicity test data. The sponsor may create an methodology for the additional information. 188 In some

			healthy humans for basic safety and pharmacology testing, Studies assessing the metabolic and pharmacological activity of the substance in humans, the working of the biologic / drug often involve. Whether the presence of another affects it or not, how well is it absorbed, how well is it tolerated, where does it go in body and how long does it stay there, and how does its metabolism and elimination takes place. Phase – II This phase involves testing of effectiveness and dose range	cases, this analysis would be adequate to resolve the risk for cancer. <u>Clinical trial</u> After satisfactory results of preclinical testing biologics under go clinical trials in order to be able to apply for marketing authorization to MAA. The Directive on Clinical Trials and guidelines from the European Commission196 define the steps a sponsor must take before starting a clinical trial. A clinical trial can start only if (1) the anticipated therapeutic and public health benefits outweigh any foreseeable

			testing in a limited population size about 100-200 patients affected with particular disease for which the biologic is intended to be used. Apart from this further safety testing, assessment of effectiveness, determination of ideal dose. Phase – III This phase involves testing on a larger scale of patients suffering through a particular disease, offering the FDA and others with ample evidence to determine the relevant statistical health and efficacy results and offering an appropriate	risks and inconveniences to the subjects; (2) the subjects of the trial shall understand the reasons and effects of the trial and only then give their informed, written consent to participate; (3) the jury defends the physical and mental gravity of the subjects; and (4) compensation shields the responsibility of the sponsor and investigator.(Trou vin) (Howie)

			framework for drug labeling.(Chauhan and Malik)	
5.9	Marketing authorization	• After successful completion of phase – III study, CSR is submitted to CDCSO • Application is done in form 44 for marketing authorization (license to manufacture and market) of drug product in India. • The application must be done under the industry guidance, 2008. • Manufacturing for trading purposes is approved on a different level or with separate process.	The **BLA** is used in place of NDA and shall contain the clinical and nonclinical details, full explanations of production processes, reliability detail, suggested labelling and boxes and containers. The format of the BLA is the official FDA in the specified 356h and the same, under 21 C.F.R and 601.2. The BLA review process – • On submitting the BLA, a review committee is	**MAA** – (marketing authorization application) • The applicant needs to file an approval request by way of a specific form and, along with a justification, the 18-7 months ago send a Marken Authorisations Query, including how a substance can be tested in compliance with the unified protocol. • The CHMP and PRAC (pharmacovigilance risk assessment)

		• After reviewing the results of clinical trial studies DCGI grants permission in form 46 &46A (for finished formulation and bulk drugs. • Then application is made to SLA for permission in form 24 for grant of permission to manufacture the particular drug. • The post marketing surveillance or monitoring is done, which reports any adverse drug reactions.(Maurya et al.) (Rathore)	formed by FDA and it determines whether to apply an application or fail to file in the first 60 days. After completion of their examination, they send a letter of rejection, or CRL (complete response letter), indicating that BLA is unable to be accepted by the Organization in any form. The claimant may request a re-submission to resolve the shortcomings; usually 2-6 months following receipt of the evaluation, although it can	appoint (co) rapporteurs to carry out scientific assessment • Even for advanced medicinal products members are appointed from CAT (committee for advanced therapy) who conduct the assessment. • Pre-submission meeting takes places usually 6-7 months prior to the planned submission date. • Also there is a follow up meeting with rapporteur at least 3 months before planned date of submission. • EU law states that the MA

			rely on the quality of this. • US law requires that the MA holder shall be established in the US. • A request for proprietary name must be submitted to FDA for approval. • The BLA process is to be used for biopharmaceuticals containing of more than 40 amino acids. • It needs to comply with ICH requirements • GMP inspection of active substance and drug product manufacturing sites is mandatory. • The approval process cannot	holder should be established in EU or EEA. • There should be two proposed names submitted to the EMA for approval. • An eligibility request needs to be submitted via CP to the EMA. • Just like in US even here compliance with ICH requirements is mandatory. • GMP inspection of active substance and drug product manufacturing sites is required. • Batch release to be performed in presence of a qualified person in EU or EEA. • A qualified person for pharmacovigilance is required

			be expedited on the basis of approval in another market.(Srilakshmi) (Hayakawa)	and must be based in EU or EEA country.
5.10	Post marketing surveillance	• The draft CDSCO monitoring guide categorizes experimental medications, ensuing 4 years products, biomedicines, radiopharmaceuticals as well as phytopharmaceuticals in 4 groups. • Identification of threats resulting from the use of pharmaceuticals "circulating the market after post licensure period" and	• There is neither fixed duration nor patient population • This process initiates immediately after marketing. • Reports all ADRs • Helps in detecting rare ADRs, drug interactions and also new uses of the drug [sometimes called as phase V] • Sources for information could be 1. Focus groups	• Advising on the health of EU accepted medicinal products and reviewing ADRs to enable successful identification, risk assessment and management at every point of the drug life cycle. • Composition of CHMP pharmacovigilance working party – 1. Chairperson 2. 1 member per state, Norway, Iceland and Liechtenstein 3. 8 co-operated

		the development of an importing and manufacturing Pharmacovigilance Program to reduce certain threats. • Site based pharmacovigilance should be handled by a medical staff or a pharmacist as a PVOI (Pharmacovigilance officer in charge). This officer collects and analyses ADR reports related to pharmaceutical product marketed by a company in India. • The PVOI will collects, process,	2. Customer surveys 3. Customer complaints and warranty claims 4. Post CE – market clinical trials. 5. Literature reviews 6. Media 7. Use of reaction during training programs. (Hayakawa)	members [expertise in risk management, communication and pharmacoepidemiology] • 2 observers – 1 from European commission and 1 from patient organizations EMEA

		assesses and reports and follows up on every individual case safety report (ICSR). • In a program where the core is PVOI the officer is also responsible for signal capture, remedial and protective action, planning and delivery periodic safety update report (PSUR), and risk control for medicinal drug. (et al.)		

Table - 1

6. Case study - Regulatory withdrawal from market due to uncertain benefits: Bevacizumab

6.1 Introduction -

- In the United States of America, FDA has implemented an accelerated medication approval plan, which tends to be of help to severe or life-threatening illnesses without appropriate care.
- This system provides drugs with a provisional approval dependent on clinical study results, which does suggest efficacy but which is not necessary for full approval. The full clearance depends on corresponding scientific confirmatory studies.
- Few nations, such as Australia, Canada, Italy and UK, have programs of public health insuring that have adopted specific 'proof coverages' schemes for the usage of licensed prescription drugs before sufficient testing results are provided at a later point.
- These new programs were appealing for policy makers as it temporarily resolves the issue of (a) conserving efficacy, safety, and cost effectiveness and (b) suffice industry and public expectation for admission.
- Though, doctors and healthcare professionals and legislative and support authorities ought to brace themselves for such a scenario not fully known to withhold conditionally licensed medications.
- For purposes of unknown efficacy after provisional approval several reports of removal of drugs have been identified. In 2011, the FDA reported its intention to revoke the FDA's accelerated approval plan for bevacizumab, (Avastin), which was used for breast cancer treatment. (Vitry et al.)

6.2 Methods –

- A research structure based on three key themes for data analysis has been developed.

(1) Rationalization of FDA decision for clearance to combat advanced breast cancer and removal of bevacizumab.

(2) Stakeholder's participation and responses to decisions.

(3) Suggestions for future risk administration plans.

- Government documents and scientific reports were primarily used to monitor bevacizumab regulatory history.

6.3 Results –

- Bevacizumab is a humanized recombinant monoclonal antibody to vascular endothelial growth factor (VEGF) by Genentech as Avastin; it inhibits the binding of VEGF to surface of endothelial cells, thereby decreasing the vascularization of cancerous tumours and stops their growth.
- FDA first approved Bevacizumab in 2004 for treatment of metastatic colorectal cancer, after which it found its application in other diseases like renal cell carcinoma and small cell lung cancer.
- In the year 2008 for the 1st time bevacizumab was permitted as first line treatment of metastatic breast cancer under FDA's accelerated approval program. The approval was based on study published in NEJM (New England Journal of Medicine).
- This trail showed a progress in survival rate of women affected by advanced breast cancer when treated with bevacizumab and paclitaxel together.
- Results of NEJM were used by Genentech to endorse drug to physicians and also claimed that at that point 9000 patients were cured with 'off label' bevacizumab.
- The official review conducted by ODAC for bevacizumab in metastatic breast cancer was less positive than the NEJM paper. It highlighted several methodological shortcomings of the NEJM trial, including the use of progression-free survival as an endpoint and the lack of blinding. Progression-free survival has not been shown convincingly to be an appropriate surrogate endpoint for breast cancer or to be predictive of overall survival
- The FDA therefore required an autonomous, unbiased assessment of radiological and clinical data of all patients in the E2100 trial. Although this confirmed that the addition of bevacizumab to paclitaxel resulted in a statistically significant improvement in progression-free survival, he estimate of the magnitude of the effect lacked reliability because of incomplete data.
- Failure in follow-ups and incoherence of radiologic illness development (34 percent of patients). The ODAC has reported major safety problems with

bevacizumab, like a 20.2% rise in toxicity (like hypertension, gastrointestinal perforation, sensory neuropathy, hemorrhage, thromboembolism) & a 1.7 percent rise in drug-related mortality in bevacizumab plus paclitaxel study in comparison with 0 percent for paclitaxel alone study.

- On the basis of proof, ODAC voted 5 to 4 in open voting not to approve acceptance of the data presented to decide if a favorable risk / benefit scenario for the use of bevacizumab + paclitaxel as the first line for metastatic breast cancer therapy is appropriate.
- Regardless of what ODAC decided, the FDA approved bevacizumab based on supplementary studies in February 2008.
- As a result of this announcement, stocks of the drug producer increased more than 8% after trading hours. However health providers and organisations including the Regional Breast Cancer Coalitative Fund have reduced the FDA requirement for therapeutic certification.
- The ODAC has reassessed clearance and reviewed the outcomes of two more clinical studies in July 2010, and has voted 12-1 to approve the elimination of the metastatic breast cancer bevacizumab label.
- The two recent findings found little change in total survival and fewer progression-free gains than in the initial NEJM report. None of the findings have shown enhanced living conditions and all display an elevated likelihood of serious harmful consequences, such as gastrointestinal perforation and extreme bleeding. In both the bevacizumab and control categories, the total number of treatment-related fatalities (1.8%) was similar.
- In December 2010, the FDA declared its plan to revoke the recommendation that at the moment, 17,000 female patients with advanced breast cancer had bevacizumab, and financial analysts predicted that revoking FDA breast cancer clearance would cost Genentech 1 billion US dollars in revenue, based on before expected estimates. Genentech demanded an administrative trial in an alternative case.
- In June 2011, the two-day hearing required the oral testimony of ODAC consultants, Genentech-designated consultants and representatives of the public. There were also encouraged to comment online or in writing on the request from the FDA to withhold permission.

- During the hearing time FDA obtained 450 public requests, many from customers, urging the FDA to uphold their belief as the medication was effective for themselves or close friends or relatives..
- The FDA recommended bevacizumab for certain user categories. Survivors provided bevacizumab their safety and existing life satisfaction and named themselves 'super-respondents.' No public statement was made on whether respondents could be separated from non-respondents in advance or whether respondents could be a minority of women. It was accepted that no means for the estimation like biological marker for bevacizumab's efficacy in clinical trials had been identified in subsequent empirical discussions of the ODAC..
- Members of the general public never expressed questions regarding bevacizumab's health during the trial, and the negative consequences of bevacizumab were generally minor or manageable. A woman from SHARE members, a group of survivors of cancer said 'there are other people we know with every woman we attest to here, a fellow of our community who bled out of every orifice and another woman that has a brain hemorrhage. And those women are not coming to bear witness.
- The National Breast Cancer Coalition's vice president and breast cancelation survivor Christine Brunswick, who said: This judgment can not be motivated by facts, was among the few who endorsed removal of bevacizumab. Technology needs to push it. At the conclusion of the meeting, ODAC voted 6–0 to withdraw the drug and in November 2011, the FDA eventually revoked its permission, after 3.5 years original conditional permission.
- FDA removal led doctors, public advocates, community providers, community decision leaders and the pharmaceutical sector to react and other doctors became very angry when one woman accused an FDA Committee of 'killing seventeen thousand women by one vote'.
- In scientific papers, the FDA withdrawal was extensively debated. The FDA was supported by a Clinical Oncology in an editorial, which reported that "The results were definitely not scientifically necessary." An oncologist who was an ODAC participant of the FDA meeting, contemplating the decision to withdraw, announced, "we do not want any medications that do not perform too well to damage citizens. We will not bring false optimism.

- By comparison, the FDAs have been refusing American access to life-saving medications through Dr. Milton Wolf, a radiologist who published a conservatory article on the Washington Times, called 'the FDA's one-man death council,' explaining the complexity and uncertainty of the FDA's procedures as "regulatory obstacles" to creative medication delivery in the United States.
- In a research carried out following the suggestion of the ODAC to revoke the sanction of bevacizumab, decisions and views of healthcare professionals on the FDA retiring decision were considered. 564 researchers from all over the country, most of them practicing oncologists, were included in the study. A limited number of citizens (52 per cent) complied with the decision by the FDA to revoke the recommendation because the results of the two additional bevacizumab trials in the original E2100 report were not the same but 48 per cent felt that this was not a compelling explanation.
- In 122 oncology procedures affecting 570 US oncologists, a further analysis explored patterns in the application of bevacizumab for breast cancer. The study concluded that usage decreased by 37% between May 2010 (only before the revoking acceptance meeting of the ODAC) and November 2010 (only before the withdrawal procedure begun), and by 63% just before the FDA's formal retraction warning, without corresponding revisions to therapeutic recommendations or insurance scheme that may justify these patterns. (Vitry et al.)

6.4 Discussion –

- The possible social and human effects of withdrawal decisions must be understood and prospectively handled by regulatory agencies & financial institutions as the conditional approval system or procurement of pharmaceutical drugs pursuant to the availability of sufficient proof is expected to broaden in the future.
- The popular response to the case may have been high because the media awareness of breast cancer and bevacizumab was previously used for other cancers. Nonetheless, the public awareness and acceptation of permissions

and reporting schemes are definitely improved based on the production of facts.

- Robust risk reduction strategies that provide the possibility for the withdrawal of the conditionally authorized signal must be established and enforced by regulators.
- At the outset of this study, there were variations in the understanding of the data as to its relevance, its therapeutic value and the comparatively small weight of the possible benefits and harms of bevacizumab.
- Regulatory policies are intended to safeguard public wellbeing and promote social protection, which can clash on certain instances with the desires of particular patients.
- Many experts raised concerns such as 'that distressed patients might divert focus from the interest of current or potential patients and the business'.
- However, members of certain cancer patients have claimed 'a month may be the correspondent of one year if the life span is reduced,' indicating that this controversy is not readily settled.
- Clearly people who prefer bevacizumab are more commonly and clearly taken into consideration who did not. For this, there have been many explanations. Survivors also link their longevity to their recovery and speak out to endorse their continued availability.
- It is clear that patients that perform less good and may not recover (and who may have experienced more harm) can not bear witness.
- The efficacy of cancer therapies generally has been overestimated by doctors. A study of advanced colorectal and lung cancer patients (metastatic) in the U.S. showed that the majority of (81% of colorectal cancer patients & 69% of lung cancer patient) did not realize that chemotherapy does not cure their cancers.
- First of all, there should be views of an early warning warning indication of possible concern where a prospective clearance or regulation is expected to be restored after the original recommendation from ODAC and the determination for clearance of the FDA. Regulators will start investigating and suggest including these arguments in education, health practitioners and media relations research whether the votes are divided

for acceptance. Risk reduction preparation may improve awareness of clinical ambiguity in the practice of the medication licensed at the time of initial authorization or treatment decisions.

- A broad variety of records, including full transcripts of the proceedings, is accessible on the FDA Web site both at the period of acceptance and the removal. The FDA records, however, can be lengthy and challenging to read, making it difficult for lay publics and health professionals to obtain details.
- Secondly, better health instruction on the efficacy and protection of the latest drugs must be given, more reasonable standards of patients and caregivers must be created, especially where there are substantial uncertainty as regards the effectiveness of medical technology. Medicines sold and approved through provisional authorisation or funding may still need somewhere to alert or remember the minimal facts and tentative character of acceptance to health staff as well as patients, possibly in line with alerts in the black box and black triangles, which were introduced to reassure the public.
- Third, medical support is a requirement for subsidization in many countries for continuing treatment focused on improved safety. Similar approaches can be implemented for reciprocal coverage systems, in which patients may be expected to accept that there is ambiguity regarding effectiveness and protection at the onset of care and acknowledge that ongoing treatment may rely on proof of efficacy or protection subsequently.
- In addition, it was considered fair to allow patients who receive uncertain-benefit medical treatments to submit their data to ongoing assessment, as part of the evidence creation support initiatives, these systems are now being implemented. (Vitry et al.)

6.5 Conclusion –

- The public will not be entirely reassured by the revocation of conditional therapeutic acceptance because of unpredictable consequences, for several

reasons, including the dynamic science assessment and growth of irrealistic expectations fueled by news and the pharmaceutical industries.

- For the implementation of risk reduction programs, legislative and financing authorities may find the suggested approaches. The packaging and labels of medications and clear patient recognition of the importance and danger of contractual consent require centered, recognizable and lasting contact with the public and media.

7. Summary –

- Biologics are drugs that are produced by living organism or contain a component of a living organism.
- Biologics have been a part of the treatment regime for a lot of disease like rheumatoid arthritis, Chron's disease and with growing rate of cancer they find their application even more as monoclonal antibodies and gene therapies.
- Regulatory bodies are made to keep a check on products entering the market and also benefit pharmaceutical companies.
- There are different regulatory bodies in different countries like USFDA in US, EMA in Europe and DCGI in India. Each regulatory has different guidelines for different pharmaceutical product.
- Regulatory compliance helps (1) eliminate risk by identifying, mitigating and eliminating risk at all stages, (2) enhance customer and investor confidence and (3) saves costs (4) ensure production and approval of drugs showing optimal efficacy, safe and non toxic.
- Regulatory compliance also helps speed up the process of marketing authorization.
- This project has helped me understand how guidelines differ from country to country and how its compliance is beneficial for industries.

8. Conclusion –

- This project not just allowed me to learn about what are guidelines but also their importance and their application in industrial practice and also how regulatory works for harmonization of two different schools of thoughts. (1) ensuring public health, (2) helping industry make more efficient and safe drugs and (3) facilitate import and export of drugs.
- The case study shows us how a law made to facilitate drug discovery and applicability but without enough consideration can chaos within the medical environment of the country and hence the regulatory system should be sound enough with all its aspects before passing any new rule.

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