Biopharmaceuticals when the product is the process

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Introduction

Biologicals refer to a wide term which includes Biopharmaceuticals as part of it. At same time Biopharmaceuticals considered the synonym of Biological medicinal products.

The term 'biopharmaceutical' was first used in the 1980s and came to describe a class of therapeutic proteins produced by modern biotechnological techniques, specifically via genetic engineering or, in the case of monoclonal antibodies, by hybridoma technology.

Definitions

In order to be able to go through the topic of biopharmaceuticals, its needed to clarify some expressions and definitions at first; Biopharmaceuticals defined as a product where the Active Pharmaceutical Ingredient (API) is biological substance, in compliance this biological API is a substance that can be produced either by Biotechnology (known as Red Biotechnology) through microbial cell, mammalian cell lines, plant cell culture and/or moss plants in bioreactors or various configurations. The other aspect of Biological API definition is the substance extracted from biological source, i.e. derived from life form such as animal, human or microorganism.

According to above definitions, the biopharmaceuticals could vary in two major categories, where the first covers the biotechnology process by which the API is being produced as non living entities such as protein, nucleic acids and/or sugars. While the second category covers the source of the API itself being a living entities such as cell or tissue or part of any.

Coming to our main considered regions in this document; Jordan, USA and EU, the following definitions where adapted in each region:

Jordan; according to 2 أسس التسجيل /المادة رقم the biopharmaceuticals defined as:

" المستحضرات البيولوجية :هي المواد التي تنتج باستخدام أحد الطراءق التالية:

أ- تنمية السلالات الجرثومية والخلايا حقيقة النواة

ب- استخلاص المواد من الأنسجة البيولوجية بما في ذلك أنسجة الإنسان او الحيوان او النبات (المستارج)

جـ- طراءق مأشوب ال"د نا" DNA

د- طراءق تهجين الخلايا

هـ- تنمية الأحياء الدقيقة في الأجنة أو الحيوانات

* المنتجات البيولوجية المصنعة بهذه الطراءق تتضمن كل من:

(Allergens) المواد المسببة للحساسية، مولدات الضد (Antigens) ، المطاعيم، الهرمونات، (Cytokines) ، الخمائر، مكونات الدم والبلازما، المصال المناعية، الجلوبينات المناعية بما في ذلك وحيدة الخلية ، مواد الحساسية (Allergen)، المواد المنتجة عن الإختمار بما فيها طرق مأشوب ال(rDNA) ".

Instructions Related to Registration of Drugs/ Criteria of registration of drugs/ Article (2):

The Biological Products: They are the materials that are produced by any of the following methods:

a- Development of Bacterial Colonies (Microbial Strains) and Eukaryotic Cells.
b- Extraction of materials from bio-tissues including Human, Animal or Plant tissues.
c- rDNA
d- Methods of Hybridization of Cells.
e- Development of micro-organisms in embryos or animals.

The biological products produced by these methods include:

Allergens, Antigens, Vaccines, Hormones, Cytokinesis, Enzymes, constituents of blood and plasma, immunological sera, immunoglobulins including mono-clonal antibodies, Allergen, components produced by Fermentation including rDNA.

- ***A draft being issued still not yet approved or implemented covering the Biological products registration including the Biosimilars as well.***

USA; according to Public Health Service Act 42 U.S.C section 262(i), defines Biological Product as:

"a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivatives, allergenic product or analogous product, or arsphenamine, or derivative of arsphenamine or any other trivalent organic arsenic compound , applicable to the prevention, treatment or cure of a disease or condition of human beings.

EU; according to ICH Topic Q 5 D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/ Biological Products – CPMP/ICH/294/95 dated March 1998:

"Cell substrate" refers to microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the desired biotechnological/biological products for human in vivo or ex vivo use.

"Biotechnological/biological products" refers to any products prepared from cells cultivated from cell banks with the exception of microbial metabolites such as, for example, antibiotics, amino acids, carbohydrates, and other low molecular weight substances.

Classification

After going through the definitions of biopharmaceuticals in different aspects it worth now to clarify a classification system for biopharmaceuticals based on their therapeutic uses:

1. Biopharmaceuticals for preventions; includes mainly Vaccine
2. Biopharmaceutical for treatment; Includes mainly
    - Blood products
    - Antineolpastic products
    - Internal secretions
    - Digestions
3. Biopharmaceuticals for in vitro diagnosis.

In other references, classification of the biopharmaceuticals could be based on the

API type to the following categories:

a. Blood factors, e.g.: Factor VIII and Factor IX
b. Thrombolytic agents, e.g.: tissue plasminogen activator
c. Hormones, e.g.: insulin, growth hormone gonadotrophins.
d. Haematopoietic growth factor, e.g.: erythropoietin, colony stimulating factors.
e. Interferons, e.g.: interferons α, β, Y
f. Interleukin-based products, e.g.: interleukin-2
g. Vaccines, e.g.: Hepatitis B surface antigen
h. Monoclonal antibodies
i. Additional products such as tumor necrosis factor and therapeutic enzymes.

In a more specific manner, our concerned regions classified Biologicals as follow:

Jordan;

- Vaccines:
  - BCG
  - Killed bacteria
  - Inactivated virus
  - Live virus
  - Polysaccharide
  - Bacterial product
- Immune sera of animal origin
- Plasma proteins of human origin
- Recombinant biological products

USA;

Two major categories:

- Blood establishments
- Tissue establishments

Under each a sub-classification is listed as below:

- **Blood establishments**
  - Whole blood
  - Red Blood cells (RBC)
  - RBC frozen
  - RBC degl ycerolized
  - RBC rejuvenated frozen
  - RBC rejuvenated ycerolized
  - Cryoprecipitated AHF
  - Platelets
  - Leukocytes/ Granulocytes
  - Plasma
  - Plasma cryoprecipitate reduced
  - Fresh frozen plasma
  - Liquid plasma

- Therapeutic exchange plasma
- Source leukocytes
- Source plasma
- Recovered plasma
- Blood products for diagnostic use
- Blood bank reagents.

- **Tissue establishments**
  - Bone
  - Cartridge
  - Cornea
  - Dura mater
  - Embryo
  - Fascia
  - Heart valve
  - Ligament
  - Oocyte
  - Pericardium
  - Peripheral Blood Stem Cells
  - Sclera
  - Semen
  - Skin
  - Somatic
  - Skin
  - Somatic Cell
  - Tendon
  - Umbilical Cord blood stem Cells
  - Vascular Graft.

EU;

Major classification based on API and process to:

- cell-derived biological products
- Recombinant DNA (rDNA) - derived products

Still further sub-classification based on the specific requirements for each group listed as below:

- Monoclonal Antibodies and Related Substances
- cell based immunotherapy medicinal products
- biological active substances produced by stable transgenic expression in higher plants
- Lentiviral Vectors
- Animal Immunoglobins and Immunosera for Human Use
- Human cell-based medicinal products
- Gene Transfer Medicinal Products
- xenogeneic cell-based medicinal products
- Cytokine Products
- Vaccines
- Allergen products.

The age of biopharmaceuticals

Biomedical research continues to broaden our understanding of the molecular mechanisms underlining both health and disease. Research undertaken since the 1950s has pinpointed a host of proteins produced naturally in the body that have obvious therapeutic applications. Examples include the interferons and interleukins (which regulate the immune response), growth factors, such as erythropoietin (EPO; which stimulates red blood cell production), and neurotrophic factors (which regulate the development and maintenance of neural tissue).

Although the pharmaceutical potential of these regulatory molecules was generally appreciated, their widespread medical application was in most cases rendered impractical due to the tiny quantities in which they were naturally produced. The advent of recombinant DNA technology (genetic engineering) and monoclonal antibody technology (hybridoma technology) overcame many such difficulties, and marked the beginning of a new era of the pharmaceutical sciences.

Recombinant DNA technology has had a fourfold positive impact upon the production of pharmaceutically important proteins:

- *It overcomes the problem of source availability;* Many proteins of therapeutic potential are produced naturally in the body in minute quantities. Examples include interferons, interleukins and colony-stimulating factors (CSFs). This rendered impractical their direct extraction from native source material in quantities sufficient to meet likely clinical demand. Recombinant production allows the manufacture of any protein in whatever quantity it is required.
- *It overcomes problems of product safety;* Direct extraction of product from some native biological sources has, in the past, led to the unwitting transmission of disease. Examples include the transmission of blood-borne pathogens such as hepatitis B and C and human immunodeficiency virus (HIV) via infected blood products and the transmission of Creutzfeldt–Jakob disease to persons receiving human growth hormone (GH) preparations derived from human pituitaries.
- *It provides an alternative to direct extraction from inappropriate/ dangerous source material;* a number of therapeutic proteins have traditionally been extracted from human urine. Follicle stimulating hormone (FSH), the fertility hormone, for example, is obtained from the urine of postmenopausal women, and a related hormone, human chorionic gonadotrophins (hCG), is extracted from the urine of pregnant

women. Urine is not considered a particularly desirable source of pharmaceutical products. Although several products obtained from this source remain on the market, recombinant forms have now also been approved. Other potential biopharmaceuticals are produced naturally in downright dangerous sources. Ancrod, for example, is a protein displaying anti-coagulant activity and, hence, is of potential clinical use. It is, however, produced naturally by the Malaysian pit viper. Although retrieval by milking snake venom is possible, and indeed may be quite an exciting procedure, recombinant production in less dangerous organisms, such as *Escherichia coli* or *Saccharomycese cerevisiae*, would be considered preferable by most.

- *It facilitates the generation of engineered therapeutic proteins displaying some clinical advantage over the native protein product;* Techniques such as site-directed mutagenesis facilitate the logical introduction of predefined changes in a protein's amino acid sequence. Such changes can be as minimal as the insertion, deletion or alteration of a single amino acid residue, or can be more substantial (e.g. the alteration/deletion of an entire domain, or the generation of a novel hybrid protein). Such changes can be made for a number of reasons, and several engineered products have now gained marketing approval.

Despite the undoubted advantages of recombinant production, it remains the case that many protein-based products extracted directly from native source material remain on the market. In certain circumstances, direct extraction of native source material can prove equally/more attractive than recombinant production. This may be for an economic reason if, for example, the protein is produced in very large quantities by the native source and is easy to extract/purify, e.g. human serum albumin (HSA). Also, some blood factor preparations purified from donor blood actually contain several different blood factors and, hence, can be used to treat several haemophilia patient types. Recombinant blood factor preparations, on the other hand, contain but a single blood factor and, hence, can be used to treat only one haemophilia type.

The advent of genetic engineering and monoclonal antibody technology underpinned the establishment of literally hundreds of start-up biopharmaceutical (biotechnology) companies in the late 1970s and early 1980s. The bulk of these companies were founded in the USA, with smaller numbers of start-ups emanating from Europe and other world regions. Many of these fledgling companies were founded by academics/technical experts who sought to take commercial advantage of

developments in the biotechnological arena. These companies were largely financed by speculative monies attracted by the hype associated with the establishment of the modern biotech era. Although most of these early companies displayed significant technical expertise, the vast majority lacked experience in the practicalities of the drug development process.

Most of the well-established large pharmaceutical companies, on the other hand, were slow to invest heavily in biotech research and development. However, as the actual and potential therapeutic significance of biopharmaceuticals became evident, many of these companies did diversify into this area. Most either purchased small, established biopharmaceutical concerns or formed strategic alliances with them. An example was the long-term alliance formed by Genentech (see later) and the well-established pharmaceutical company Eli Lilly. Genentech developed recombinant human insulin, which was then marketed by Eli Lilly under the trade name Humulin. The merger of biotech capability with pharmaceutical experience helped accelerate development of the biopharmaceutical sector.

Many of the earlier biopharmaceutical companies no longer exist. The overall level of speculative finance available was not sufficient to sustain them all long term (it can take 6–10 years and US$800 million to develop a single drug. Furthermore, the promise and hype of biotechnology sometimes exceeded its ability actually to deliver a final product. Some biopharmaceutical substances showed little efficacy in treating their target condition, and/or exhibited unacceptable side effects. Mergers and acquisitions also led to the disappearance of several biopharmaceutical concerns.

List of the major pharmaceutical concerns which now manufacture/market biopharmaceuticals approved for general medical use in USA and EU are:

Hoechst AG	Wyeth
Genzyme	Abbott
Roche	Novartis
Boehringer Ingelheim	Organon
Amgen	GlaxoSmithKline
Cytogen	Immunomedics
Biogen	Bayer
Sanofi –Aventis	Isis Pharmaceuticals
Novo Nordisk	Centocor
Genentech	Galenus Ingelheim
Merck Serono	Ortho Biotech
Eli Lilly	Hoffman-la-Roche
Bayer Schering Plough	Chiron
IPSEN	Celgene

Short time line in pharmaceutical biotechnology

Year	*Historic event*
1797	Jenner inoculates child with viral vaccine to protect him from smallpox
1857	Pasteur proposes that microbes cause fermentation
1928	Penicillin is discovered by Fleming
1944	Avery proves DNA as carrier of genetic information
	Waksman isolates streptomycin as antibiotic for tuberculosis
1953	Structure elucidation of double helix of DNA
1967	First protein sequencer is perfected
1970	Discovery of restriction enzymes
1973	Cohen and Boyer produce first recombinant DNA in bacteria with restriction enzymes and ligases
1977	First expression of human protein in bacteria
1980	US patent for gene cloning to Cohen and Boyer
1981	First transgenic animal
1982	Humulin as first recombinant biotech drug approved by FDA
1983	Invention of Polymerase Chain Reaction (PCR)
1986	First recombinant vaccine for Hepatitis B (Recombivax HB)
1988	First US patent for genetically modified mouse (Onkomouse)
1990	Launching of the Human Genome Project
	First somatic gene therapy to cure ADA-SCID
	First transgenic cow produces human proteins in milk
1994	Approval of DNAse for cystic fibrosis
1997	First animal cloned from adult cell (Dolly)
2000	Rough draft of the human genome is announced
2002	Draft version of the complete map of the human genome is published.

Regulatory framework & time line

A. Jordan

- Biological products are regulated under:

"أسس تسجيل الأدوية والأمصال والمطاعيم والمواد البيولوجية وتجديد تسجيلها والغاء تسجيل أي منها الصادرة عن اللجنة العليا للدواء والصيدلة استنادا للمادة رقم (٥) من قانون الدواء والصيدلة رقم (٨٠) وتعديلاته".

"The foundations of registration of drugs, sera, vaccines and biological products and the registration renewal, registration cancellation of any of them for the year 2010 issued by the higher committee of medicine and pharmacy in accordance with Article no. (5) of the "Drug and pharmacy law no. (80) for the year (2001) and its amendments".

- Committee responsible for registration of biological products:
  "Committee for sera & vaccines" لجنة الأمصال والمطاعيم
- Prior to any registration of pharmaceutical &/ or biological product the manufacturing site must be approved according to JFDA rules & regulations.

Registration is as follows:

1. New pharmaceutical product &/ or biological product submission of application along with the requirements;
   - For pharmaceutical products &/ or biological products, conditions must be met according to appendix no. (1) when application being submitted.
   - In case of contract manufacturing, conditions must be met according to appendix no. (2) in addition to appendix no. (1) when application being submitted.
   - In case of license manufacturing, appendix no. (3), conditions must be met according to appendix no. (3) in addition to appendix no. (1) when application being submitted.

2. JFDA committee for sera & vaccines will study the submitted file.
   - **Note:**
   - **Article no. (6)/ 6:**
     "Sera, vaccines and biological products, including sensitive products to be allowed to be used and used already in the country of origin with the same composition.
   - **Article no. (6)/ 7:**
     "In the event that the sera, vaccines and biological products, including cosmetics and allergens are registered but not marketed in the country of origin for reasons acceptable to the Committee, adopted by the Committee to be registered and the drug circulating in countries accredited by the Ministry".

3. The Committee shall decide on any application for registration of new drugs and drugs that have an instance of it is contained within a period not exceeding one hundred and eighty days (180) of the date of submission of the completed application documents to the Directorate.

*Special consideration regarding Biological Product.

In reference to the ICH guideline "Comparability of Biotechnological/ Biological products subject to changes in their manufacturing process (ICH Topic Q5E – June 2005)"; Potency test is a requirement.

- A draft being issued still not yet approved or implemented covering the Biological products registration including the Biosimilars as well.

B. US

- Responsible party for registering biological products: "Center for Biologics Evaluation & Research" (CBER).

Development & Approval Process, prior to establishment registration;

Biologics License Applications (BLA) Process / CBER

- A request to have permission to introduce or deliver for introduction, a biologic product into U.S., which regulated according to section 600-680 of the Federal Food, Drug, and Cosmetic Act.

- BLA requirements as specified by the "New Drug Application Form-FDA 356h" are:

  - Applicant information
  - Product/Manufacturing information
  - Pre-clinical studies
  - Clinical studies
  - Labeling.

- Establishment registration & product listing process (through NDA) is not performed until investigational manufacturer biological product is approved through a Biologics License Application (BLA).

Biologics Establishment Registration

A. Blood Establishment
B. Tissue Establishment

A. Blood Establishment Registration & Product Listing

On this regard, blood products manufacturers are required to register their products according to pursuant section 510 of the Federal Food, Drug, and Cosmetic Act, unless they are exempt under 21 CFR 607.65.

For any blood product manufactured, prepared, or processed for commercial distribution, products must be:

1. Registered and list their products
2. Update lists of blood products which are in commercial distribution /bi-annually every June and December.
3. To list changes within 6 months of change.

Notes:

- In case of blood products imports or offer to import into the U.S., these products also need to be registered with FDA.
- Alternative to the blood establishment registration & product listing, the information may be submitted electronically by email.

  Blood Establishment Registration referred to "Guidance; Providing Regulatory Submissions in Electronic Format - May 2009".

Related Biologic Forms:

- Form FDA-2830; Blood Establishment Registration & Product Listing.
- Form FDA-356h; Application to market a new drug, biologic, or an antibiotic drug for human use.
- Form FDA-3613; Supplementary Information Certificate to foreign government requests.
- Form FDA-2253; Transmittal of advertisements & promotional labeling for drugs & biologics for human use.
- Form FDA-2252; Transmittal of annual reports for drugs & biologics for human use.
- Form FDA-2567; Transmittals of labels & circulars.
- Form "VAERS-1(FDA)"; Vaccine Adverse Event Reporting System.

B. Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) Establishments

- Tissue products manufacturer are required to register their products according to section 1271 of the Federal Food, Drug, and Cosmetic Act.
- Similarly to blood establishment registration products establishments covered by the final rule must register within 5 days after beginning operations, annual update of product listing & changes listing within 6 months of change.
- Establishments that manufacture HCT/Ps that are regulated solely under section 361 of the PHS Act and the regulations in part 1270 are required to register and list under 21 CFR Part 1271 in 2001.

- Related Biologic Forms:

- Form FDA-3356; Establishment Registration & product listing of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps).

- Alternative to the blood establishment registration & product listing, the information may be submitted electronically by email.

C. EU

- European Medicinal Agency, responsible party:
  "The Committee for Medicinal Products for Human Use (CHMP) - Biologics Working Party (BWP)", composed of experts selected from European experts list according to their specific expertise.
- The application for a marketing authorization of a medicinal product (including biological product) should meet the requirements listed in:
  "The Notice to Applicants – Volume 2B – Common Technical Document – Module 1 – Administrative information".

* Special for Blood Products & Vaccines to provide details of the official or designated laboratory for the batch release;

"2.5.1 b) Official batch release for Blood Products and Vaccines:
Details of the Official Medicines Control Laboratory (OMCL) or laboratory designated for the purpose of official batch release (in accordance with Articles 111(1), 113, 114(1)-(2) and 115 of Directive 2001/83/EC as amended)".

- Submitting the application form according to any one or more of the following procedures in reference to Heads of Medicines Agencies.

National Procedure

- Manufacturers could apply for a national approval; accordingly the product can only be sold in the particular country to which they submitted.
- Market authorization is valid for 5 years, after the first renewal it's valid for an unlimited period.

The Mutual Recognition Procedure

- Procedure which facilitates any of EU countries approves the decision regarding medicinal product by another EU country.
- The pharmaceutical company must submit the application to the country which chosen to carry the assessment work.
- Working groups to facilitate the procedure: “Coordination Group for mutual recognition & Decentralised procedures (human)” (CMD (h)).
- The CMD (h) either approves or rejects the application, within 90 days the other countries have to decide whether to approve or reject the decision made by the original country.
- If a member state cannot approve the assessment report, the SmPC, labeling & package leaflet due to potential serious risk to human or to the environment then a pre-referral procedure should be issued by the relevant coordination group, if in any case the member state(s) fail to reach an agreement during the 60-day a referral to the “Committee for Medicinal Products For Human Use (CHMP).

The Decentralised Procedure

- Used for products which have not received authorisation in an EU country.
- The applicant is able to submit the request to one or more concerned member states to approve a draft assessment report, summary of product characteristics, labeling & package leaflet as proposed by the chosen reference member state within 210 days.
- Working groups to facilitate the procedure: “Coordination Group for mutual recognition & Decentralised procedures (human)” (CMD (h)).
- If a member state cannot approve the assessment report, the SmPC, labeling & package leaflet due to potential serious risk to human or to the environment then a pre-referral procedure should be issued by the relevant coordination group, if in any case the member state(s) fail to reach an agreement during the 60-day a referral to the “Committee for Medicinal Products For Human Use (CHMP).

The Centralised Procedure

- This procedure is followed when an approval for a medicinal product is intended to be used in all EU countries, by applying to the European Medicinal Agency in London.
- Responsible committee: “Committee for Medicinal Products for Human Use” (CHMP), the member states have one representative in each committee.
- An opinion is prepared proceeding to the formal approval, where the assessment work can be done by any of the EU countries.

- When centralized application has been received by European Medicinal Agency the responsible committee will appoint a rapporteur/co-rapporteur.
- Based on the opinion from the scientific committees the Commission issues the formal decision to authorise a product in the centralised procedure. The Commission is assisted in the decision-making procedure by a Standing Committee with representatives from each Member State.

Administrative

Jordan

Module 1: Administrative Documents

1. Cover Letter.
2. Comprehensive Table of Contents (Module 2-5).

Administrative information (Application Forms)

3. Check List (F1/RDP-1/2010) (Signed & Stamped)
4. Drug Registration form (LF 4-RDP-7\2008)
5. Technical Committee Form (F2/RDP-7\2008) (5 copies)
6. Computer application Form (F3/RDP-7\2008)
7. JFDA Stability Report Form (F5/RDP-7\2008).

Product Information

8. SPC (Summary of product characteristics)
9. Labeling
10. Proposed Patient information leaflets (PIL) (Package leaflet) /insert. (5 copies)
11. Artwork (Mock-up of the outer & inner label)
12. One Registration sample.

Declarations:

13. List of Similar Product Available in Local Market
14. Declaration from the manufacturer about the ingredient from human or animal origin entering in the composition of the product and their source and the related certificates (TSE CEP)

15. List from manufacturer to declare the worldwide registration status (registered \ Marketed, under registration, rejected).

Certificates

16. Certificate of Pharmaceutical product (CPP) according to WHO format Certified and Legalized.
17. SmPC Certified and Legalized from country of origin.
18. A valid Certificate of Suitability (CoS) from EDQM for Drug substance (from each manufacturer):
19. GMP certificate for (API) Manufacturer (form each manufacturer) only if CoS is not available.
20. JFDA approval letter of the Manufacturing site/s (or copy of request letter for approval (date and number).

Information relating to Pharmacovigilance

21. Pharmacovigilance System.
22. Risk-management System.

Additional requirements:

1. Fulfilled special registration forms*
2. Batch record for three consecutive production batches.
3. Suitability certificate (for products containing bovine origin materials) EDQM
4. Certificate to prove freedom of BSE
5. Plasma master file for products contains human plasma derivatives.

Special registration forms include the following types:

1- Plasma proteins of human origin: it includes information on donors testing for infectious agents, summary of method of preparation and viral inactivation method used.
2- Live viral vaccine: it includes information on origin of plasma used, tests performed on serum, cell culture, and viral seed and pooling of single harvest.
3- BCG Vaccine: it includes information on history of the strain, production control, single harvest and preparation of bulk and tests for virulence and contaminating microorganisms.
4- Immune Sera of animal origin: it includes information on animal used, antigen used

for immunogenicity and control of bulk material and purification process.
5- Recombinant biological products: it includes information on validation and control of manufacturing process, manufacturing working cell bank MWCB, production control, single harvest, Purification and final bulk before addition of adjuvant (aqueous bulk).
6- Inactivated viral vaccines like Measels, mumps, rubella vaccines.
7- Vaccines of Bacterial product like tetanus and diphyjeria vaccines.

8- Killed Bacterial vaccine like influenza, cholera vaccines.

9- Poly Saccharide vaccine like pneumococcal vaccine.

*All the above nine forms include information on the starting materials, bulk materialal, final product, filling and labeling and shipping conditions.
*Common tests for all types performed on finished product are: Identity, potency, sterility, purity, pyrogenicity, stability, and preservative content and infectious agents.

USA

USA CTD Module 1:

Can be provided in a single volume, where the environmental assessments should be submitted separately.

1. FDA form 356h

The first document in Module 1 should be FDA form 356h.

BLA requires the following as specified by the "New Drug Application Form-FDA 356h":

- Applicant information
- Product/Manufacturing information
- Pre-clinical studies
- Clinical studies
- Labeling.

2. Comprehensive table of contents

The next document in Module 1 should be the comprehensive table of contents for the entire submission. Each NDA and ANDA submission is required to have a comprehensive

table of contents or index for the entire submission as described in 21 CFR 3 14.50 and 3 14.94. The comprehensive table of contents significantly enhances the usefulness of the document. It should include a complete list of all documents provided in the submission by module.
In the table of contents, you should identify the location of each document by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document (e.g., patent certification, financial disclosure) or section heading according to the CTD format (e.g., 3.2.P.4.2). If the full name of the document is too long for the tab identifiers, you should substitute an alternative name that adequately identifies the document. You should not use page numbers in the table of contents to refer to documents, but use tab identifiers as described above.

3. Administrative documents

a. Administrative documents

You should provide the appropriate administrative documents with the submission. Examples of administrative documents are listed below. See 21 CFR 3 14.50, 3 14.94, and 601.2 for details on the administrative documents needed for specific submissions. FDA form 356h lists most of the administrative documents to be included in Module 1. The order of such documents should be consistent with that in FDA Form 356h.

1. Patent information on any patent that claims the drug, if applicable
2. Debarment certification
3. User fee cover sheet
4. Financial disclosure information
5. Letters of authorization for reference to other applications or drug master files
6. Waiver requests
7. Environmental assessment or request for categorical exclusion
8. Statements of claimed exclusivity and associated certifications.

Since these documents are small, you should place them in the same volume, Module 1

If you submit an environmental assessment, you should provide it as a separate volume.

b. Prescribing information

You should include all copies of the labels and all labeling for the product in Module 1. The type of labeling provided depends on the submission. Examples of prescribing information include container and package labels as well as package inserts, draft labeling, patient leaflets, information sheets, and required Medication Guides. You should separate each sample of labeling by tab identifiers.

c. Annotated labeling text

For the NDA, you should provide a copy of the proposed labeling text with annotations directing reviewers to the information in the summaries and other modules that support each statement in the labeling, as described in 21 CFR 3 14.50(c)(2)(i). The annotated labeling text should include the content of the labeling described under 21 CFR 201.57 and all text, tables, and figures used in the package insert.

*Applicants often choose to submit a cover letter with their submissions. If you plan to include a cover letter, it should be placed at the beginning of Module 1.

EU;

Module 1 Table of Content:

1.0 Cover Letter
1.1 Comprehensive Table of Contents
1.2 Application Form

1.3 Product Information
1.3.1 SPC, Labelling and Package Leaflet
1.3.2 Mock-up
1.3.3 Specimen
1.3.4 Consultation with Target Patient Groups
1.3.5 Product Information already approved in the Member States
1.3.6 Braille

1.4 Information about the Experts
1.4.1 Quality
1.4.2 Non-Clinical
1.4.3 Clinical

1.5 Specific Requirements for Different Types of Applications
1.5.1 Information for Bibliographical Applications

1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications
1.5.3 (Extended) Data/Market Exclusivity
1.5.4 Exceptional Circumstances
1.5.5 Conditional Marketing Authorisation

1.6 Environmental Risk Assessment
1.6.1 Non-GMO
1.6.2 GMO

1.7 Information relating to Orphan Market Exclusivity
1.7.1 Similarity
1.7.2 Market Exclusivity

1.8 Information relating to Pharmacovigilance
1.8.1 Pharmacovigilance System
1.8.2 Risk-management System

1.9 Information relating to Clinical Trials
1.10 Information relating to Paediatrics
Responses to Questions
Additional Data

Comparison Table

	Jordan	USA	Europe
Cover Letter.			
Comprehensive Table of Contents.			
Administrative information (Application Forms).			
	Check List (F1/RDP-1/2010) (Signed & Stamped)		
	Drug Registration form (LF 4-RDP-7\2008) + special application form	**FDA form 356h**	**application form revised_rev9_en-EU**
	Technical Committee Form (F2/RDP-7\2008)(5 copies)		
	Computer application Form (F3/RDP-7\2008)		

	JFDA Stability Report Form(F5/RDP-7\2008)		
		Patent information on any patent that claims the drug, if applicable	Market Exclusivity
		Debarment certification	
		User fee cover sheet	
		Financial disclosure information	
		Letters of authorization for reference to other applications or drug master files	
		Waiver requests	
		Environmental assessment or request for categorical exclusion	Environmental Risk Assessment for GMO and Non GMO
		Statements of claimed exclusivity and associated certifications.	Extended) Data/Market Exclusivity
Product Information.			
	SPC (Summary of product characteristics).	container and package labels , package inserts, draft labeling, patient leaflets, information sheets, and required medications guide	Labelling and ,SPC Package Leaflet
	Proposed Patient information leaflets (PIL) (Package leaflet) /insert. (5 copies).		
	Artwork (Mock-up of the outer & inner label).	Prescribing information (copies of the labels and all labeling for the product)	Mock-up

		Annotated labeling text directing reviewers to the information in the summaries and other modules that support each statement in the labeling. modules that support each statement in the labeling	
	One Registration sample.		Specimen
			Braille
			Consultation with Patient Groups Target
			Product Information already approved in the member states
Declarations :			
	List of Similar Product Available in Local Market.		
	Declaration from the manufacturer about the ingredient from human or animal origin entering in the composition of the product and their source and the related certificates (TSE CEP).		
	List from manufacturer to declare the worldwide registration status (registered \ Marketed, under registration, rejected).		
Certificates			
	Certificate of Pharmaceutical product (CPP) according to WHO format Certified and Legalized.		
	SmPC Certified and Legalized from country of origin.		
	JFDA approval letter of the Manufacturing site/s (or copy of request letter for approval (date and number).		
Information relating to Pharmacovigilance			

	Pharmacovigilance System.		Pharmacovigilance System.
	Risk-management System.		Risk-management System.
Additional requirements:			
	Fulfilled special registration forms.		
	Batch record for three consecutive production batches.		
	Suitability certificate (for products containing bovine origin materials) EDQM		
	Certificate to prove freedom of BSE		
	Plasma master file for products contains human plasma derivatives.		
			Information about the Experts, Quality, non-clinical and clinical
			Information relating to Clinical Trials
			Information relating Paediatrics to
			Responses to Questions
			Additional data
Requirements for Specific Different Types of applications			
			Bibliographical Applications
			Information for Hybrid' or ' ,Generic Bio-similar
			Exceptional Circumstances
			Conditional Marketing Authorisation
			Information relating Orphan Market to Exclusivity

Quality technical aspects

A. Jordan

According to the registration checklist, quality module includes that for drug substance & drug product.

Drug substance requirements:

- General information (nomenclature, structure, general properties)
- Manufacture; manufacturers (names, address).
- Control of drug substance (specifications, analytical procedures, reference standards materials).
- Certificate of analysis of API stamped & signed (from API manufacturer & drug product manufacturer).

Drug product requirements:

- Description and composition of the drug product
- Drug product (formulation development, overages)
- Manufacture (manufacturer(s), batch formula)
- Description of manufacturing process & process controls
- Control of excipients (specifications, analytical procedures, excipients of human or animal origin)
- Control of drug product (specification(s), analytical procedures, validation of analytical procedures, batch analyses, characterization of impurities, justification of specification
- Container closure system (primary & secondary)
- Stability
    - stability summary & conclusion for the proposed shelf life & storage condition
    - post-approval stability protocol & stability commitments
    - stability data (real stability data with raw data & chromatograms, accelerated stability with raw data & chromatograms, photostability (if needed)
    - in-use stability according to dosage form (reconstitution, inverted position)
- Certificate of analysis of finished product
- Electronic copy of technical file.

**Quality technical aspects include both for drug substances & drug products, those of which required for pharmaceutical drug product with the following special considerations regarding biological products:*

- *To provide batch record for three consecutive production batches.*
- *To provide suitability certificate (for products containing bovine origin material/ EDQM).*
- *Common Technical Document Summarizes is not included in the checklist.*
- *The API supplier must be accredited as a manufacturing site.*
- *Plasma Master File must also be provided.*

Batch Record:

A detailed step-by-step description of the whole production process, which provides practical instructions for both the manufacturing technician &/or operator indicating the specific types, quantities of components & raw materials, processing parameters, in-process quality controls & environmental controls.

B. US

In reference to the "New Drug Application" form the following table clarifies what is included in the checklist when submitting the application.

□	3. Summary (21 CFR 314.50 (c))
□	4. Chemistry section
□	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)

Additional requirements regarding biological products as published in rules, notices specifically related on case by case basis to general biologics, blood, tissue & vaccines are available at US FDA website.

Chemistry, manufacturing & Controls - Active Pharmaceutical Ingredient

ACTIVE PHARMACEUTICAL INGREDIENT
Description of the Physical and Chemical Properties
Nomenclature - International non-proprietary name (INN), USAN
Structural Formula
General Properties
Manufacturers
Address of the Manufacturing Facilities
Method of Manufacturing
General Description of the Process Chemistry
Schematic Flow Chart
Specifications for the Drug Substance
European Pharmacopoeia Monograph
Non-Compendial Analytical Methods and Validations for the Drug Substance
Stability of the Drug Substance

Chemistry, manufacturing & Controls – Drug Product

DRUG PRODUCT
Composition of the Drug Product
1- Unit Formula
2- Batch Formula
Specifications for Inactive Compounds
Monographs and Listings for Inactive Compounds
Address of the Manufacturing Facilities
1- MANUFACTURER OF THE DOSAGE FORM
2- PACKAGING AND LABELLING
3- CONTROL AND RELEASE
Method of Manufacturing
1- PRODUCTION OPERATIONS
2- FLOW CHART
3- IN-PROCESS CONTROLS
4- PACKAGING
Specifications for the Drug Product
1- REGULATORY SPECIFICATIONS AND TESTS FOR RELEASE
2- REGULATORY SPECIFICATIONS FOR THE PROPOSED SHELF-LIFE
Non-Compendial Analytical Methods for the Drug Product
Analytical Validation of Non-Compendial Procedures for Drug Product
Batch Analysis – 3 lots

Packaging specifications and controls
Stability of the Drug Product
1- RECOMMENDED EXPIRATION DATING AND STORAGE CONDITIONS
2- PROTOCOL FOR STABILITY STUDIES
3- SUMMARY OF THE DATA
4- STABILITY DATA

C. EU

The common technical document for the registration of pharmaceuticals for human use guideline – Quality (M4Q (R1)):

Module 2: Common Technical Document Summarizes

CTD section	Description
2.3.S	**DRUG SUBSTANCE (NAME, MANUFACTURER)**
2.3.S.1	General Information (name, manufacturer)
2.3.S.2	Characterisation (name, manufacturer)
2.3.S.3	Manufacture (name, manufacturer)*
2.3.S.4	Control of Drug Substance (name, manufacturer)
2.3.S.5	Reference Standards or Materials (name, manufacturer)
2.3.S.6	Container Closure System (name, manufacturer)
2.3.S.7	Stability (name, manufacturer)
2.3.P	DRUG PRODUCT (NAME, DOSAGE FORM)
2.3.P.1	Description & Composition of the Drug Product (name, dosage from)
2.3.P.2	Pharmaceutical Development (name, dosage from)
2.3.P.3	Manufacture (name, dosage from)
2.3.P.4	Control of Excipients (name, dosage from)
2.3.P.5	Control of Drug Product (name, dosage from)
2.3.P.6	Reference Standards or Materials (name, dosage from)
2.3.P.7	Container Closure System (name, dosage from)
2.3.P.8	Stability (name, dosage from)
2.3.A	**APPENDICES***
2.3.A.1	Facilities & Equipment (name, manufacturer) *
2.3.A.2	Adventitious Agents Safety Evaluation
2.3.A.3	Excipients
2.3.R	**REGIONAL INFORMATION**

*Special consideration regarding Biological Product.

*2.3.S.3: Characterisation as described in 3.2.S.3.1

*****2.3.A.1: Facilities & Equipment as described in 3.2.A.1

***2.3.S.3: Characterization**

The quality overall summary should summarize:

1. The data on potential & actual impurities which arise either during synthesis, manufacture & degradation.
2. What were the basis for setting the acceptance criteria fir both individual & total impurities.

Quality – Module 3 (DRUG SUBSTANCE & DRUG PRODUCT)

	Description
3.2.S	**DRUG SUBSTANCE (NAME, MANUFACTURER)**
3.2.S.1	*General Information (name, manufacturer)*
3.2.S.1.1	Nomenclature (name, manufacturer)
3.2.S.1.2	Structure (name, manufacturer)*
3.2.S.1.3	General Properties (name, manufacturer)
3.2.S.2	*Manufacture (name, manufacturer)*
3.2.S.2.1	Manufacturer(s) (name, manufacturer)
3.2.S.2.2	Description of Manufacturing Process and Process Controls (name, manufacturer)*
3.2.S.2.3	Control of Materials (name, manufacturer) *
3.2.S.2.4	Controls of Critical Steps and Intermediates (name, manufacturer)
3.2.S.2.5	Process Validation and/or Evaluation (name, manufacturer) *
3.2.S.2.6	Manufacturing Process Development (name, manufacturer) *
3.2.S.3	*Characterisation (name, manufacturer)*
3.2.S.3.1	Elucidation of Structure and other Characteristics (name, manufacturer) *
3.2.S.3.2	Impurities (name, manufacturer)
3.2.S.4	*Control of Drug Substance (name, manufacturer)*
3.2.S.4.1	Specification (name, manufacturer)
3.2.S.4.2	Analytical Procedures (name, manufacturer)
3.2.S.4.3	Validation of Analytical Procedures (name, manufacturer)
3.2.S.4.4	Batch Analyses (name, manufacturer)
3.2.S.4.5	Justification of Specification (name, manufacturer)
3.2.S.5	*Reference Standards or Materials (name, manufacturer)*
3.2.S.6	*Container Closure System (name, manufacturer)*
3.2.S.7	*Stability (name, manufacturer)*

3.2.S.7.1	Stability Summary and Conclusions (name, manufacturer)
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment (name, manufacturer)
3.2.S.7.3	Stability Data (name, manufacturer)

*Special consideration regarding Biological Product.

*3.2.S.1.2: Structure

The structure must indicate glycosylation sites, post-translational modifications & the relative molecular mass, as appropriate.

*3.2.S.2.2: Description of Manufacturing Process and Process Controls

Information should be adequate to describe the manufacturing process & process controls regarding the following:

- Batch(es) & scale definition
- Cell culture & harvest
- Purification & modification reactions
- Filling, Storage & transportation (shipping).

Reference ICH Guidelines: Q5A, Q5B, and Q6B.

*3.2.S.2.3: Control of Materials

To demonstrate information about the quality & control of the materials such as monoclonal antibodies, enzymes & that the standards appropriate for their intended use including:

- Control of source starting materials of biological origin (summary of viral safety)
  Reference: Q5A (R1).
- Source, history & generation of the cell substrates
- Cell banking system, characterization & testing.

Reference ICH Guidelines: Q5A, Q5B, Q5C and Q5D.

*3.2.S.2.5 Process Validation and/or Evaluation

Regarding the aseptic processing & sterilization:

- To demonstrate that the manufacturing process is suitable for its intended purpose.

- To substantiate the selection of critical process controls & their limits for the critical manufacturing steps as cell culture, harvesting, purification & modification.

*3.2.S.2.6 Manufacturing Process Development

- Description of changes made to include the changes to the process or to the critical equipment & explained reason of change.
- Relevant information on drug substance batches manufactured during development; batch no., manufacturing scale & use in relation to the change. e.g. Stability batch, non-clinical, reference material.
- Assessing the significance of change.

Reference ICH Guideline: Q6B, Q5E.

3.2.S.3.1 Elucidation of Structure and other Characteristics

To provide details on primary, secondary & higher-order structure, post-translational forms such as glycoforms, biological activity, purity & immunochemical properties (when relevant).

Reference ICH Guideline: Q6B.

DRUG PRODUCT

3.2.P	**DRUG PRODUCT (NAME, DOSAGE FORM)**
3.2.P.1	*Description and Composition of the Drug Product (name, dosage form)*
3.2.P.2	*Pharmaceutical Development (name, dosage form)*
3.2.P.2.1	Components of the Drug Product (name, dosage form)
3.2.P.2.1.1	Drug Substance (name, dosage form)
3.2.P.2.1.2	Excipients (name, dosage form)
3.2.P.2.2	Drug Product (name, dosage form)
3.2.P.2.2.1	Formulation Development (name, dosage form)
3.2.P.2.2.2	Overages (name, dosage form)
3.2.P.2.2.3	Physicochemical and Biological Properties (name, dosage form)
3.2.P.2.3	Manufacturing Process Development (name, dosage form)
3.2.P.2.4	Container Closure System (name, dosage form)
3.2.P.2.5	Microbiological Attributes (name, dosage form)
3.2.P.2.6	Compatibility (name, dosage form)
3.2.P.3	*Manufacture (name, dosage form)*
3.2.P.3.1	Manufacturer(s) (name, dosage form)
3.2.P.3.2	Batch Formula (name, dosage form)

3.2.P.3.3	Description of Manufacturing Process and Process Controls (name, dosage form)
3.2.P.3.4	Controls of Critical Steps and Intermediates (name, dosage form)
3.2.P.3.5	Process Validation and/or Evaluation (name, dosage form)
3.2.P.4	*Control of Excipients (name, dosage form)*
3.2.P.4.1	Specifications (name, dosage form)
3.2.P.4.2	Analytical Procedures (name, dosage form)
3.2.P.4.3	Validation of Analytical Procedures (name, dosage form)
3.2.P.4.4	Justification of Specifications (name, dosage form)
3.2.P.4.5	Excipients of Human or Animal Origin (name, dosage form)
3.2.P.4.6	Novel Excipients (name, dosage form)
Section	**Description**
3.2.P.5	*Control of Drug Product (name, dosage form)*
3.2.P.5.1	Specification(s) (name, dosage form)
3.2.P.5.2	Analytical Procedures (name, dosage form)
3.2.P.5.3	Validation of Analytical Procedures (name, dosage form)
3.2.P.5.4	Batch Analyses (name, dosage form)
3.2.P.5.5	Characterisation of Impurities (name, dosage form)
3.2.P.5.6	Justification of Specification(s) (name, dosage form)
3.2.P.6	*Reference Standards or Materials (name, dosage form)*
3.2.P.7	*Container Closure System (name, dosage form)*
3.2.P.8	*Stability (name, dosage form)*
3.2.P.8.1	Stability Summary and Conclusion (name, dosage form)
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment (name, dosage form)
3.2.P.8.3	Stability Data (name, dosage form)
3.2.A	**APPENDICES**
3.2.A.1	Facilities and Equipment (name, manufacturer)
3.2.A.2	Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)*****
3.2.A.3	Excipients
3.2.R	**REGIONAL INFORMATION**

*Special consideration regarding Biological Product.

* 3.2.R REGIONAL INFORMATION

The information from evaluation studies about the manufacturing steps intended to remove or inactivate viral contaminants should be provided in this section.

Reference ICH Guideline: Q5A(R1).

Examples:

- Executed Batch Records (USA only)
- Method Validation Package (USA only); Form FDA-365h
- Comparability Protocols (USA only)
- Process Validation Scheme for the Drug Product (EU only).

Comparability of Biotechnological/ Biological Products subject To Changes in their manufacturing process (Q5E);

1. To assess the comparability of biotechnological/ biological products before & after changes on manufacturing process of the drug substance or product.
2. To collect technical information to serve as evidence that the manufacturing process changes do not have an adverse impact on the quality, safety & efficacy (quality aspects & does not serve in any particular analytical, nonclinical or clinical strategy).

Quality - Comparison Table

Description	**Jordan**	**US**	**EU**
DRUG SUBSTANCE (NAME, MANUFACTURER)	**3-1**	**Description of physical & chemical prop.**	3.2.S
General Information (name, manufacturer)	**3-1-1**		**3.2.S.1**
Nomenclature (name, manufacturer)		Nomenclature-INN, USAN	3.2.S.1.1
*Structure (name, manufacturer)**		Structural formula	3.2.S.1.2
General Properties (name, manufacturer)		General Properties	3.2.S.1.3
Manufacture (name, manufacturer)	**3-1-2**	**Address of Manufacturing facilities**	**3.2.S.2**
Manufacturer(s) (name, manufacturer)			3.2.S.2.1

*Description of Manufacturing Process and Process Controls (name, manufacturer)**		Method of manufacturing	3.2.S.2.2
Control of Materials (name, manufacturer)*	**3-1-3**		**3.2.S.2.3**
Controls of Critical Steps and Intermediates (name, manufacturer)			3.2.S.2.4
*Process Validation and/or Evaluation (name, manufacturer)**			3.2.S.2.5
*Manufacturing Process Development (name, manufacturer)**			3.2.S.2.6
Characterisation (name, manufacturer)			3.2.S.3
*Elucidation of Structure and other Characteristics (name, manufacturer)**			3.2.S.3.1
Impurities (name, manufacturer)			3.2.S.3.2
Control of Drug Substance (name, manufacturer)			3.2.S.4
Specification (name, manufacturer)		Specification	3.2.S.4.1
Analytical Procedures (name, manufacturer)		Non-compendial analytical	3.2.S.4.2
Validation of Analytical Procedures (name, manufacturer)		Validation	3.2.S.4.3
Batch Analyses (name, manufacturer)			3.2.S.4.4
Justification of Specification (name, manufacturer)			3.2.S.4.5
Reference Standards or Materials (name, manufacturer)	**3-1-4**		**3.2.S.5**
Container Closure System (name, manufacturer)			3.2.S.6
Stability (name, manufacturer)		Stability	3.2.S.7
Stability Summary and Conclusions (name, manufacturer)			3.2.S.7.1
Post-approval Stability Protocol and Stability Commitment (name, manufacturer)			3.2.S.7.2
Stability Data (name, manufacturer)			3.2.S.7.3
DRUG PRODUCT (NAME, DOSAGE FORM)	**3-2**		**3.2.P**
Description and Composition of the Drug Product (name, dosage form)	**3-2-1**	**Composition**	**3.2.P.1**
Pharmaceutical Development (name, dosage form)			3.2.P.2

Components of the Drug Product (name, dosage form)	**3-2-2**		**3.2.P.2.1**
Drug Substance (name, dosage form)			3.2.P.2.1.1
Excipients (name, dosage form)			3.2.P.2.1.2
Drug Product (name, dosage form)			3.2.P.2.2
Formulation Development (name, dosage form)			3.2.P.2.2.1
Overages (name, dosage form)			3.2.P.2.2.2
Physicochemical and Biological Properties (name, dosage form)			3.2.P.2.2.3
Manufacturing Process Development (name, dosage form)		Section 10.2 "Form 2830"	3.2.P.2.3
Container Closure System (name, dosage form)			3.2.P.2.4
Microbiological Attributes (name, dosage form)			3.2.P.2.5
Compatibility (name, dosage form)			3.2.P.2.6
Manufacture (name, dosage form)	**3-2-3**	**Address of manufacturing facilities**	**3.2.P.3**
Manufacturer(s) (name, dosage form)			3.2.P.3.1
Batch Formula (name, dosage form)			3.2.P.3.2
Description of Manufacturing Process and Process Controls (name, dosage form)	**3-2-4**	**Method of manufacturing**	**3.2.P.3.3**
Controls of Critical Steps and Intermediates (name, dosage form)			3.2.P.3.4
Process Validation and/or Evaluation (name, dosage form)			3.2.P.3.5
Control of Excipients (name, dosage form)	**3-2-5**	**Monographs & listing**	**3.2.P.4**
Specifications (name, dosage form)		Specification of inactive	3.2.P.4.1
Analytical Procedures (name, dosage form)			3.2.P.4.2
Validation of Analytical Procedures (name, dosage form)			3.2.P.4.3
Justification of Specifications (name, dosage form)			3.2.P.4.4
Excipients of Human or Animal Origin (name, dosage form)			3.2.P.4.5
Novel Excipients (name, dosage form)			3.2.P.4.6

Control of Drug Product (name, dosage form)	**3-2-6**		**3.2.P.5**
Specification(s) (name, dosage form)		Specification of drug product	3.2.P.5.1
Analytical Procedures (name, dosage form)		Non-compendial	3.2.P.5.2
Validation of Analytical Procedures (name, dosage form)		Validation of non-compendial	3.2.P.5.3
Batch Analyses (name, dosage form)		batch analysis (3 lots)	3.2.P.5.4
Characterisation of Impurities (name, dosage form)			3.2.P.5.5
Justification of Specification(s) (name, dosage form)			3.2.P.5.6
Reference Standards or Materials (name, dosage form)			3.2.P.6
Container Closure System (name, dosage form)	**3-2-7**	**Packaging specifications & controls.**	**3.2.P.7**
Stability (name, dosage form)	**3-2-8**	**Stability**	**3.2.P.8**
Stability Summary and Conclusion (name, dosage form)			3.2.P.8.1
Post-approval Stability Protocol and Stability Commitment (name, dosage form)			3.2.P.8.2
Stability Data (name, dosage form)			3.2.P.8.3
CD (Electronic copy of technical file)	**3-2-10**		
APPENDICES			**3.2.A**
Facilities and Equipment (name, manufacturer)			3.2.A.1
Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)			3.2.A.2
Excipients			3.2.A.3

REGIONAL INFORMATION	**3-1-7; COA of API, from API manufacturer & drug product manufacturer. 3-2-9; COA of finished product.**		**3.2.R**

Non Clinical

Jordan; Not Applicable

US, in addition to what is listed in EU-ICH section below

NDA application CHECKLIST:

- Nonclinical pharmacology and toxicology section (e.g., **21 CFR 314**.50(d)(2); 21 **CFR 601**.2)

CFR 21.314

- **Nonclinical pharmacology and toxicology section:**

A section describing, with the aid of graphs and tables, animal and in vitro studies with drug, including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, sub-acute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

(iii) Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

(v) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58 a statement that it was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

EU (ICH which covers both EU & USA)

4: Nonclinical Study Reports

4.1 Module 4 Table of Contents

4.2 Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics:

Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic agent. Do not need to be conducted in compliance with GLP.

4.2.1.2 Secondary Pharmacodynamics:

Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target. Do not need to be conducted in compliance with GLP, results from secondary pharmacodynamics studies conducted during the compound selection process may contribute to the safety pharmacology evaluation; when there is no cause for concern (e.g., there are finding for the safety pharmacological endpoint or the chemical or therapeutic class),these studies need not be repeated in compliance with GLP. In some circumstances, results of secondary pharmacodynamic studies may make a pivotal contribution to the safety evaluation for potential adverse effects in humans, and these are normally conducted in compliance with GLP.

4.2.1.3 Safety Pharmacology:

Investigation of the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above.
In some cases, information on the primary and secondary pharmacodynamics properties of the substance may contribute to the safety evaluation for potential adverse effect(s) in humans and should be considered along with the findings of safety pharmacology studies.
Conducted in compliance with GLP.

4.2.1.4 Pharmacodynamic Drug Interactions:

It's the phenomenon that occurs when the effects of a drug are addictive / synergistic or antagonistic to the effects of a concomitant drug, or when a drug changes the tissue sensitivity / reactivity to the investigational drug.

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports:

This section includes detection and quantification limits of an analytical procedure, validation data for the analytical method and stability of biological samples. The potential impact of different methods of analysis on the interpretation of the results should also be discussed.

4.2.2.2 Absorption:

Extent and rate of absorption, in vivo and in situ studies. As well as kinetic parameters, bioequivalence and/or bioavailability (Serum/plasma/blood PK studies).

4.2.2.3 Distribution:

Tissue distribution, protein binding and distribution in blood cells and placental transfer studies should be included in this section.

4.2.2.4 Metabolism:

This section should include chemical structures and quantities of metabolites in biological samples, possible metabolic pathways, pre-systemic metabolism (GI/hepatic first-pass effects), and in vitro metabolism including P450 studies and enzyme induction and inhibition.

4.2.2.5 Excretion:

Route and extent of excretion are discussed, as well as excretion in milk.

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical):

Pharmacokinetic drug interactions occur when on drug alters the absorption, distribution, metabolism or excretion of another drug, this can either decrease or increase plasma concentration of the interacting drug(s). As a result therapeutic failure or enhancement or emergence of toxic effects may occur. Pharmacokinetic drug interactions which occur with one drug cannot be assumed to occur with drugs in the same class unless their pharmacokinetic properties are similar

4.2.2.7 Other Pharmacokinetic Studies:

Such as studies which have been performed in nonclinical models of disease (e.g., renally impaired animals).

4.2.3 Toxicology

The scope of toxicologic evaluation should be described in relation the proposed clinical use. GLP status of the studies should also be addressed.

4.2.3.1 Single-Dose Toxicity:

It is the toxicity produced by a pharmaceutical when it is administered in once.
Single dose toxicity test studies should be conducted in such a way that signs of acute-toxicity are revealed and the mode of death determined. These studies may give some indication of the likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing on the relevant animal species. In suitable species a quantitative evaluation of the approximate lethal dose and information on the dose-effect relationship should be made.

4.2.3.2 Repeat-Dose Toxicity:

The primary goal of repeated dose toxicity studies is to characterize the toxicological profile of the test compound following repeated administration. This includes identification of potential target organs of toxicity and exposure/response relationship, and may include the potential reversibility of toxic effects. This information should be part of the safety assessment to support the conduct of human clinical trials and the approval of a marketing authorization.

4.2.3.3 Genotoxicity:

An assay for gene mutation is generally considered sufficient to support all single dose clinical development trials. To support multiple dose clinical development trials, an additional assessment capable of detecting chromosomal damage in a mammalian system(s) should be completed. It includes:

- In vitro non-mammalian cell system,
- In vitro mammalian cell system,
- In vivo mammalian system (including supportive toxicokinetics evaluation), and
- Other systems.

4.2.3.3.1 In vitro:

4.2.3.3.2 In vivo:

4.2.3.4 Carcinogenicity

The objective of carcinogenicity studies are to identify a tumorigenic potential in animals and to assess the relevant risk in humans. Any cause for concern derived from laboratory investigations, animal toxicology studies, and data in humans may lead to a need for carcinogenicity studies.
Carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months.

4.2.3.4.1 Long-term studies:

4.2.3.4.2 Short- or medium-term studies:

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity

4.2.3.5.1 Fertility and early embryonic development:

Tests for toxic effects/disturbances resulting from treatment from before mating (males/females) through mating and implantation. For females this should detect effects on the oestrous cycle, tubal transport, implantation, and development of preimplantation stages of the embryo. For males it will permit detection of function effects (e.g. on libido, epididymal sperm maturation) that may not be detected by histological examinations of the male reproductive organs.

4.2.3.5.2 Embryo-fetal development:

Detects the adverse effects on the pregnant female and development of the embryo and fetus consequent to exposure of the female from implantation to closure of the hard palate.

4.2.3.5.3 Prenatal and postnatal development:

Any adverse effect induced prior to attainment of adult life. It includes effects induced or manifested in the embryonic or fetal period and those induced or manifested postnatally or to detect adverse effects on the pregnant/lactating female and on development of the conceptus and the offspring following exposure of the female from implantation through weaning. Since manifestations of effect induced during this period may be delayed, observations should be continued through sexual maturity

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated:

Juvenile animal studies can be used to investigate findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials.

4.2.3.6 Local Tolerance:

The purpose of these studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the product as a result of its administration in clinical use. The testing strategy should be such that any mechanical effects of administration or purely physicochemical actions of the product can be distinguished forming toxicological or pharmacodynamic ones.

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity:

Antigenicity is the ability of a chemical structure (referred to as an Antigen) to bind specifically with certain products of adaptive immunity: T cell receptors or Antibodies (a.k.a. B cell receptors).

4.2.3.7.2 Immunotoxicity:

Immunotoxicity is an adverse effect on the immune system or the reaction to a toxin by the immune system; includes reactions to agents that are not being used for immunotherapy, but some drugs or chemicals may have an unwanted immunosuppressive side effect.
As stated in the ICH S8 guidance, all new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity using standard toxicity studies and additional immunotoxicity studies conducted as appropriate based on a weight-of-evidence review, including immune-related signals from standard toxicity studies. If additional immunotoxicity studies are indicated, these should be completed before exposure of a large population of patients (e.g., Phase III).
Evaluation of potential adverse effects of human pharmaceuticals on the immune system should be incorporated into standard drug development. Toxicity to the immune system encompasses a variety of adverse effects. These include suppression or enhancement of the immune response. Suppression of the immune response can lead to decreased host resistance to infectious agents or tumor cells. Enhancing the immune response can exaggerate autoimmune diseases or hypersensitivity. Drug or drug-protein adducts might also be recognized as foreign and stimulate an anti-drug response. Subsequent exposures to the drug can lead to hypersensitivity (allergic) reactions.
One aspect of immunotoxicological evaluation includes assessment of potential immunogenicity. Many biotechnology-derived pharmaceuticals are intended to stimulate or suppress the immune system and therefore may affect not only humoral but also cell-mediated immunity. Inflammatory reactions at the injection site may be indicative of a stimulatory response. It is important, however, to recognise that simple injection trauma and/or specific toxic effects caused by the formulation vehicle may also result in toxic changes at the injection site. In addition, the expression of surface antigens on target cells may be altered, which has implications for autoimmune potential. Immunotoxicological testing strategies may require

screening studies followed by mechanistic studies to clarify such issues. Routine tiered testing approaches or standard testing batteries, however, are not recommended for biotechnology-derived pharmaceuticals.

4.2.3.7.3 Mechanistic studies (if not included elsewhere):

Explore potential mechanisms for observed human toxicities.

4.2.3.7.4 Dependence:

Dependence is a continuum of physical and psychological attachments related to the concept of behavioral addiction

4.2.3.7.5 Metabolites:

Quantitative and/or qualitative differences in metabolic profiles and metabolite concentrations may exist between humans and animals as well as across animal species. When such differences occur, it is especially important to identify metabolites that may be unique to humans.

4.2.3.7.6 Impurities:

Animal tests on the toxic potential of identified impurities.

4.2.3.7.7 Other

4.3 Literature References.

Clinical

Jordan

5.3	**Clinical Study Reports**
5.3.1	**Reports of Biopharmaceutic Studies**
5.3.1.1	**Bioavailability (BA) Study Reports**
5.3.1.2	**Comparative BA and Bioequivalence (BE) Study Reports:**
5.3.3	**Reports of Human Pharmacokinetic (PK) Studies**
5.3.4	**Reports of Human Pharmacodynamic (PD) Studies**
5.3.4.1	**Healthy Subject PD and PK/PD Study Reports**
5.3.4.2	**Patient PD and PK/PD Study Reports**
5.3.5	**Reports of Efficacy and Safety Studies**
5.3.5.1	**Study Reports of Controlled Clinical Studies Pertinent to the**
5.3.6	**Reports of Post-Marketing Experience**
5.4	**Literature References**

- Further to the above PcV and RMP are requested.
- Detail regarding each part is found in EU – ICH.

US, in addition to what is listed in EU-ICH section below

NDA application CHECKLIST:

- Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)

CFR 21.314

- **Human pharmacokinetics and bioavailability section:**

A section describing the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the submission of in vivo bioavailability data under subpart B of part 320, including the following:

(i) A description of each of the bioavailability and pharmacokinetic studies of the drug in humans performed by or on behalf of the applicant that includes a description of

the analytical procedures and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under 56.104 or 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(ii) If the application describes in the chemistry, manufacturing, and controls section tests, analytical procedures, and acceptance criteria needed to assure the bioavailability of the drug product or drug substance, or both, a statement in this section of the rationale for establishing the tests, analytical procedures, and acceptance criteria, including data and information supporting the rationale.

(iii) A summarizing discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability or bioequivalence, or both, of the drug product.

- **Clinical data section:**

A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients

with renal failure or patients with different levels of severity of the disease, also shall be presented.

(vi) A summary and updates of safety information, as follows:

i. The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data shall be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also shall be presented, such as for patients with renal failure or patients with different levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under Clinical data section (ii).

ii. The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in Clinical data section (VI) (i). In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant shall submit these reports (1) 4 months after the initial submission; (2) in a resubmission following receipt of a complete response letter; and (3) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations

in part 56, or was not subject to the regulations under 56.104 or 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(x) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer--in lieu of a listing of the specific obligations transferred--may be submitted.

(xi) If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed.

- **Statistical section:**

A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under Clinical data section (ii) concerning the description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under Clinical data section (VI) (i) concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

- **Pediatric use section:**

A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs Human pharmacokinetics and bioavailability section and Clinical data section and information required to be submitted under 314.55.

- **Case report forms and tabulations:**

The archival copy of the application is required to contain the following case report tabulations and case report forms:

(i) Case report tabulations: The application is required to contain tabulations of the data from each adequate and well-controlled study under 314.126, tabulations of the data from the earliest clinical pharmacology studies, and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the

drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the application. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the application, in accordance with paragraph (iii) of this section.

(ii) Case report forms: The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

(iii) Additional data: The applicant shall submit to FDA additional case report forms and tabulations needed to conduct a proper review of the application, as requested by the director of the FDA division responsible for reviewing the application. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally.

EU - (ICH which covers both EU & USA)

Module 5: Clinical Study Reports

5.1 Module 5 Table of Contents

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports:

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. It should include:

- Studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form.

- Dosage from proportionality studies, and
- Food-effect studies.

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports:

Studies in this section compare the rate and extent of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between:

- The drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product,
- The drug product used in clinical studies supporting effectiveness and the drug product used in stability batched, and
- Similar drug products from different manufacturers.

5.3.1.3 In vitro-In vivo Correlation Study Reports:

US FDA definition is the predictive mathematical model describing the relationship between an in vitro property of a dosage form and a relevant in vivo response. Generally, the in vitro property is the rate or extent of drug dissolution or release while the in vivo response is the plasma drug concentration or amount of drug absorbed.
In vitro dissolution studies that provide BA information, including studies used in seeking to correlate in vitro data with in vivo correlations should be included.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies:

Necessary to construct a concentration-time profile. Chemical techniques are employed to measure the concentration of drugs in biological matrix, most often plasma. They should be selective and sensitive.

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports:

The degree of protein binding of the investigational drug should be determined. If the investigational drug is extensively protein bound to a specific saturable binding site, the risk of displacement of the other drugs known to be subject to clinically relevant displacement interactions should be evaluated, after an in-vitro prediction of such.

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies:

Human biomaterials such as hepatocytes and/or hepatic microsomes are of particular importance to study metabolic pathways and to assess drug-drug interactions with these pathways.

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports:

Initial tolerance refers to the degree of sensitivity or resistance displayed on the first exposure to the drug; it is expressed in terms of the degree of effect (as measured on some specified test) produced by a given dose of the drug, or by the concentration of drug in the body tissues or fluids resulting from that dose: the smaller the effect produced by that dose or concentration, the greater is the tolerance. Initial tolerance can vary markedly from one individual to another or from one species to another, as a result of genetic differences, constitutional factors, or environmental circumstances. It is investigated here in healthy subjects.

5.3.3.2 Patient PK and Initial Tolerability Study Reports:

Initial tolerance as defined in 5.3.3.1 but investigated in patient subjects.

5.3.3.3 Intrinsic Factor PK Study Reports:

5.3.3.4 Extrinsic Factor PK Study Reports:

Intrinsic and extrinsic factors that influence the pharmacokinetic of the investigational drug are featured below:

INTRINSIC		EXTRINSIC
Genetic	Physiological and pathological conditions	Environmental
Gender	Age (children-elderly)	Climate Sunlight Pollution
Height Bodyweight		Culture Socioeconomic factors Educational status Language
	Liver Kidney Cardiovascular functions	
ADME Receptor sensitivity		Medical Practice Disease definition/Diagnostic Therapeutic approach Drug compliance
Race		
Genetic polymorphism of the drug metabolism		Smoking Alcohol Food habits Stress
Genetic diseases	Diseases	Regulatory practice/GCP Methodology/Endpoints

5.3.3.5 Population PK Study Reports:

Is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug interest. Certain drug patient demographic, pathophysiological and therapeutic features, such as body weight, excretory and metabolic functions and the presence of other therapies can regularly alter dose-concentration relationships. It seeks to identify the measurable pathophysiological factors that cause changes in the dose-concentration relationship and other extent of these changes, so that if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified, e.g. renally cleared drugs given to patients with renal failure.

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects if a drug product in humans are placed in this section. This section should include reports of:

- Studies of pharmacologic properties known or thought to be related to the desired clinical effects (Biomarkers)
- Short-term studies of the main clinical effect, and
- PD studies of other properties not related to the desired clinical effect.

Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose response studies or together with drug concentration information in PK studies (concentration-response or PK/PD studies). Relationships between PK and PD effects are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose-response studies or in some cases for interpreting effects of concentration differences in population subsets.
Dose-finding, PD and/or PK-PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication.

5.3.4.1 Healthy Subject PD and PK/PD Study Reports:

Reports of dose-finding, PD and/or PK/PD studies conducted in healthy subjects.

5.3.4.2 Patient PD and PK/PD Study Reports:

Reports of dose-finding, PD and/or PK/PD studies conducted in patients.

5.3.5 Reports of Efficacy and Safety Studies

This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all

ongoing studies of the drug in proposed and non-proposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application.
Within this section, studies should be organized by design and, within controlled studies, by type of control. Within each section, studies should be further categorized, ordered by whether the study report is complete or abbreviated, with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.
Reports of studies whose primary objective is to establish efficacy or to accumulate safety data.
In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies.

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication:

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses),
- No-treatment control
- Dose-response (without placebo),
- Active control (without placebo), and
- External (historical) control, regardless of the control treatment.

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use should be included here.
It also includes the following: where a pharmacodynamic study contributes to evidence of efficacy, the placebo-controlled trials, whether early or late, controlled safety studies including studies in conditions that are not the subject of the application.

5.3.5.2 Study Reports of Uncontrolled Clinical Studies:

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies). This includes studies in conditions that are not the subject of the marketing application.

5.3.5.3 Reports of Analyses of Data from More Than One Study:

Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate

report. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect of variables such as dose, demographics, and concomitant medications. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the clinical summary.

5.3.5.4 Other Clinical Study Reports

This section can include:

- Reports of interim analyses of studies pertinent to the claimed indications,
- Reports of controlled safety studies not reported elsewhere,
- Reports of controlled or uncontrolled studies not related to the claimed indication,
- Published reports of clinical experience with the medicinal product those are not included in section 5.3.5.1. however, when literature is important to the demonstration or substantiation of efficacy, it should be included in 5.3.5.1,and
- Reports of ongoing studies.

5.3.6 Reports of Post-Marketing Experience:

If the drug has already been marketed, all relevant post-marketing data available to the applicant (published and unpublished, including periodic safety update reports, if available, and all significant safety observations) should be summarized. Details of the number of subjects estimated to have been exposed should be provided and categorized, as appropriate, by indication, dosage, route, treatment duration, and geographic location. The methodology used to estimate the number of subjects exposed should be described. If estimates of the demographic details are available from any source, these should be provided.
A tabulation of serious events reported after the drug is marketed should be provided, including nay potentially serious drug interactions.

5.3.7 Case Report Forms and Individual Patient Listings:

A Case Report Form (or CRF) is a paper or electronic questionnaire specifically used in clinical trial research. The Case Report Form is the tool used by the sponsor of the clinical trial to collect data from each participating site. All data on each patient participating in a clinical trial are held and/or documented in the CRF, including adverse events.
Such reports are generated for regulatory purposes and in addition to presenting the sponsor's analysis and interpretation of results, must provide, in considerable detail, a description of the trial (including the protocol) and all the data collected from the case record form and/or patient diaries. These data are represented in the form of 'patient listings'. The purpose of these is to

present faithfully the data obtained during the course of the trial so that, if necessary, the applicant's analyses and interpretations may be checked the regulator.

5.4 Literature References

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the clinical overview, and copies of important references cited in the clinical summary or in the individual technical reports that were provided in Module 5, section 5.3.

Comparison Table

Jordan	US	EU - ICH	
---	Pharmacological studies	M4 Pharmacology	Primary Pharmacodynamics
			Secondary Pharmacodynamics
			Safety Pharmacology
			Pharmacodynamic Drug Interactions
	Pharmacokinetic studies	M4 Pharmacokinetics	Analytical Methods and Validation Reports
	Absorption		Absorption
	Distribution		Distribution
	Metabolism		Metabolism
	Excretion		Excretion
			Pharmacokinetic Drug Interactions
			Other Pharmacokinetic Studies

		Toxicology	Acute toxicity	M4 Toxicology	Single-Dose Toxicity
			Sub-acute toxicity		Repeat-Dose Toxicity
			Chronic toxicity		Genotoxicity
			Carcinogenicity		Carcinogenicity
			Reproductive and Developmental Toxicity		Reproductive and Developmental Toxicity
			Condition of use toxicity		Local Tolerance
			Mode of administration toxicity		Other Toxicity Studies
Published literature				M4 Literature References	
Reports of Biopharmaceutic Studies	Bioavailability (BA) Study Reports	BA		M5 Reports of Biopharmaceutic Studies	Bioavailability (BA) Study Reports
	Comparative BA and Bioequivalence (BE) Study Reports	BE			Comparative BA and Bioequivalence (BE) Study Reports
	---				In vitro-In vivo Correlation Study Reports
	---				Reports of Bioanalytical and Analytical Methods for Human Studies

---			M5 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	Plasma Protein Binding Study Reports
				Reports of Hepatic Metabolism and Drug Interaction Studies
				Reports of Studies Using Other Human Biomaterials
Reports of Human Pharmacokinetic (PK) Studies			M5 Reports of Human Pharmacokinetic (PK) Studies	Healthy Subject PK and Initial Tolerability Study Reports
				Patient PK and Initial Tolerability Study Reports
				Intrinsic Factor PK Study Reports
				Extrinsic Factor PK Study Reports
				Population PK Study Reports
Reports of Human Pharmacodynamic (PD) Studies	Healthy Subject PD and PK/PD Study Reports	Pharmacology studies with comparison with data obtained from nonclinical studies	M5 Reports of Human Pharmacodynamic (PD) Studies	Healthy Subject PD and PK/PD Study Reports
	Patient PD and PK/PD Study Reports			Patient PD and PK/PD Study Reports

Reports of Efficacy and Safety Studies	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	Safety and efficacy studies	M5 Reports of Efficacy and Safety Studies	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
	---	Uncontrolled Clinical Studies		Study Reports of Uncontrolled Clinical Studies
	---			Reports of Analyses of Data from More Than One Study
	---			Other Clinical Study Reports
Reports of Post-Marketing Experience		Commercial marketing experience	M5 Reports of Post-Marketing Experience	
---		Case Report Forms	M5 Case Report Forms and Individual Patient Listings	
Literature References		Published and literature references	M5 Literature References	

Clinical Trial Example

Study Name	Biological therapy in treating stage IV breast cancer
Study status	This study is ongoing, but not recruiting participants
Official Title	Treatment of Stage IV Breast Cancer With OKT3 x Herceptin Armed Activated T Cells, Low Dose IL-2, And GM-CSF (Phase I/II)
Study no.	NCT00027807
Estimated 1ry completion date	August 2011
Current Primary Outcome Measures	• Maximum tolerated dose [Designated as safety issue: Yes] • Toxicity profile [Designated as safety issue: Yes] • Clinical responses [Designated as safety issue: No] • Overall survival and progression-free survival [Designated as safety issue: No]
Current Secondary Outcome Measures	Immune changes [Designated as safety issue: No]
Brief Summary	RATIONALE: Biological therapies use different ways to stimulate the immune system and stop cancer cells from growing. Combining different types of biological therapies may kill more tumor cells. PURPOSE: Phase I/II trial to study the effectiveness of combining different biological therapies in treating women who have stage IV breast cancer.
Study Phase	Phase I/ II
Study type	Interventional
Intervention	• Biological: aldesleukin • Biological: sargramostim • Biological: therapeutic autologous lymphocytes.

Reference: Clinicaltrials.gov

Important perspective in Biopharmaceuticals

- **Biosimilars**

Biosimilars which are the generic version of Biologics also called as follow-up biologics.

In a more specific way Biosimilars defined as a new biological medicinal product claimed to be similar (Similar Biological Medicinal Product) in terms of Quality, Safety and Efficacy to an original, reference medicinal product, which has been granted a marketing authorization in the Community

The concept of Biosimilars arose from the following concepts:

- Biologics have high molecular complexity
- Biologics are sensitive to manufacturing process changes
- Follow-up manufacturer does not have access to the originator manufacturing process
- Undetectable differences in impurities and/or breakdown products have serious health implications
- Complexity of the production process which may induce unwanted immune response if changes than the originator
- Difficulties to analyze/ characterize all quality attributing to the safety and efficacy profile.

World-wild, separate guidelines were issued and implemented for the Biosimilars, where in our concerned regions the below is applicable in each:

Jordan; no specific guidelines adapted yet, still a draft being studied by relevant committee. Meanwhile the submission of Biosimilars products is treated as a new product application with all additional needed documents studies.

USA;

The FDA announced in 2001 that it was working on guidelines for pharmaceutical companies to produce generic versions of synthetic insulin and human growth hormone. Although the Agency had promised that the guidelines were forthcoming, the FDA announced in April 2006 that it would not be releasing the guidelines as anticipated,

instead it intended to publish broader guidelines that applied to ALL generic versions of protein-based drugs, also known as follow-on protein products, and therefore the FDA would not be outlining specific guidelines for insulin or human growth hormone. In August 2006, four state governors, looking to ease drug costs under state programs, petitioned the FDA to provide guidelines for generic versions of insulin and human growth hormone. In their petition, the governors joined other critics in accusing the Agency of dragging its feet

In the United States the FDA has taken the position that new legislation will be required to address these concerns. Additional Congressional hearings have been held, but no legislation had been approved as of June 2008. A lack of FDA manufacturing guidelines for generic versions of synthetic insulin and human growth hormone presents problems for generics manufacturers

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act (PPAC Act). The PPAC Act contains a subtitle called the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) that amends the Public Health Service Act (PHS Act) and other statutes to create an abbreviated approval pathway for biological products shown to be Biosimilars to, or interchangeable with, an FDA licensed reference biological product.

EU version

In the European Union, a biological medicinal product is one the active substance(s) produced from or extracted from a biological (living) system, and requires, in addition to physico-chemical testing, biological testing for full characterization. The characterization of a biological medicinal product is a combination of testing the active substance and the final medicinal product together with the production process and its control.

In the European Union a specially-adapted approval procedure has been authorized for certain protein drugs, termed "similar biological medicinal products". This procedure is based on a thorough demonstration of "comparability" of the "similar" product to an existing approved product.

The following below list of guidance covers almost all aspects for Biosimilars manufacturing, registration and/or marketing:

Overarching Biosimilars guidelines

Topic	Reference number
Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues	CHMP/42832/05
Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues	CHMP/49348/05
Similar Biological Medicinal Product	CHMP/437/04

Product specific Biosimilars guidelines

Topic	Reference number
Similar biological medicinal products containing recombinant follicle stimulation hormone	EMA/CHMP/BMWP/94899/2010
Similar biological medicinal product containing recombinant interferon beta	CHMP/BMWP/86572/10
Similar biological medicinal products containing monoclonal antibodies	CHMP/BMWP/632613/09
Similar biological medicinal products containing recombinant Erythropoietins	EMEA/CHMP/BMWP/301636/08
Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Recombinant Erythropoietins Erythropoietins (Superseded by EMEA/CHMP/BMWP/301636/08)	CHMP/94526/05
Similar biological medicinal products containing low-molecular-weight-heparins	CHMP/BMWP/118264/07
Non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha	CHMP/BMWP/102046/06
Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as	CHMP/31329/05

Topic	Reference number
Active Substance: Non-Clinical and Clinical Issues - Guidance on Biosimilar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor	
Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Somatropin	CHMP/94528/05
Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Recombinant Human Insulin	CHMP/32775/05

Other guidelines relevant for Biosimilars

Topic	Reference number
Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use	EMEA/CHMP/114720/2009
Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process - Non-Clinical and Clinical Issues	CHMP/BMWP/101695/06
Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins	CHMP/BMWP/14327/06
Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substance - Quality Issues (Superseded by ICH Q5E - CPMP/ICH/5721/03)	CPMP/BWP/3207/00 Rev. 1, CPMP/ICH/5721/03
Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues (Superseded by CHMP/BMWP/101695/06)	CPMP/3097/02
Development of a CPMP Guideline on Comparability of Biotechnology-derived Products	CPMP/BWP/1113/98

Biopharmaceuticals; current status and future prospects

Approximately one in every four new drugs now coming on the market is a biopharmaceutical.
By mid 2006, some 160 biopharmaceutical products had gained marketing approval in the USA and/or EU. Collectively, these represent a global biopharmaceutical market in the region of US$35 billion, and the market value is estimated to surpass US$50 billion by 2010.

Many of the initial biopharmaceuticals approved were simple replacement proteins (e.g. blood factors and human insulin). The ability to alter the amino acid sequence of a protein logically coupled to an increased understanding of the relationship between protein structure and function has facilitated the more recent introduction of several engineered therapeutic proteins. Thus far, the vast majority of approved recombinant proteins have been produced in the bacterium *E. coli*, the yeast *S. cerevisiae* or in animal cell lines (most notably Chinese hamster ovary (CHO) cells or baby hamster kidney (BHK) cells.

At least 1000 potential biopharmaceuticals are currently being evaluated in clinical trials, although the majority of these are in early stage trials. Vaccines and monoclonal antibody-based products represent the two biggest product categories. Regulatory factors (e.g. hormones and cytokines) and gene therapy and antisense-based products also represent significant groupings.

Although most protein-based products likely to gain marketing approval over the next 2–3 years will be produced in engineered *E. coli*, *S. cerevisiae* or animal cell lines, some products now in clinical trials are being produced in the milk of transgenic animals. Additionally, plant-based transgenic expression systems may potentially come to the fore, particularly for the production of oral vaccine.

Interestingly, the first generic biopharmaceuticals are already entering the market. Patent protection for many first-generation biopharmaceuticals (including recombinant human GH (rhGH), insulin, EPO, interferon-α (IFN-α) and granulocyte-CSF (G-CSF)) has now/is now coming to an end. Most of these drugs command an overall annual market value in excess of US$1 billion, rendering them attractive potential products for many biotechnology/pharmaceutical companies. Companies already/soon producing generic biopharmaceuticals include Biopartners (Switzerland), Genemedix (UK), Sicor and Ivax (USA), Congene and Microbix (Canada) and BioGenerix (Germany). Genemedix, for example, secured approval for sale of a recombinant CSF in China in

2001 and is also commencing the manufacture of recombinant EPO. Sicor currently markets hGH and IFN-αin Eastern Europe and various developing nations. A generic hGH also gained approval in both Europe and the USA in 2006.

To mid 2006, no gene-therapy-based product has thus far been approved for general medical use in the EU or USA, although one such product ('Gendicine') has been approved in China. Although gene therapy trials were initiated as far back as 1989, the results have been disappointing. Many technical difficulties remain in relation to, for example, gene delivery and regulation of expression. Product effectiveness was not apparent in the majority of trials undertaken and safety concerns have been raised in several trials.

Only one antisense-based product has been approved to 2006 (in 1998) and, although several such antisense agents continue to be clinically evaluated, it is unlikely that a large number of such products will be approved over the next 3–4 years. Aptamers represent an additional emerging class of nucleic-acid-based therapeutic. These are short DNA- or RNA-based sequences that adopt a specific three-dimensional structure, enabling them to bind (and thereby inhibit) specific target molecules. RNA interference (RNAi) represents a yet additional mechanism of achieving downregulation of gene expression .It shares many characteristics with antisense technology and, like antisense, provides a potential means of treating medical conditions triggered or exacerbated by the inappropriate overexpression of specific gene products. Despite the disappointing results thus far generated by nucleic-acid-based products, future technical advances will almost certainly ensure the approval of gene therapy and antisense-based products in the intermediate to longer term future.

Technological developments in areas such as genomics, proteomics and high-throughput screening are also beginning to impact significantly upon the early stages of drug development. By linking changes in gene/protein expression to various disease states, for example, these technologies will identify new drug targets for such diseases. Many/most such targets will themselves be proteins, and drugs will be designed/ developed specifically to interact with. They may be protein based or (more often) low molecular mass ligands.

Additional future innovations likely to impact upon pharmaceutical biotechnology include the development of alternative product production systems, alternative methods of delivery and the development of engineered cell-based therapies, particularly stem cell therapy. As mentioned previously, protein-based biotechnology products produced to date are produced in either microbial or in animal cell lines. Work

continues on the production of such products in transgenic-based production systems, specifically either transgenic plants or animals.

Virtually all therapeutic proteins must enter the blood in order to promote a therapeutic effect. Such products must usually be administered parenterally. However, research continues on the development of non-parenteral routes which may prove more convenient, less costly and obtain improved patient compliance. Alternative potential delivery routes include transdermal, nasal, oral and bucal approaches, although most progress to date has been recorded with pulmonary-based delivery systems. An inhaled insulin product (Exubera) was approved in 2006 for the treatment of type I and II diabetes.

A small number of whole-cell-based therapeutic products have also been approved until 2006. All contain mature, fully differentiated cells extracted from a native biological source. Improved techniques now allow the harvest of embryonic and, indeed, adult stem cells, bringing the development of stem-cell-based drugs one step closer. However, the use of stem cells to replace human cells or even entire tissues/organs remains a long term goal. Overall, therefore, products of pharmaceutical biotechnology play an important role in the clinic and are likely to assume an even greater relative importance in the future.

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