Regulatory Process of Biotechnological Products

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KFDA

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Biotechnology Drugs
(Biopharmaceuticals)

- Recombinant proteins
- Monoclonal antibodies
- (Nucleic acid products)

The Regulation of Biotechnology Pharmaceuticals

- U S A
- EUROPE
- JAPAN
- KOREA

National Control Authority

and

National Control Laboratory

Requirements for an Effective National Control Authority

- **Legislative basis with enforcement provisions**
- **Authority to establish standards and grant licenses or approvals**
- **Authority to revoke licenses or withdraw approvals**
- **Authority to inspect**
- **Authority to conduct post-approval monitoring**

WHO Technical Report Series 822, 1992

Responsibilities of the National Control Laboratory

- Advice to the NCA on technical matters
- Evaluation of manufacturer's procedures, SOP's validation experiments and batch protocols
- Pre-licensing control testing
- Evaluation of stability protocols and data
- Review quality defect reports
- Establish national reference materials
- Develop effective internal control measures

Responsibilities of the NCA/NCL Post-Approval

- **Release of production lots (batches)**
  - Review and testing
- **Inspection of manufacturing facility**
- **Monitoring system for adverse event reports**
- **Lot recall and license revocation systems**
- **Approval of manufacturing changes**
- **Approval of new uses/indications**

	NCA	NCL
USA	FDA (CDER, CBER)	FDA
Europe	EMEA	OMCL
Japan	MHW	NIHS, NIID
Korea	KFDA	KFDA

What is a 'Biologicals'?

- **Derived from genetic expression in a living organism**
- **Frequently have complex molecular structure**
- **Most importantly, they require special quality control consideration because :**

I) Biological nature of starting materials

II) Biological basis of manufacturing process

III) Biological test methods needed to characterize batches of the product to ensure the level of purity and potency

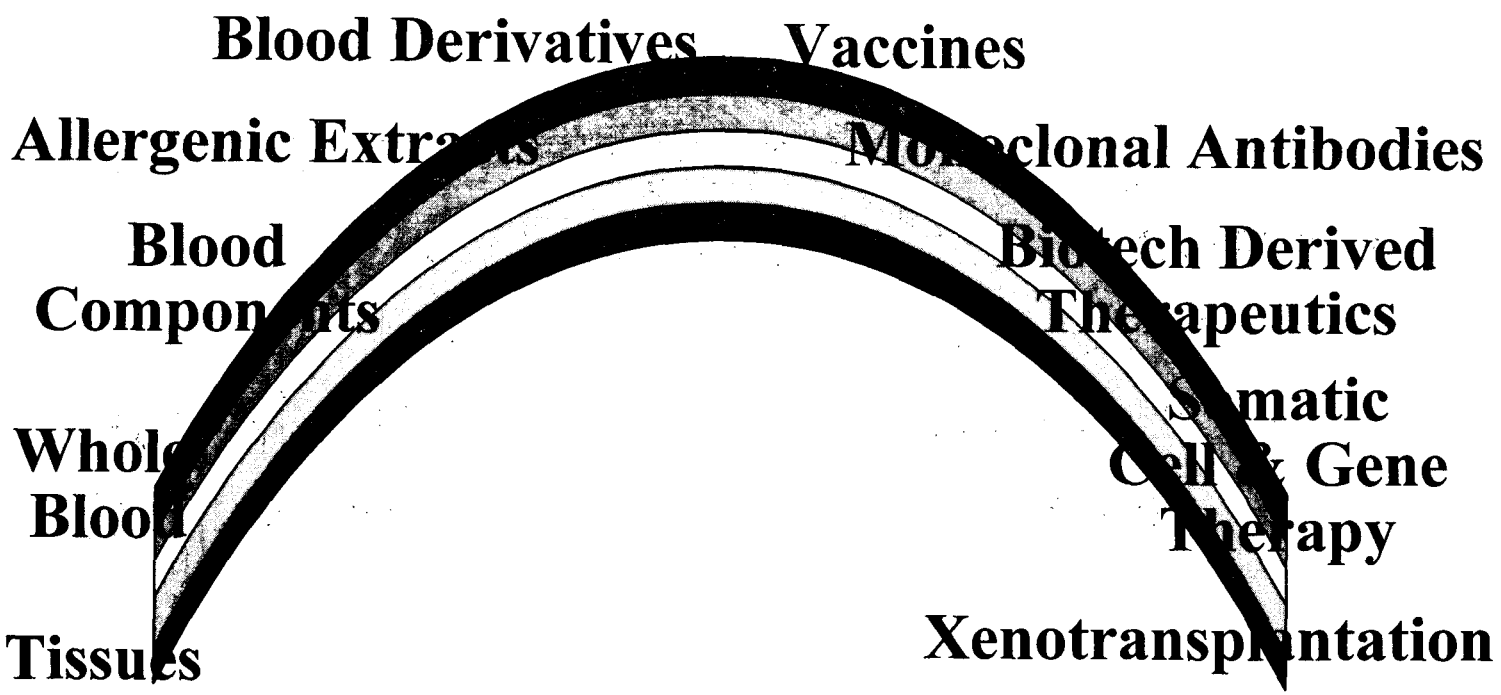
Conventional Drug	Biologics
Synthetic, organic compounds	Protein- or carbohydrate-based product Extracted from living Organism Complex physicochemical structure
Defined structure, physical & chemical characteristics	Less well-defined
Chemical Synthesis micromolecule	Macromolecule(>500kd) Tertiary structure Location, extent and type of glycosylation
Stable	Heat- and shear-sensitive

US Definition

‘ Biological Product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries in man’. (21CFR600.3)

U.S.A

BIOLOGICAL PRODUCTS REGULATED BY CBER



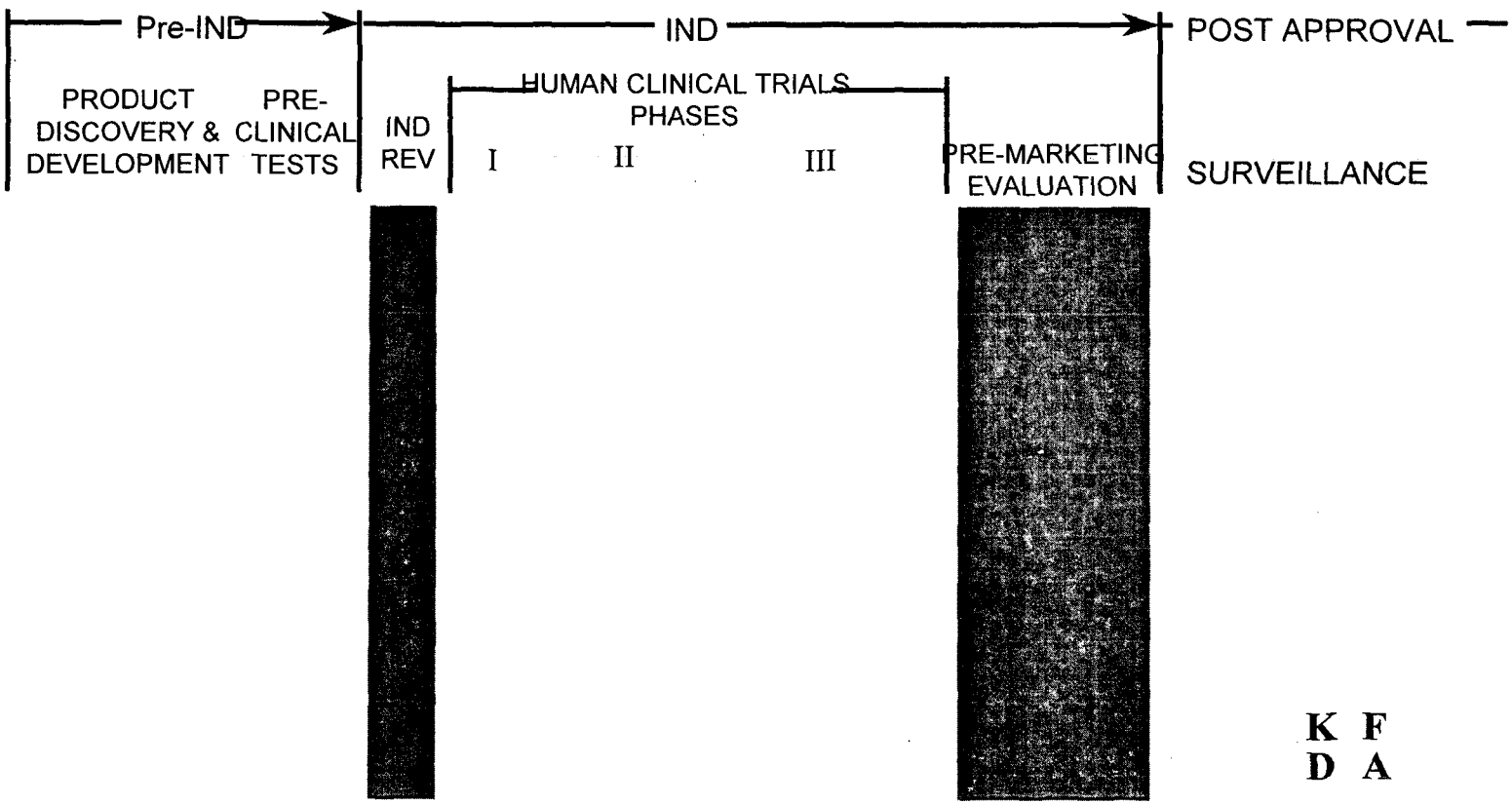
생물의약품의 개발과정

Ave $ 2억 ~ 3.5 억
12년의 기간

① 치료제개발 대상질환 선정 및 연구 **(Therapeutic Target)**
② 시험생산 **(Pilot-Scale Manufacturing)**
③ 전임상시험 **(Preclinical Study)**
④ 임상평가 **(Clinical Evaluation)**
Phase I : Safety
Phase II : Efficacy
Phase III
⑤ 허가과정 **(Marketing Approval)**
CBER : BLA, PLA/ELA
CDER : NDA
⑥ 승인후 감시 **(Post-Approval Monitoring : Phase IV)**

U.S.A

Drug Development Process



K F
D A

U.S.A

Specified Biotechnology Products

Final Rule : *14 May 1996* (61FR 24227)

1. Therapeutic DNA plasmid product:gene therapy product

2. Therapeutic synthetic peptide products of 40 or fewer amino acids : PTH

3. Monoclonal antibody products for *in vivo* use : Daclizumab
Herceptin

4. Therapeutic recombinant DNA- derived products : insulin, somatropin, interferon, EPO, G-CSF

U.S.A

IND

(The Investigational New Drug Application)
임상시험을 실시하기 위한 허가

1 . **Protocol**

2 . **Chemistry, Manufacturing and Control Data**

a) Drug Substance

b) Drug Product

3 . **Pharmacology and Toxicology Data**

U.S.A

BLA , PLA / ELA

1. CMC Section
   - A. Chemistry, Manufacturing and Control Information
   - B. Sample
   - C. Methods Validation Package
2. Nonclinical Pharmacology and toxicology Section
3. Human Pharmacokinetic and Bioavailability Section
4. Clinical Data
5. Manufacturing facility information U.S.A

Approved Biotech Products in U.S.A.

CBER

물질명	제품명	개발회사	적응증	승인년도
Aldesleukin	Proleukin	Chiron	metastatic renal cell carcinoma	5/5/92 PLA 1/9/98 BLS
Alteplase	Activase	Genetech	acute ischemic stroke	6/18/96 PLS
Antihemophilic Factor/ Von Willebrand Factor Complex (Human)	Humate-P	Centeon Pharama Gmbh	hemophilia A, von Willebrend disease	4/1/99 PLA
Autologous Cultured Chondrocytes	Carticel SM Service	Genzyme Tissue Repair	acute or repetitive trauma	8/22/97 BLA
Basiliximab	Simulect	Novartis	Prophylaxis of acute organ rejection	5/12/98 BLA
Becaplermin	Regranex	OMJ	diabetic neuropathic ulcers	12/16/97 BLA
Coagulation Factor VIIa (Recombinant)	NovoSeven	Novo Nordisk	hemophilia A or B	3/25/99 BLA
Coagulation Factor IX (Recombinant)	Benefix	Genetics	control and prevention of hemorrhagic episodes in patients with hemophilia B	2/11/97 BLA
Daclizumab	Zenapax	Roche	immunosuppressive regimen	12/10/97 BLA
Denileukin diftitox	Ontak	Seragen	cutaneous T-cell lymphoma	2/5/99 BLA
Etanercept	Enbrel	Immunex	rheumatoid arthritis	11/2/98 BLA 5/27/99 BLS
Filgrastim	Neupogen	Amgen	febrile neupenia, non-meyloid malignancy	2/20/91 PLA 4/2/98 BLAS
Infliximab	Remicade	Centocor	Crohn's disease for the reduction in the number of draining enterocutaneous	8/24/98 BLA

물질명	제품명	개발회사	적응증	승인년도
Interferon α-n1	Wellferon	Wellcome Research Lab	chronic hepatitis C	3/25/99 BLA
Interferon α-2a	Roferon-A	Hoffmann-La Roche	〃	11/1/96 PLS
Interferon α-2b	Intron A	Schering	follicular lymphoma	11/6/97 PLS
Interferon alfacon -1	Infergen	Amgen	chronic hepatitis C	10/6/97 BLA
Interferon β-1a	Avonex	Biogen	relapsing forms of multiple sclerosis	5/17/96 BLA
Oprelvekin	Neumega	Genetics	prevention of thrombocytopenia, nonmeyloid malignancies	11/25/97 BLA
Palivizumab	Synagis	Med Immune	respiratory tract disease, RSV disease	6/19/98 BLA
Pegaspargase	Oncaspar	Enzon	acute lymphoblastic leukemia	2/1/94 PLA
Reteplase	Retavase	BM	acute myocardial infarction	10/30/96 BLA
Rituximab	Rituxan	Genetech	B-cell non-Hodgkin's lymphoma	11/26/97 BLA
Sargramostim	Leukine, Prokine	Immunex		11/7/96 PLS
Trastuzumab	Herceptin	Genetech	metastatic breast cancer	9/25/98 BLA

Approved Biotech Products in U.S.A.

CDER

물질명	제품명	제조회사	적응증	승인연도
Glucagon Hydrochloride	Glucagen	Novo Nordisk	Hyperglycemic Hormone	6/22/98
Insulin Biosynthetic	Humulin R	Lilly	control diabetes	4/31/94
Insulin Lispro	Humalog	〃	〃	6/14/96
Insulin Lispro	Humalog Pen	〃	〃	8/6/98
Somatropin, Biosynthetic	Bio-tropin	Bio Tech Gen	Growth Hormone	5/25/95
〃	Nutropin	Genetech	〃	11/17/93
〃	Nutropin AQ	〃	〃	12/29/95
〃	Humatrope	Lilly	〃	5/8/87
〃	Norditropin	Novo Nordisk	〃	5/8/95
〃	Genotropin Preservative free	Pharmacia and Upjohn	〃	8/24/95
〃	Genotropin	〃	〃	10/23/96
〃	Serostim	Serono	〃	7/25/97
〃	Saizen	〃	〃	10/8/96

EMEA

- Created 1993; operational, 1995
- Two Committees: CPMP, CVMP
- Supervise safe and effective use of medicinal products in the EU
- Co-ordinate GMP, GLP, GCP, inspections

Biodrugs (EC definition)

- **Provisions of Directive 87/22**
  - **Recombinant DNA**
  - **Monoclonal antibodies**
  - **cell culture**

- **Require obligatory referral to CPMP**

Europe

The Centralised Licensing Procedure

STEP 1: application. EMEA driven

Pre-application	**4 mths**
Application and validation	**14ds**

STEP 2: assessement. CPMP driven

File review; assessment report	
Consolidated list of questions	**210 ds +**
(CLOCK STOPS : applicant's answers)	**(< 90 ds)**
Scientific OPINION	

STEP 3: Decision making process. European commission driven

Transfer by EMEA to Commission	30 ds
Draft Commission decision	30 ds
Standing Committee advice	30 ds

⇩

(NO Qualified majority: 90 ds procedure Council of Ministers)

Qualified majority: Decision adopted and published in O. J.

Registration dossier

- Part I

  administrative data

  summary of product characteristics (SPC)

  packaging, leaflet

  Expert reports

- Part II

  Technical, biological pharmaceutical data

- Part III

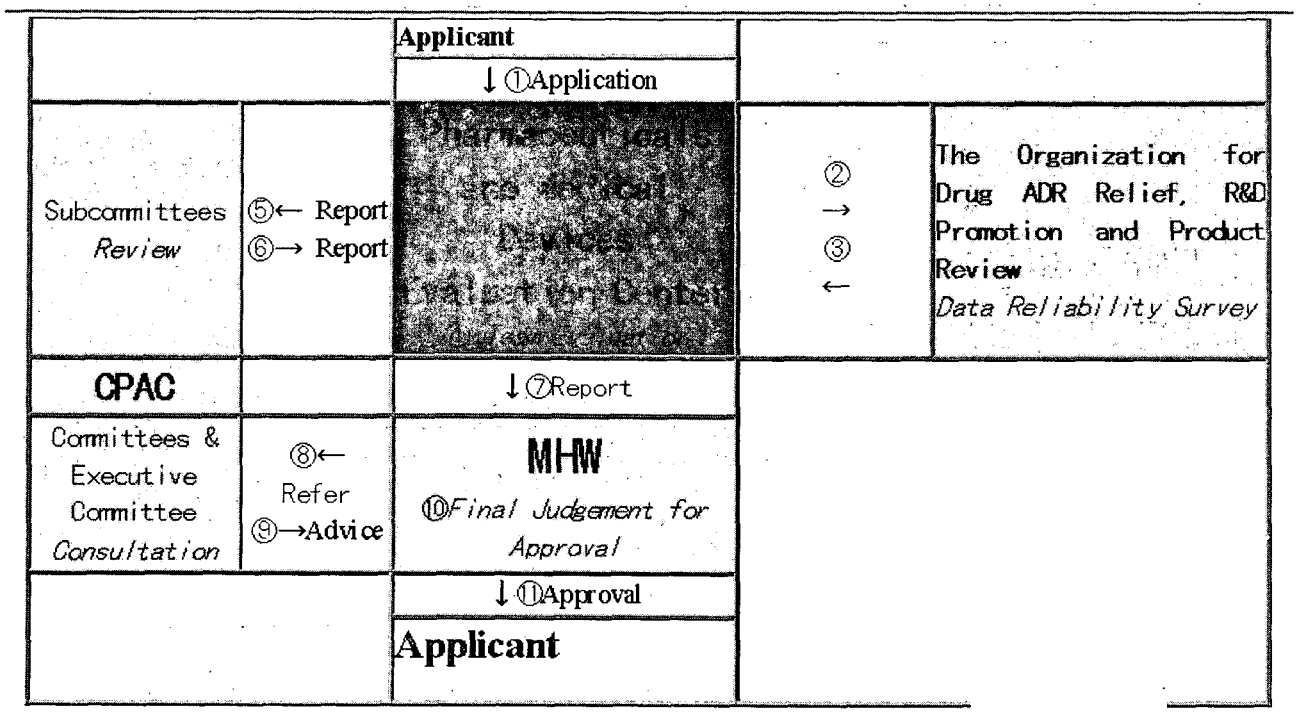
  Toxicopharmalogical data

- Part IV

  Clinical data, Pharmacovigilance

identical in the 15 EU countries

Evaluation Process of a New Drug

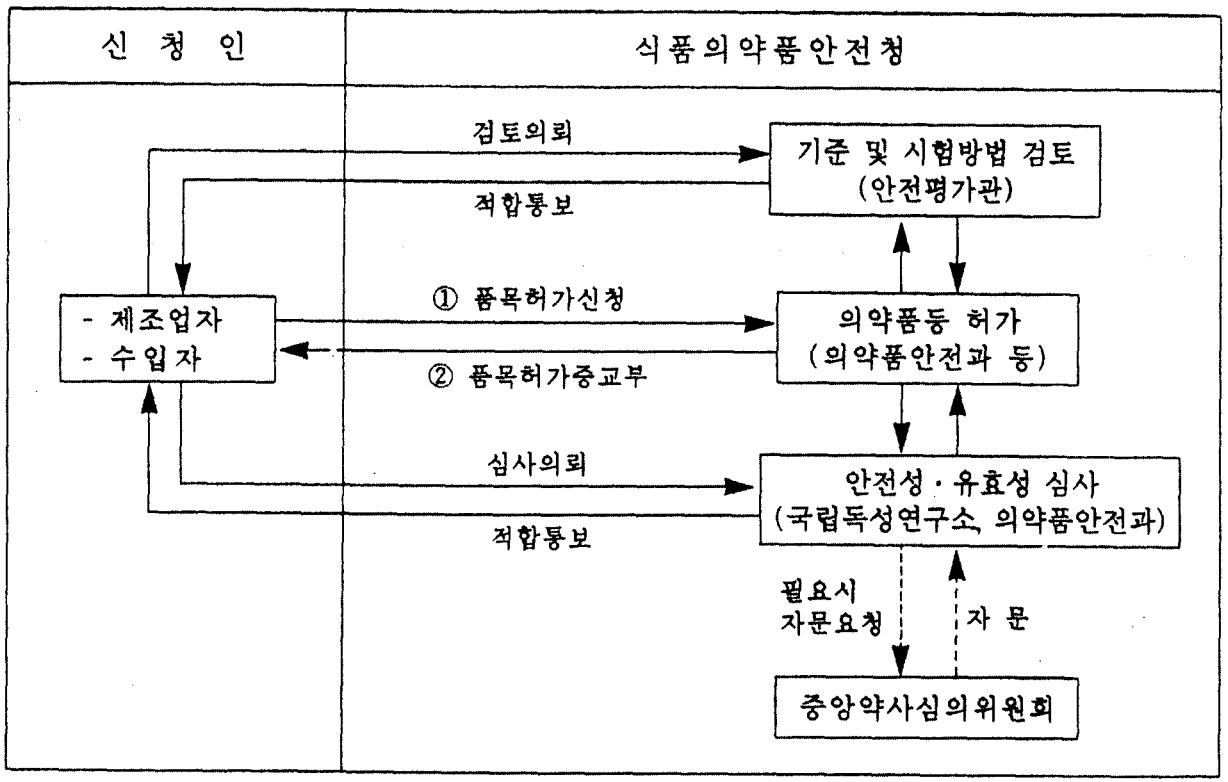


CPAC : Central Pharmaceutical Affairs Council

MHW : Ministry of Health and Welfare

Japan

의약품등의 제조(수입)품목 허가절차



Korea

재조합의약품의 제조(수입) 신청시 첨부자료

1. 기원 또는 발견의 경위 및 외국에서의 사용 현황

2. 물리적 화학적 성질과 규격 및 시험방법

가. 제조방법

(1) 목적 펩타이드 또는 단백질의 구조유전자
(2) 숙주 벡타계
(3) 배양
(4) 정제

나. 구조 결정 및 물리적 화학적 성질

(1) 구조조성
가. 아미노산 조성
나. 말단 아미노산
다. 디설파이드 결합이 있는 경우에는 그 위치
라. 펩타이드 분석
마. 아미노산 배열

(2) 물리화학적 성질
가. 분광학적 성질
나. 전기영동적 성질
다. 등전점
라. 분자량
마. 액체크로마토그라피 패턴
바. 고차구조
(3) 면역화학적 성질
(4) 생물학적 성질
가. 생물학적 활성
나. 효소의 경우에 효소화학적 성질

다. 기준 및 시험방법
(1) 완제품의 규격
(2) 원료의 규격

3. 안정성
4. 독성
5. 약리작용
6. 흡수•분포• 대사• 배설
7. 임상시험
8. 국내 유사제품과의 비교검토

Approved Biotech Products in Korea

- Hep B Virus Vaccine
- IFN- α and IFN- γ
- Insulin
- Growth Hormone
- Erythropoietin
- G-CSF, GM-CSF
- FSH
- EGF
- IL-2

Approved Biotech Products in Korea

KFDA

물 질 명	제 품 명	허 가 회 사	적 응 증	HOST	비 고
인터루킨-2	프로루킨	(주)카이론	항암제, 초기에이즈치료		허가
혈액응고인자VIIa	노보세븐주	노보노디스크	헤모필리아A,B		//
인터루킨-2 수용체단클론항체(다클리주마부)	제나팍스주	한국로슈	신장이식후 장기 거부반응 예방		//
인터루킨-2 수용체단클론항체(바시리지맵)	시뮬렉트주사	한국노바티스	신장이식후 장기 거부반응 예방		//
CD20단클론항체 (리툭시맙)	맙테라주	한국로슈	B-cell non-Hodgkin's Lymphoma		//
혈소판당단배 II b/IIIa 수용체 단클론항체 (압시시맙)	리오프로주	한국릴리	경피적 관동맥 혈관확장수술중 환자의 허혈성 심합병증 예방		//

ICH

Have common requirements

quality, safety, efficacy of new medicines accepted wherever in the world

The ICH Topics

Scope : harmonization of requirements

Q : Quality (technical)
S : Safety (toxicology)
E : Efficacy (clinical)

These three criteria are those considered by Regulatory Authorities for granting a Marketing Authorization to a new medicinal product

STANDARDS FOR LICENSURE

- **Safe**
- **Pure**
- **Potent**
- **Effective**
- **Consistent**

- Characterization of Products
- Manufacturing Process
- Stability
- Preclinical Testing
- Clinical Trials
- Specification & Testing Methods

PRODUCTION PROCESSES FOR BIOTECHNOLOGY DERIVED PRODUCTS

- Cloning/preparation of seed stock
  - Prokaryotes
  - Eukaryotes
  - Hybridomas
- Fermentation
- Conversion, if necessary, from primary to final product
- Purification
- Formulation

ISSUES OF CONCERN FOR BIOTECH PRODUCTS

- **Product Characterization**
- **Manufacturing Process**
- **Specification**

PRODUCT CHARACTERIZATION

- **Structure and Composition of Products**
- **Physico-chemical Properties**
- **Immunological tests**
- **Biological tests**

Structure & Composition of Products

- Amino Acid Composition Analysis
- Partial Sequence Analysis
- Peptide Mapping
- Position of Disulfide Linkage

Physicochemical Properties

- PAGE and IEF
- Circular Dichroism and ORD
- Molecular Weight

Immunological Tests

- **Ab used in the Tests for Identity & Purity**
- **RIA, ELISA, Immunoelectrophoresis or Western blot**
- **Analysis of the Structure of the Carbohydrate Moiety**

Biological Tests for Identity & Potency

- **Bioassays**
  - ***in vivo* Bioassays**
  - ***in vitro* Bioassays**

QUALITY TOPICS, Biotechnology products.

Q5A: Viral safety evaluation

Q5B: Genetic stability

Q5C: Stability testing

Q5D: Cell substrates

Q6B: Specifications, biotech. products

ICH Biotech. Topics. (1)

Q5A: Viral safety

Scope

Biotech./biologicals derived from characterized cell banks of human or animal origin; r-DNA products concerned; classical vaccines excluded.

Highlights:

Potential contamination (master Cell Bank, adventitious)
Cell line testing, virus (MCB, WCB, cells, age limit, retroviruses, antibody, in vivo, in vitro)
Bulk testing, viral clearance procedures (choice of viruses, design, inactivation, removal,...)

ICH Biotech. Topics. (2)

Q5B: Genetic stability

Scope: **Characterisation of expression constructs for the production of r-DNA protein productions in eukaryotic / prokaryotic cells.**

Highlights :

Rationale for analysis of expression construct.
Characterisation of expression system, MCB, WCB.
Limit for cell age production

Aim: Consistent production through analysis of DNA and purified protein.

ICH Biotech. Topics. (4)

Q5D: Cell substrates

Scope: **Standards for animal / human cell lines, primary cells, microbes, used to prepare biotech. / biologicals.**

Highlights:

Source, history, generation of cells.

Cell banking.

Characterization of cell banks: identity, purity, stability.

Primary cell substrates.

Specification

- **A list of tests**
- **References to Analytical Procedures**
- **Acceptance Criteria**

⇒ **One part of a total control strategy designed to ensure product quality and consistency**

- Characterization
- GMP
- Validated Manufacturing Process
- Raw Material Testing
- In-Process Testing
- Stability Testing

Justification of the Specification

- Linked to a manufacturing process
- Account for the stability of drug substance and drug product
- Linked to preclinical and clinical studies
- Linked to analytical procedures

Drug Substance Specification

- Appearance and description
- Identity
- Purity and impurities
  - Process-related impurities
    - Cell culture media
    - Host cell proteins, DNA
    - Monoclonal Ab or Chromatographic media
    - Solvent
  - Product-related impurities
    - Molecular variant
- Potency
- Quantity

Drug Product Specification

- Appearance and description
- Identity
- Purity and Impurities
- Potency
- Quantity
- General Tests
- Additional Testing for Unique Dosage Forms

HOW TO GET INFORMATION

- CBER http://www.fda.gov/cber/
- EMEA http://www.eudra.org
- MHW http://www.mhw.go.jp
- KFDA http://www.kfda.go.kr
- ICH http://www.ich.org