

Regulation of Biological and
Biotechnology Derived Medicinal
Products in the European Union
Past, Present & Future

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Economic and Legislative Background for Biological Medicinal Products in the European Union Today

Biopharmaceuticals Europe (2000)

(Source Ernst &Young 's Eighth Annual European Life Sciences Report 200)

	Europe	USA
Turnover (€million)	8,679	23,750
R&D Expenditure (€million)	4,977	11,400
Net loss (€million)	1,570	5,964
Number of Companies	1,570	1,273
Number of Employees	61,104	162,000

EU Biotechnology Expenditure – the gap is closing

- US still remains three times higher overall than total EU revenue
- Biotechnology company revenues increased 38% between 1999 and 2000 in EU but only 10% in US
- R&D expenditure grew by 48% in the EU and only 1% in the US in the same time period
- A positive trend in the EU but the gap is still there and may be explained by significant differences in economic, legislative and regulatory environment

EU/US Comparison between Economic and Legislative Environments

- European Union
 - Basic patent 20yrs
 - Supplementary protection max 5 yrs (1992)
 - Biotech Patent Directive (1998) only implemented in 6 MS
 - Lower level of intellectual property protection in some MS
 - European research framework programme
 - Economic environment
 - No direct access
 - Price control
 - Free movement of goods
 - Limited incentives to scientific and technological innovation
- United States
 - Basic patent 20years
 - Patent term –Restoration max 5 years (1984)
 - Biotech Patent Act for 30 years(1983)
 - Same level of intellectual property protection across states
 - Bayh-Dole Act and National institutes of Health
 - Economic Environment
 - Direct access to large unified market
 - Competitive market pricing
 - Financial and fiscal incentives for scientific and technological innovation (credits, capital incentives, company aids etc)

Comparison Between the EU & US Healthcare Environments

European Union

- National health services dependent upon the restrictive requirements of public budgets
- No difference between the payer/buyer and regulator of health service
- Rigid economic environment marked by fragmented legislation and policies (lack of a single EU market)
- Orphan drug regulation (2000) is embryonic

United States

- A less regulated health system than EU and no purchasing monopoly
- Difference between payer and supplier of healthcare services
- Scientific and economic system which is flexible and ready for changes
- Orphan drugs Act (1984) is well established

Overview of Key EU Legislative and Regulatory Developments Affecting Biological Medicinal Products in the 30 year Period between 1965 and 1995

A Brief History of Pharmaceutical Legislation Affecting Biological Medicinal Products in the EU 1965-1995

- Dir 65/65 EEC - Framework Directive designed to provide a high safeguard of public health post-thalidomide
- Dir 75/318 EEC – Establishing the laws in Member States relating to analytical, pharmacotoxicological and clinical standards (quality, safety and efficacy) and outlining contents required in the registration dossier
- Dir 75/319 EEC – Established the CPMP (to determine whether products complied with 65/65 EEC) and introduced the concept of mutual recognition

A Brief History of Pharmaceutical Legislation in the EU 1965-1995

- Dir 87/22 EEC Establishes the national measures required relating to the approval of high technology medicinal products particularly those derived from biotechnology. First definition of a high technology medicinal product and scientific review by the CPMP
- Dir 89/342 EEC – extends the scope of Directives 65/65EEC & 75/319 EEC to include additional provisions for immunological medicinal products such as vaccines, toxins, serums or allergens
- Dir 89/381 EEC –extended the scope of directives 65/65 EEC and 75/319 EEC to include additional products derived from human blood or human plasma

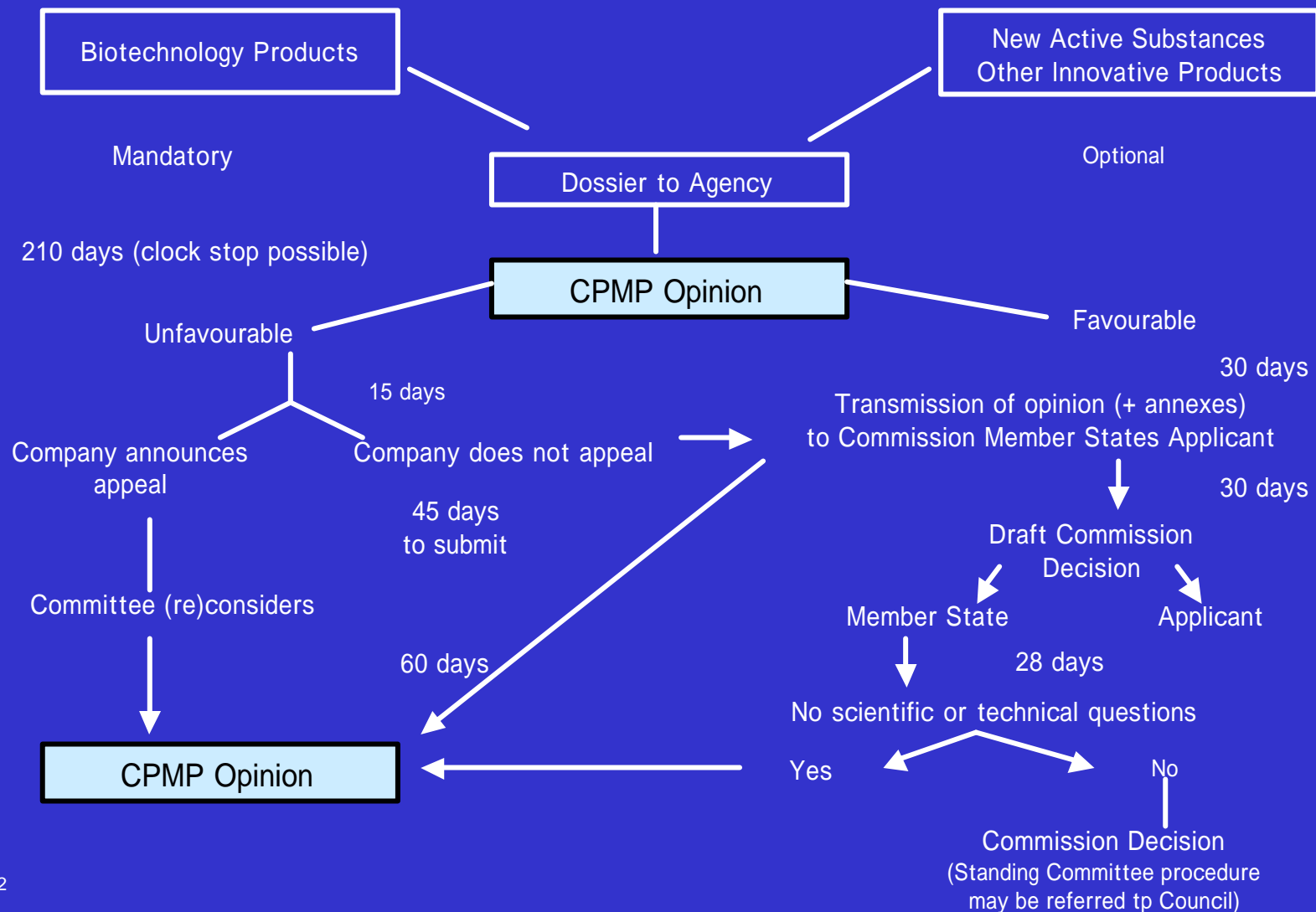
A Brief History of Pharmaceutical Legislation Affecting Biological Medicinal Products in the EU 1965-1995

- Dir 91/356 EEC – lays down the principles and of GMP for medicinal products for human use
- Council Regulation EEC 2309/93 – Creation of the European Agency for the Evaluation of Medicinal Products (EMA) & unification of regulatory processes

1995 New Procedures for the Approval of Medicinal Products

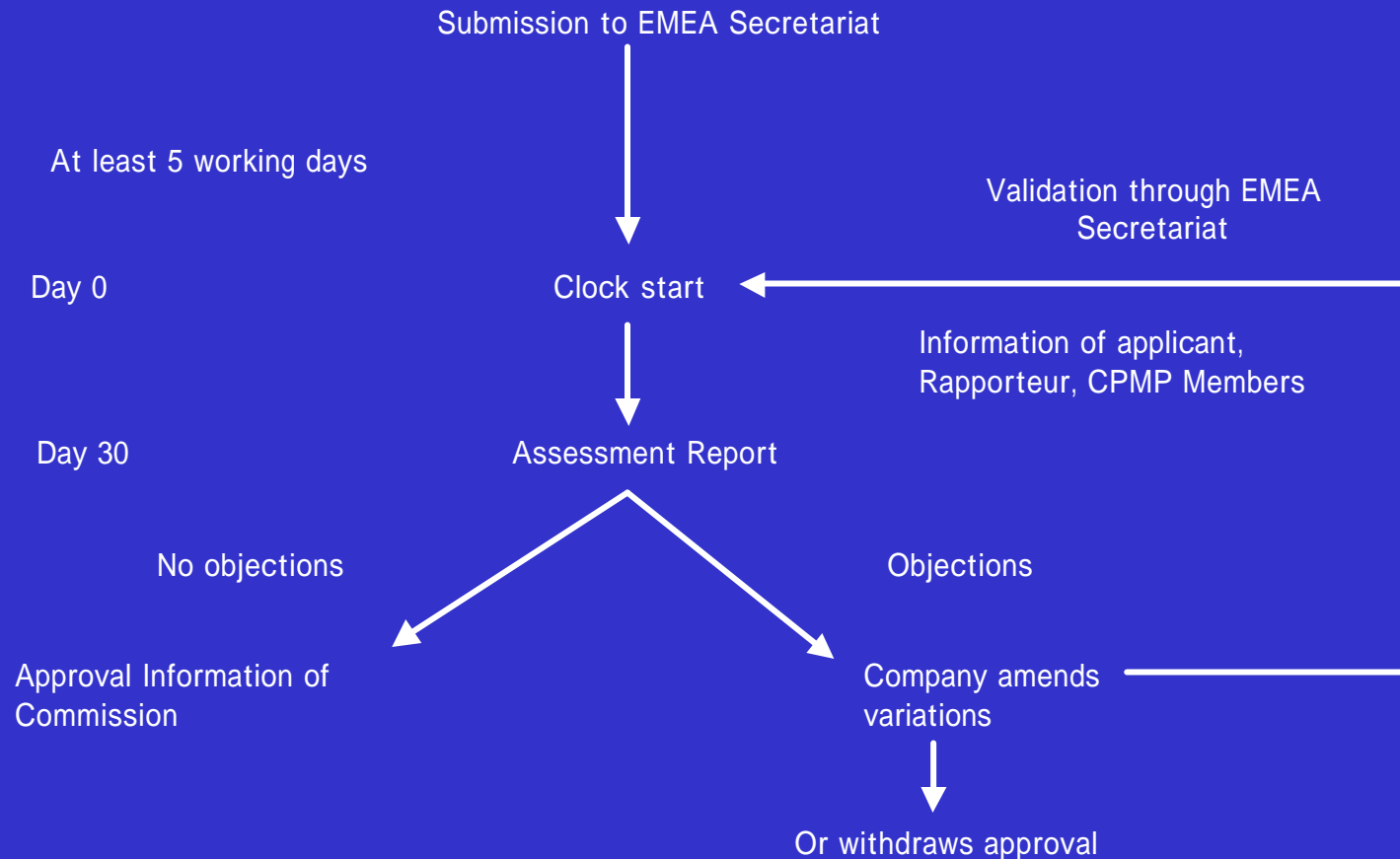
- ? Regulation 2309/93 Provisions went into operation in February 1995. Reform of the registration systems
- ? Creation of the EU Centralised Procedure with specific timelines and performance goals
- ? Amended the legislation affecting mutual recognition of product approval between national authorities

Centralised Procedure



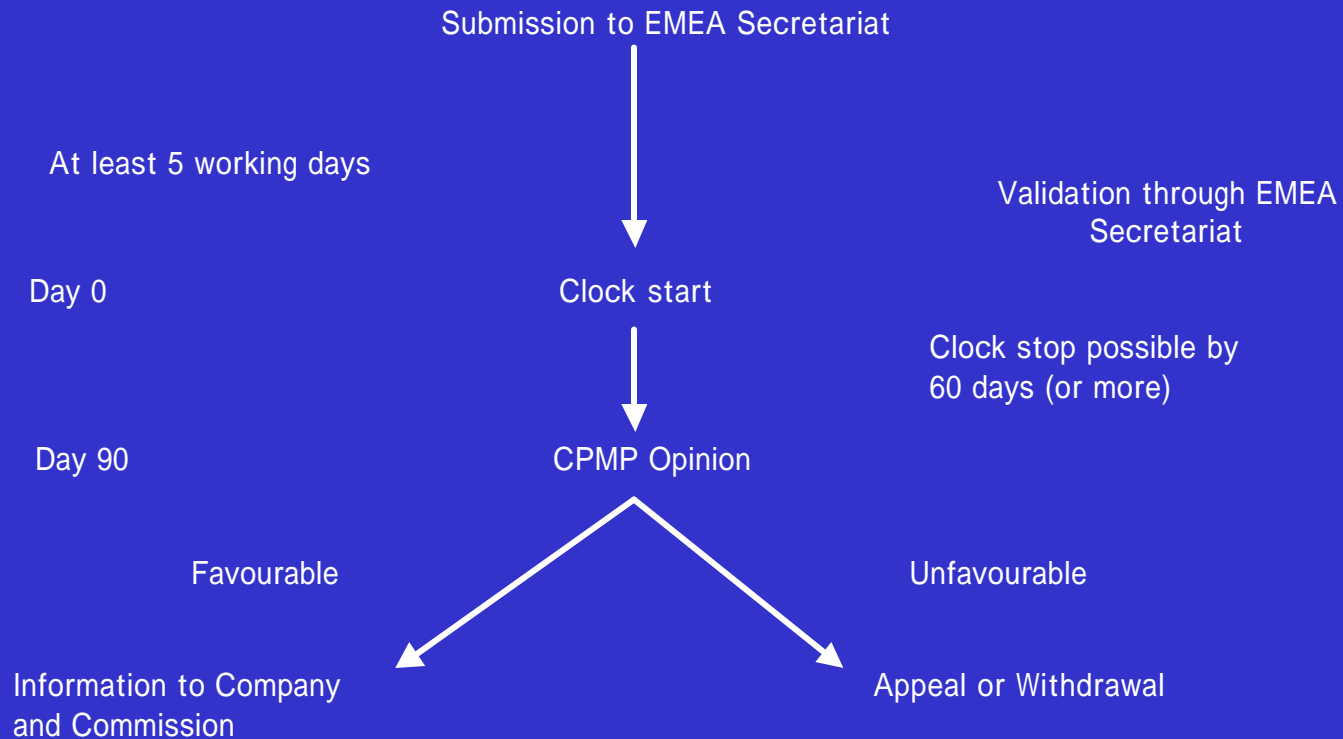
Centralised Procedure

Type I variation



Centralised Procedure

Type II variation



Centralised Procedure

Advantages

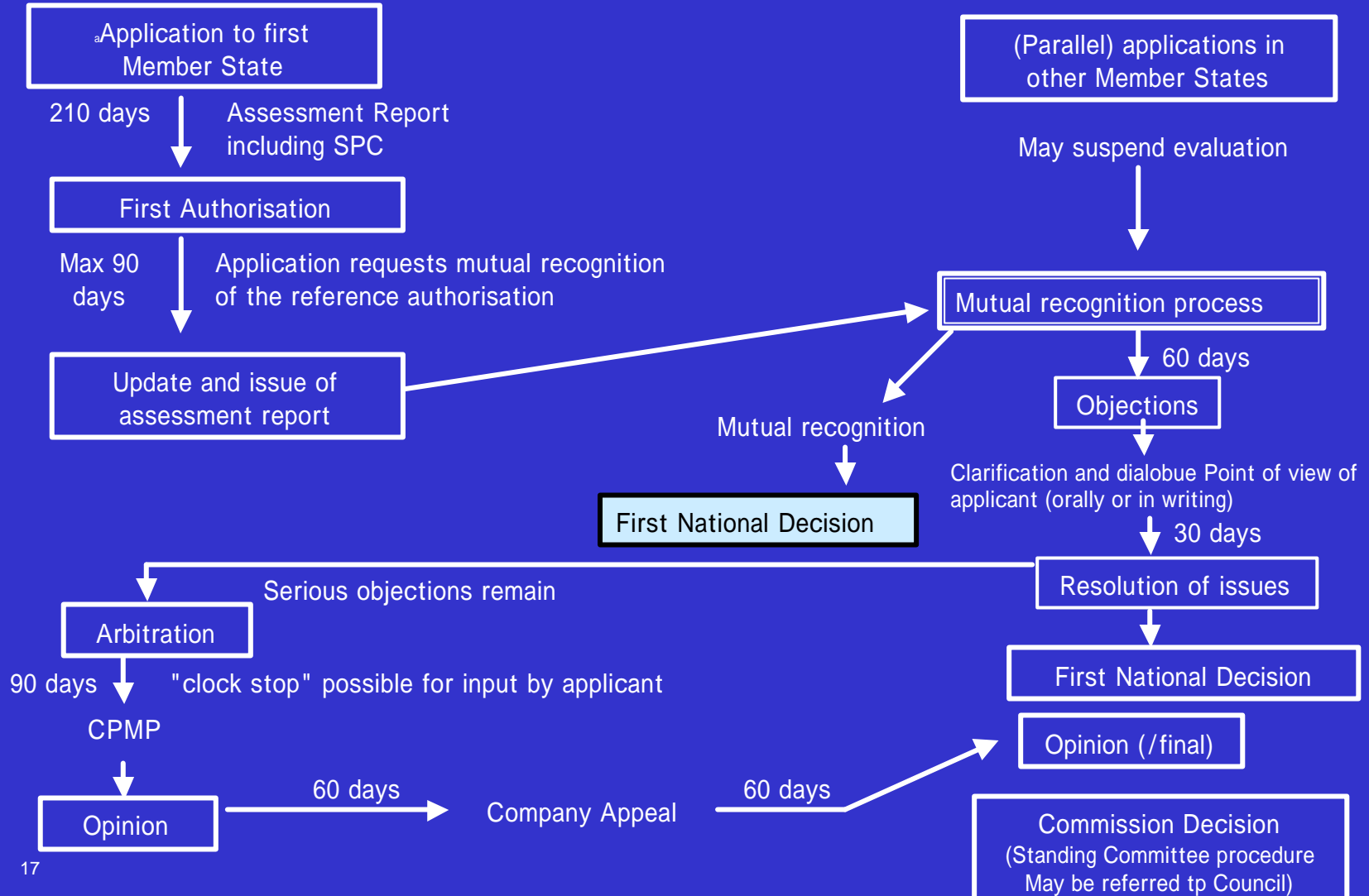
- ? Single Marketing Authorisation at the same time in all Member States of the European Union
- ? Robust scientific assessment
- ? No national variations
- ? Protection period of 10 years in all EU-Member States
- ? Reliable planning of market introduction of products in the whole EU. Defined scientific and legal assessment period anticipated to stimulate investment in biotechnology
- ? Scientific Advice Facility with one Authority only (EMA) on key issues such as clinical development planning
- ? Centralisation of registration activities within the pharmaceutical companies
- ? Recognition of approval / acceleration of registration procedure in other states, e.g. Hungary, Czech Republic, Slovakia, Poland, Bulgaria, Australia, Canada

Centralised Procedure

Disadvantages

- ? No free choice of Rapporteur (dependent upon workload of MS)
- ? Refusal of marketing authorisation is valid in all 15 Member States
- ? Only one trade name possible
- ? Restrictive labelling (e.g. regarding indications and warnings)
- ? Risk of delay if no consensus is reached among Member States
- ? Co-promotion and Co-Marketing difficult

Mutual Recognition Procedure(s)



Mutual Recognition Procedure(s)

Advantages

- ? Free choice of Reference member State
 - Possibility of establishing good contacts with the evaluating Authority prior to and during the registration procedure
- ? Speedy evaluation within a fixed timeframe
- ? Registration in other EU-States also within a fixed timeframe
- ? Exact planning of market introduction possible
- ? Co-promotion possible
- ? Different trade names in the various EU-Member States possible
- ? Variations in pack sizes possible in the various EU-Member States

Mutual Recognition Procedure(s)

Disadvantages

- ? In case of arbitration involvement also of Member States that did originally not take part in the licensing procedure
- ? Time delay in case of arbitration
- ? Start of the protection period at the time of licensure in the first Member State
- ? Withdrawal of application in one Member State possible in order to avoid arbitration.
In the past no risk involved, but now the Member States or the Commission may refer the matter to Committee for consideration → time delay, refusal of licensure
- ? MS perform there own assessment instead of true mutual recognition

Regulatory Issues Affecting Biological and Biotechnological Medicinal Products in the EU Past, Present and Future

Biological Products in the EU before 1980

- Narrow Spectrum of products, largely limited to
 - Vaccines (live & inactivated)
 - Hormones
 - Blood products (plasma derivatives)
 - Immunologicals and antisera
- Low purity, complex mixes, limited characterisation
- Manufacturing process critical in defining the product
- Changes in process/equipment/facility could result in major changes in product (eg pd FVIII cases)
- All regulated on a national basis

Biologics in EU After 1980

- rDNA technology – new biotherapeutics
- High purity and better characterisation
- Modern, sensitive analytical techniques and improved ability to assess impact of manufacturing changes
- Emerging concept of comparability and development of guidance documents
 - FDA 1996 & 1999 (Mab)
 - MHLW 2001
 - JPMA 2002
 - EU 2001 & 2003 (Annex on Non-Clinical & Clinical)
 - ICH Q5E Draft 2003

EU Key Regulatory Issues for Biologics 1980 v 2003

- Use of immortalised cell lines
- Host cell impurities
- Host cell & total DNA
- Reproducibility of production process
- Viral and microbial contamination
- Impurity profiles
- Stability
- Specifications
- TSE
- Viral and microbial contamination
- Cost of goods, clinical trial design and endpoints
- Licensing and manufacturing agreements
- Ethical issues and patient safety
- Comparability
- Therapeutic equivalence and “biogenerics”

Current EU Legislative/Regulatory Developments for Biological /Biotechnological Medicinal Products

- “Biogeneric”, second source or “similar” medicinal products at political and technical levels
- Comparability (EU non-clinical annex & draft ICH Guideline)
- TSE compliance & revised NfG
- Immunogenicity (recent Eprex and Refacto Cases)
 - Revised SmPC & labelling
 - Formulation issues
- Implementation of Directive 98/44 EEC on biotech patents in all MS
- Orphan medicinal products legislation

Current EU Regulatory Issues

- Review of Regulatory Systems to include:
 - Definition of a “biologic”
 - CP Exclusively for biotech products & NCE’s
 - EU enlargement
 - Accelerated review & fast track procedures
 - CTD in Dir 75/318 EEC
 - Update to Variations regulations
 - Clinical trial directive
 - Scientific advice
 - Pharmacovigilance (e2B & EPPV)
 - eCTD Submissions.
 - EU wide Compassionate use program

Future Biotechnology related Regulatory Issues

- Human Tissue and Cells Directive
- Tissue Engineering
- Cloning
 - Therapeutic benefits of stem cell vs. ethical issues
 - Future impact on gene therapy
- Pre and post-natal genetic testing
 - Medical diagnosis of genetic disorders e.g. diabetes, cardiovascular disease and Alzheimer's

Future Biotechnology Regulatory Issues

- Pharmacogenetics and Pharmacogeneomics
 - Data privacy and prevention of misuse of genetic data
 - Practical, scientific legal and ethical issues in clinical trial design
- Mimetics
- Gene Therapy
- Cell Therapy
- Xenotransplantation

Future Biotechnology Regulatory Issues

How Will the Regulations Evolve ?

- Definition of a medicinal product
 - Modifications to Dir. 65/65 EEC(now codified in Dir 2001/83) facilitate definition of medicinal product so that it can easily cover the technology products
 - Some technology products will be borderline and need to be regulated as medical devices or on a case by case basis
 - Concepts of Quality , Safety and Efficacy still apply. Viral safety issues, traceability, GLP.GMP,GCP of critical importance
 - European Commision working on future definition of a biological medicinal product as an amendment to Dir 2001/83

Current Definition of a Medicinal Product

Article 1 of Directive 65/65 EEC (now codified in Directive 2001/83) Defines a Medicinal Product as any substance or combination of substance or combination of substances presented for treating disease in human beings or animals. Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product

A substance is any matter irrespective of origin, which may be

- human e.g. human blood and human blood products
- animal, e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products etc
- vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts etc
- chemical, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis

Thanks for Your
Attention & Have a
Nice Day !