Some Aspects of Development, Evaluation and Control of Biologics in Japan

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PMDA
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Regulatory Concerns on Biologics Evaluation and Control in Japan (1)

Scope of Products:

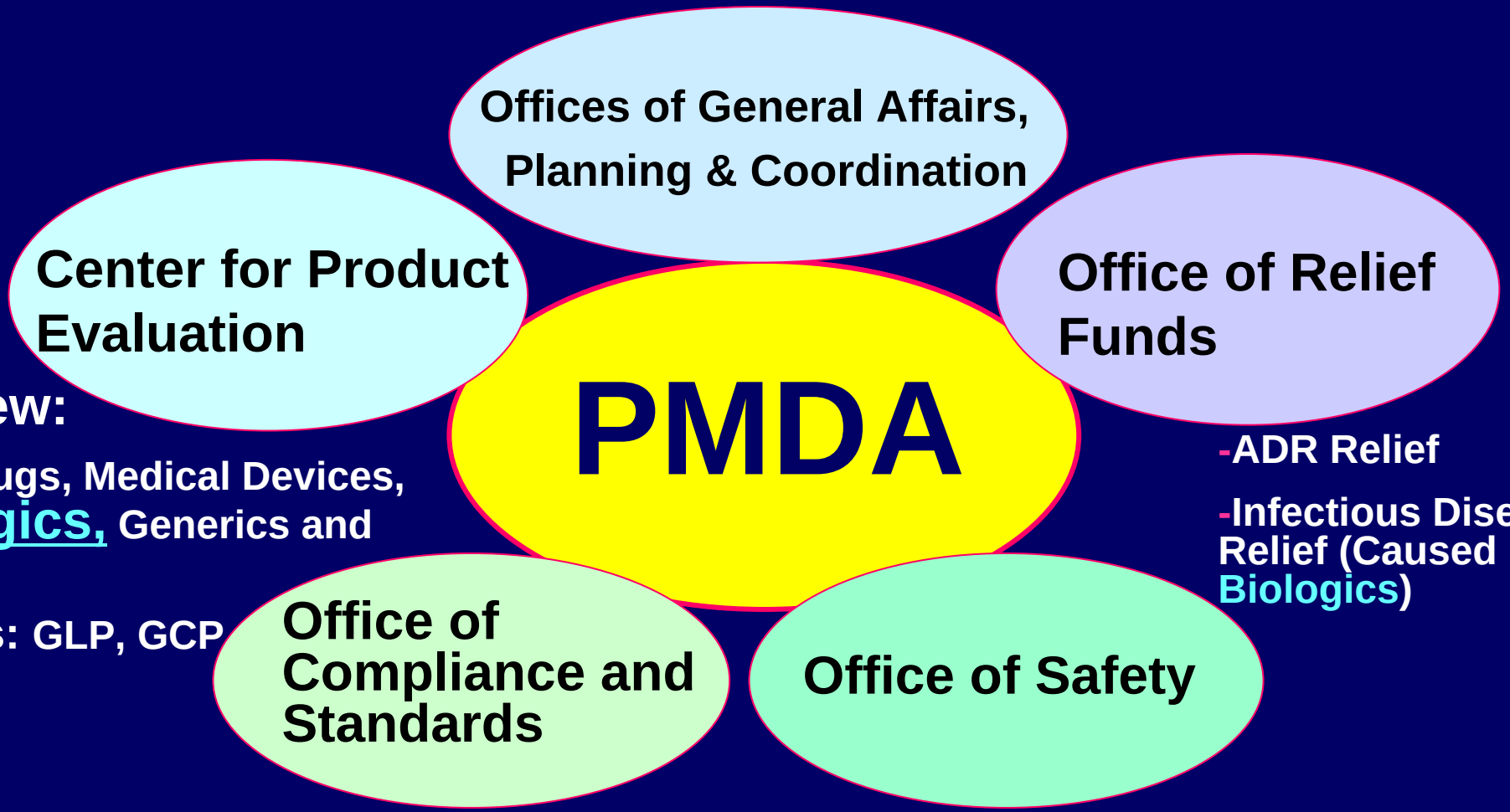
- Biotechnology Products
  - cell substrate derived protein products
  - gene therapy products
  - cell/tissue-based products
- Blood Products
- Vaccines
- Antitoxins
- Other Medicinal Products of human or animal origin

Regulatory Concerns on Biologics Evaluation and Control in Japan (2)

Regulatory Agencies and National Institutes:

- Ministry of Health, Labour and Welfare (MHLW):
  - Pharmaceutical and Food Safety Bureau
  - Pharmaceutical Affairs Food Sanitation Council (PAFSC)
- Pharmaceutical and Medical Device Agency (PMDA)
- National Institute of Health Sciences (NIHS)
- National Institute of Infectious Diseases (NIID)

Organization and Main Functions of PMDA



-**Review:**

New Drugs, Medical Devices, Biologics, Generics and OTC

-**Audits:** GLP, GCP

-ADR Relief

-Infectious Disease Relief (Caused by Biologics)

-**Audits:** Drug GMP and MD Quality System

-**Standards: making JP draft**

Post-market Safety Information

Regulatory Concerns on Biologics Evaluation and Control in Japan (3)

Official Documents:

- Pharmaceutical Affairs Law (PAL)
- Japanese Pharmacopoeia (JP)
- Minimum Requirements for Vaccines, Antitoxins and Blood Products
- Guidance and Notifications from relevant offices of MHLW

Provisions of Article 2,41&56 of the Pharmaceutical Affairs Law

- Article 2 The term “drug” in this Law refers to the following items:(1)Items recognized in JP. (2)...
- Article 41-1 To standardize and control the properties and quality of drugs, the Minister shall establish and publish JP, after hearing the opinion of the Pharmaceutical Affairs Food Sanitation Council (PAFSC).

Provisions of Article 2,41&56 of the Pharmaceutical Affairs Law (*cont'd*)

- Article 41-2 The Minister shall consult the PAFSC on the investigation and the revision of the whole of JP at least every 10 years.

- Article 56 A JP drug for which the quality or properties are not in conformity with the standards established by JP shall not be sold or supplied, or manufactured, imported, stored, or exhibited for the purpose of sale or supply.

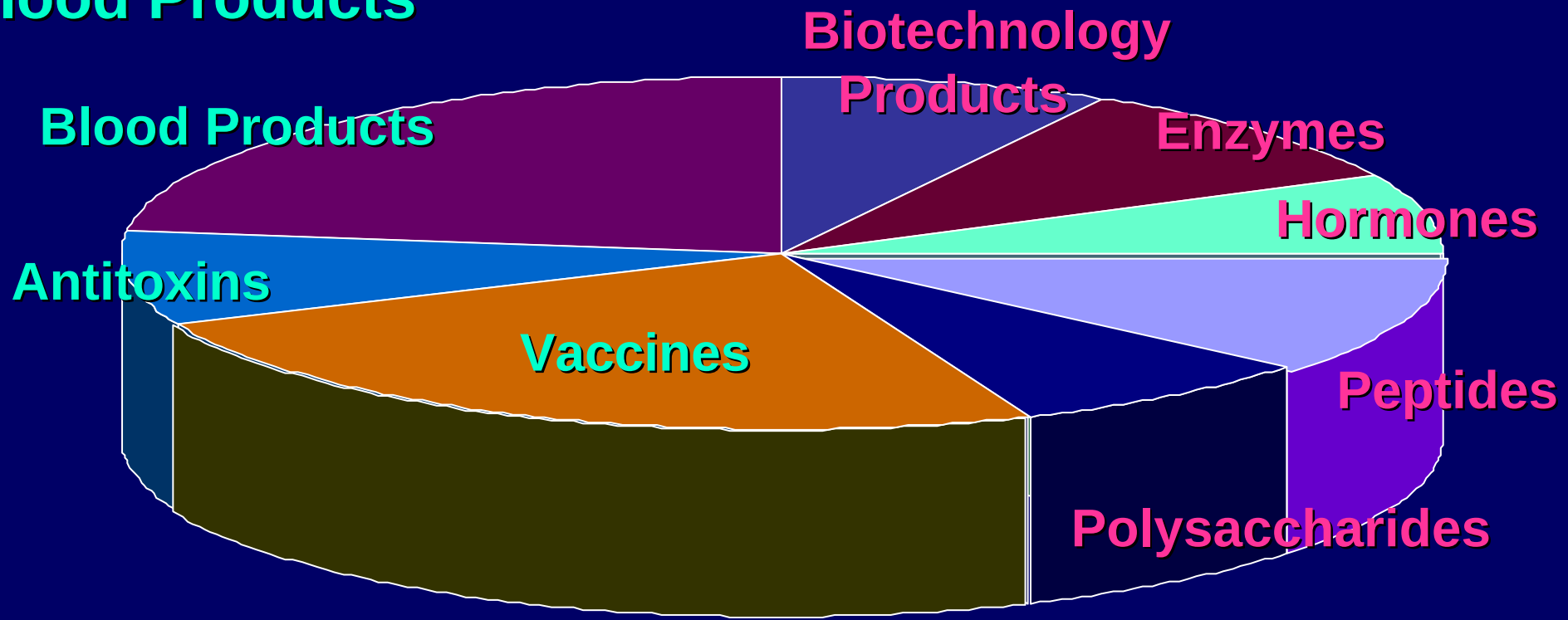
Vaccines, Antitoxins and Blood Products

- Provisions of Article 42-1 of the Pharmaceutical Affairs Law: The Minister may promulgates the necessary standards, after hearing the opinion of the Pharmaceutical Affairs Food Sanitation Council (PAFSC) related to the manufacturing process, properties, quality, storage method, etc. of those drugs which require special attention concerning public health and hygiene.
- Formulation of "Minimum Requirements for Vaccines, Antitoxins and Blood Products
- No vaccines, antitoxins and blood products should be used in Japan unless they conform to the existing minimum requirements for the said products

Classification of Biologicals in JP and Minimum Requirements for Vaccines, Antitoxins and Blood Products

Minimum Requirement for Vaccines, Antitoxins and Blood Products

JP



System of Establishing JP

MHLW, JP Committee/ PAFSC

- Basic Policies
- Determination of Items to be included in JP

(e.g.,Rules,Tests, Drugs and Dosage Forms)

PMDA

Company's Draft

Secretariat's Draft

Expert Committees

(19 Committees:150 Experts)

- Review
- End of Reviews

JP Draft

Request

Draft Submission

Questions

Answers

Com-pany

MHLW, JP Committee/ PAFSC

- Adoption and Promulgation of JP
- Publishing of JP (English Translation)

Main Policies of the Standardization and Control of Biologicals in JP (3)

- Special Concerns on Adventitious Agents Safety Evaluation

- General Notices 6 of JP(Qualification of Animals as Origin of Animal-derived Medicinal Products)
- Qualification of Animals as Origin of Animal-derived Medicinal Products provided in the General Notices 6 of JP and Other Standards
- Viral Safety of Biotechnological/Biological Products listed in JP *(Especially, Products Derived from Human Tissues or Body Fluids)*
- Mycoplasma Testing for Cell Substrates used for the Production of Biotechnological/Biological Products

Materials Used for Manufacture of Biologics

Human, Animal

Source Materials

(e.g.,Blood・Plasma, Collected Cells・Tissue, Parental Cell Line, Body Fluid, Virus)

Starting Materials

(Critical Materials for Manufacturing and Ensuring the Quality and Safety of the Drug Substance)

e.g.,Pooled Blood・Plasma, Tissue Extract, Processed Cells, Cell Bank, Pooled Urine or Milk, Cell Culture Supernatant, DNA, Vector

Qualification of Animals as Origin of Animal-derived Medicinal Products provided in JP General Notices 6 (2)

Donor Eligibility Tests/Criteria

1. Plasma Derivatives
   - Serological tests and NATs on 20 pooled plasma for HBV, HCV, HIV
2. Human Urine-derived Products
   - No contamination of pathogenic bacteria, fungi, viruses in source materials and/or justification of their clearance during manufacturing process
   - NATs for HBV, HCV and HIV
3. Animal-derived Products
   - Animals from a colony appropriately controlled under specific pathogen-free (SPF) environment;or animals that met the Food Standard; or animals that are proved to be free from pathogen by appropriate tests, if necessary.

Qualification of Animals as Origin of Animal-derived Medicinal Products provided in JP General Notices 6 (3)

Measures to avoid transmission or spread of transmissible spongiform encephalopathies (TSE):

1. Avoidance of use of animals, which are raised in the areas where relatively high incidence or high risk of TSEs is reported, and humans, who stayed a defined period in such areas, as raw materials for drug production;
2. Avoidance of use of any substance that is derived from an individual infected with TSEs;
3. Avoidance of using a material derived from organs, tissues and cells, etc. of high risk of TSEs;
4. Avoidance of use of any human-derived materials from countries where an incidence of vCJD is reported; and
5. Taking appropriate measures based on the information collected, which includes incidence of TSEs, the results of epidemiological investigation and the experimental research on prions, and incidence of late infection in donors after collection of raw materials, etc.

Principle of BSE measures for pharmaceuticals, medical devices and cosmetics marketed in Japan under the Pharmaceutical Affairs Law

Countries of origin	BSE highly affected countries (UK, Portugal) e.q. to GBR-4	BSE affected countries (European countries, Japan) e.q. to GBR-3 and US and Canada	Countries of unknown risk (risk ssessment was not performed by EU)	Lower Risk Countriese. q. to GBR-1 or 2
High risk tissues and organs	NO USE regardless of the countries of Origin			
Others	NO USE	NO USE with exemption(*)		Usable

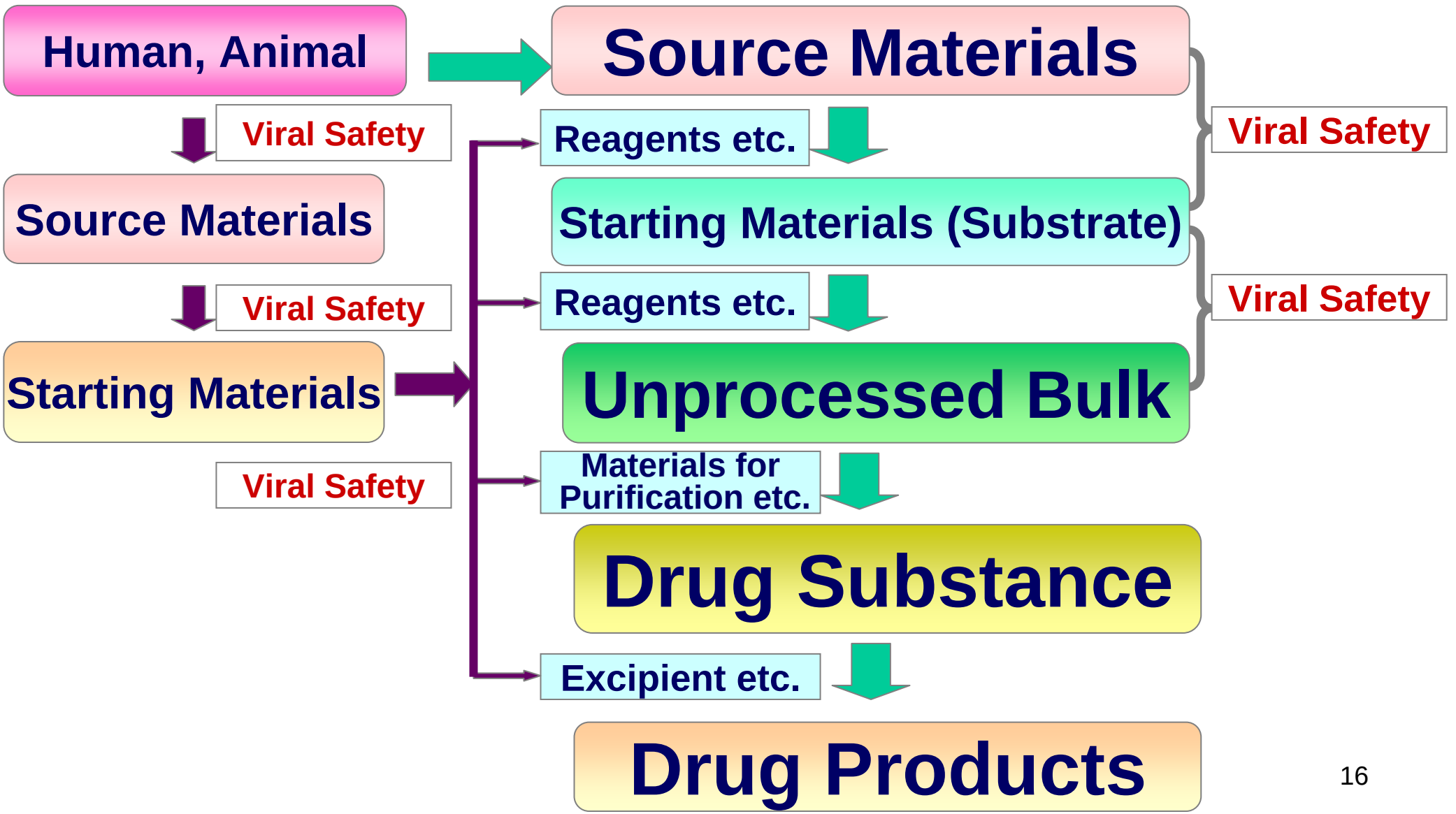
* The source materials are exempted where they meet the following conditions

Closed Herd Criteria: The materials are to be used for unavoidable manufacturing reasons

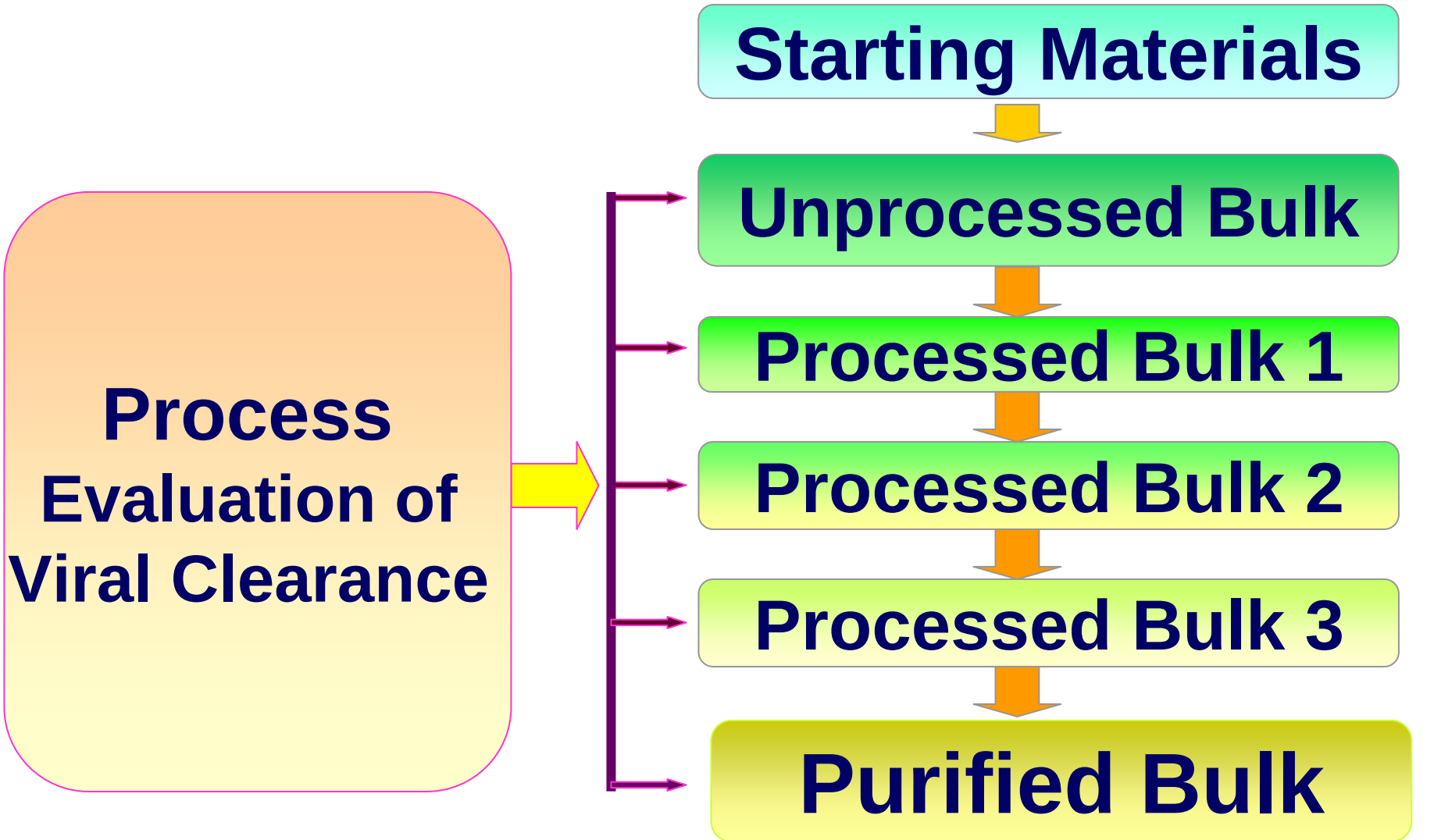
1. The materials were collected from the animals which were certified (by governmental authorities) to be free from BSE affected animals
2. The countries of origins take measure to combat BSE
3. The animals from which the source materials were collected were certified to have been grown by non-ruminant protein feedings

Milk derivatives(except UK and Portugal), hide gelatins/collagens and lanoline derivatives are exempted for restrictions of countries of origin

Viral Safety Concerns on Biologics Manufacture using Materials derived from Human or Animal



Process Evaluation of Viral Clearance



Revise of Pharmaceutical Affairs Law

- Modification of Approval and Licensing System Including Enhancement of Safety Measures in PMS → April 2005
- Enhancement of Safety Securing of Biologics → July 2003
- Drastic Change of Safety Measures of Medical Devices → April 2005
- Drug Master File → April 2005
- Doctor-initiated Clinical Trials → July 2003

Framework of Safety Regulation in New Bio-Era

Uniform Safety Regulation across All Biologicals

Overall measures to prevent contamination of infectious agents

Inactivation & Removal of infectious agents

Prevention of emerging / spreading infectious disease , for high risk products (Look back & traceability)

Outcome of Safety Regulation

- **Protection of Patients**
- **Public acceptance of new technology through safety assurance**
- **Promoting Sound Biologicals Development**

Provision of Promising Innovative Biological Products

Medical Devices

Dermal, Cartilage Cell Culture Products, etc.

Pharmaceutical Products

Cancer Immuno-cellular therapy, etc.

Product Development

Promising new indication

Innovative Therapies

Classification of Medicinal Products including Ingredients derived from Human or Biological (excluding plant) Source Materials

- Revised PAL requires the Minister of Health, Labour and Welfare to classify individual products *including ingredients derived from human or biological source materials* into three categories (Specified Biological Products, Biological Products and Others).
- *Product classification is done, based on sound scientific assessment of potential risk of infection transmission, according to the advice from the Pharmaceutical and Food Sanitation Council (advisory committee to the Minister)*

What is “Biological Products” under revised PAL

Biological Products:

Products including ingredients derived from human or biological *(excluding plants)* **source materials** *(such as cell, tissue, blood, body fluid, etc.)* **, which should be subject to particular attention from a public health point of view. (Article 2.9 of PAL)**

Specified Biological Product:

Among “biological products” with particular care for preventing the onset and transmission of infection (Article 2.10 of PAL)

Designation of Biological Products

Others (not designated)

- Oral, dermal administration
- Vigorous temperature, chemical treatment
- Use of non-pathogenic bacteria
- Less possibility of human-animal infection

Specified Biological Products

- Blood product/ Plasma derivatives
- Human cellular/tissue based products
- Human extracts

Biological Products

- Vaccines
- Human urine extract
- Animal extracts
- Recombinant proteins

Some of those containing Human plasma derivative

If risk is estimated to be equivalent to blood products/plasma derivatives in terms of usage, dose, quantities and duration : Specified biological products (e.g.Recombinant Factor-IV)

Consolidation of Safety Measures for Biological Products

For higher risk products

Information review and corrective actions

Preventing spread of infection

Source materials | Manufacturing | Post-marketing

"ADD-ON" for Biological Products

Safety measures for source materials incl. donor deferral criteria

- **Establishment requirements**
- **Record retention**
- **Prevention of contamination**

- Proper labeling/use information provision
- Look back/traceablity
- Periodic infectious disease surveillance report

Chemical drug / normal devices

GMP (Good Manufacturing Practices) : manufacturing /quality control to keep consistent quality of products

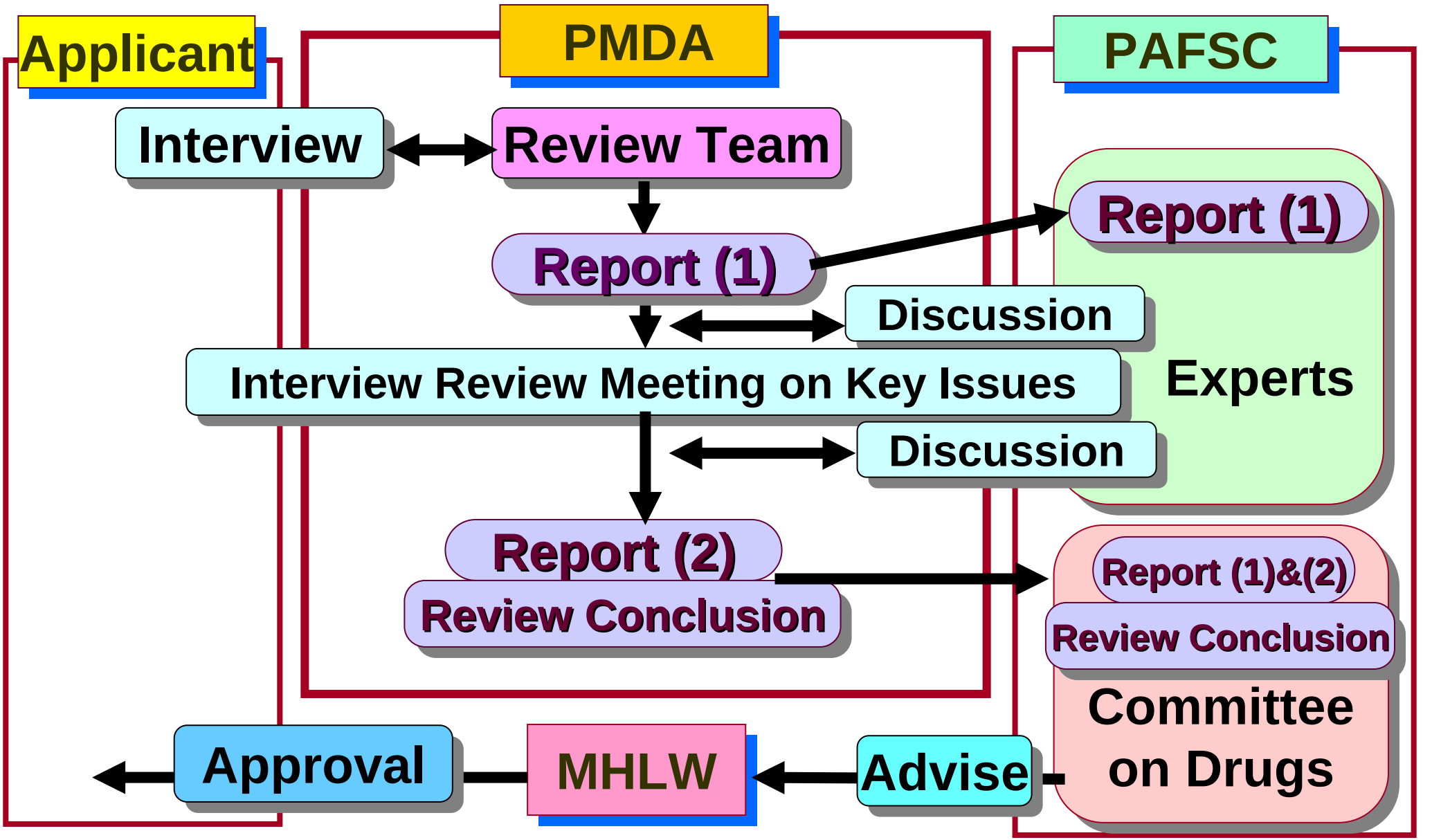
Starting materials selection criteria

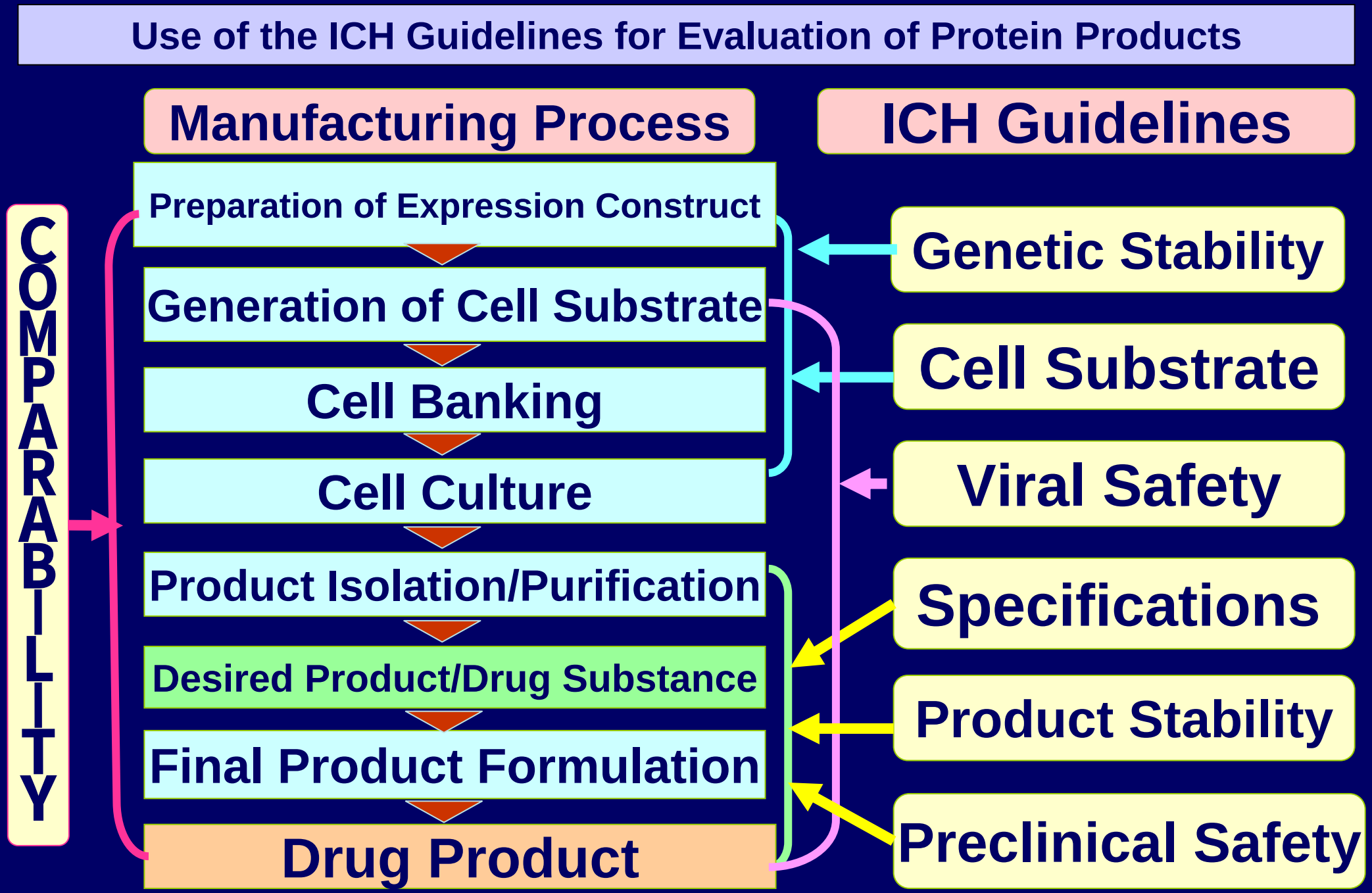
***e.g.* sterilized condition for aseptic products**

GPMSP: Postmarketing practices for safety vigilance

***e.g.* safety management of companies to deal with vigilance information**

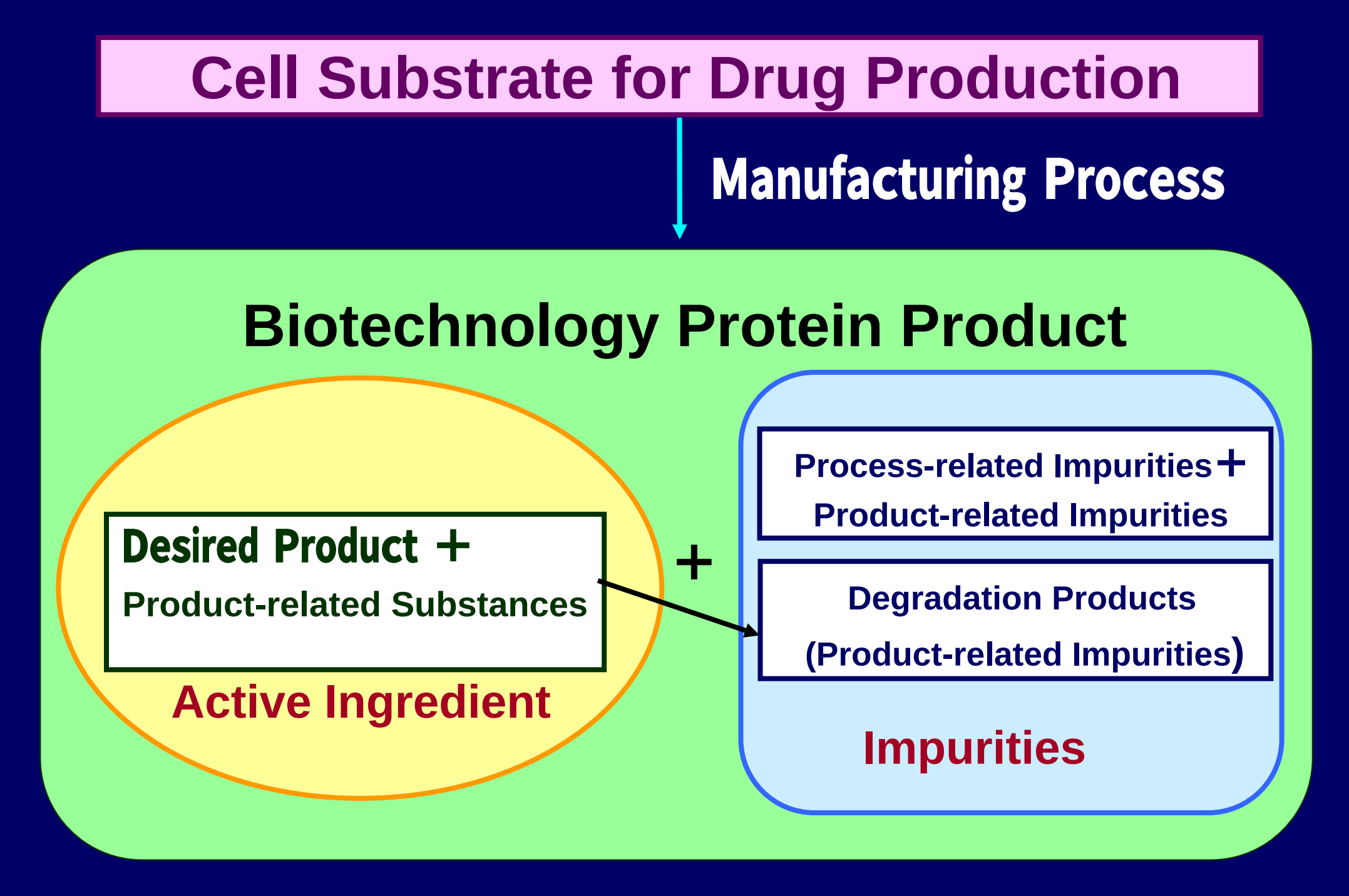
NDA Review Process in Japan

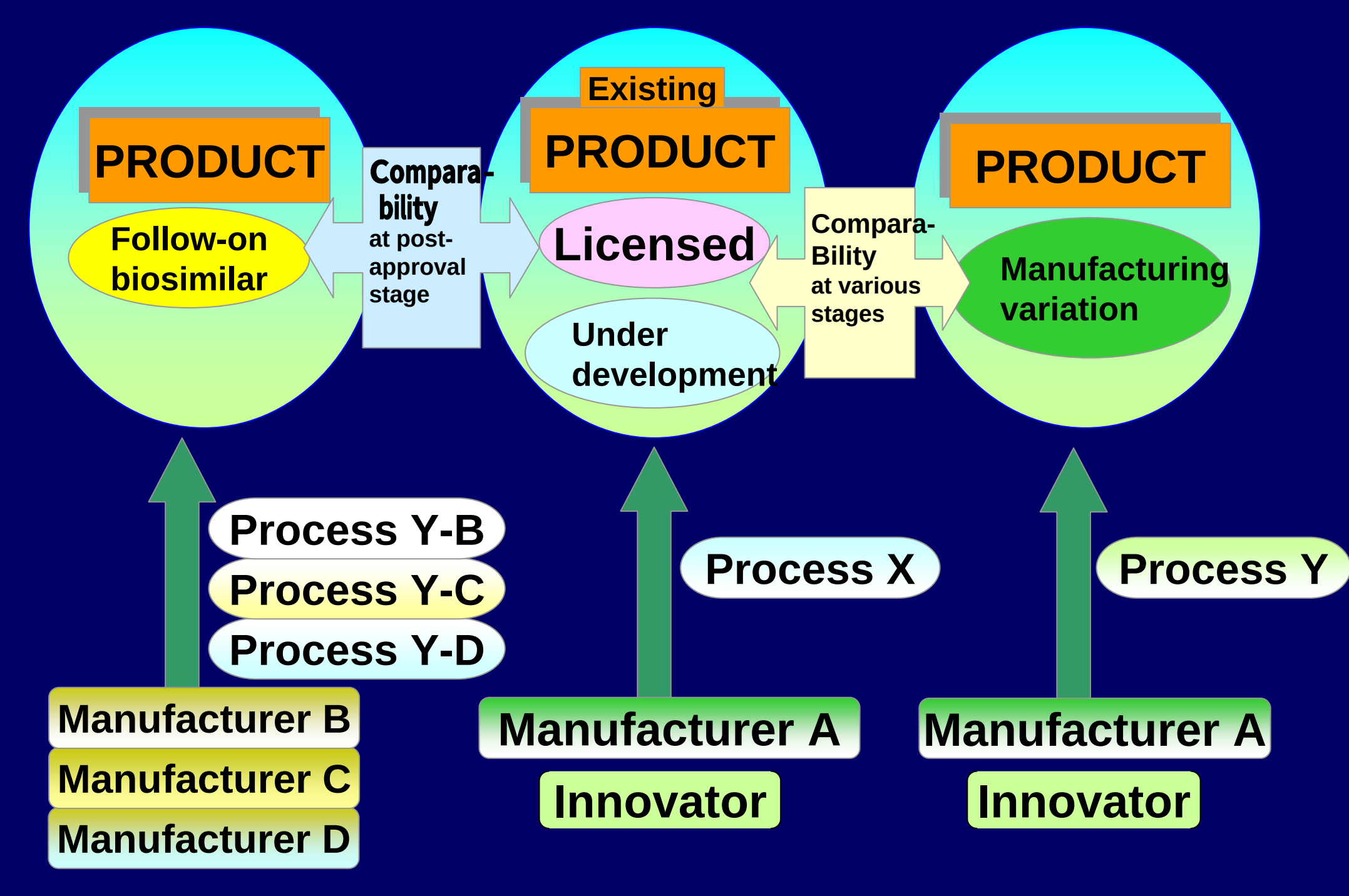



Use of the ICH Guidelines for Evaluation of Protein Products
Manufacturing Process
ICH Guidelines
COMPARABILITY
Preparation of Expression Construct
Generation of Cell Substrate
Cell Banking
Cell Culture
Product Isolation/Purification
Desired Product/Drug Substance
Final Product Formulation
Drug Product
Genetic Stability
Cell Substrate
Viral Safety
Specifications
Product Stability
Preclinical Safety

Heterogeneity and Evaluation/Control of Biotechnology Protein Products

- An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them; therefore, the desired product can be a mixture of anticipated post-translationally modified forms (e.g.,glycoforms).
- Heterogeneity can also be produced during manufacture and/or storage of the drug substance or drug product.
- These molecular entities or variants of the desired product may be active and their presence may have no deleterious effect on the safety and efficacy.

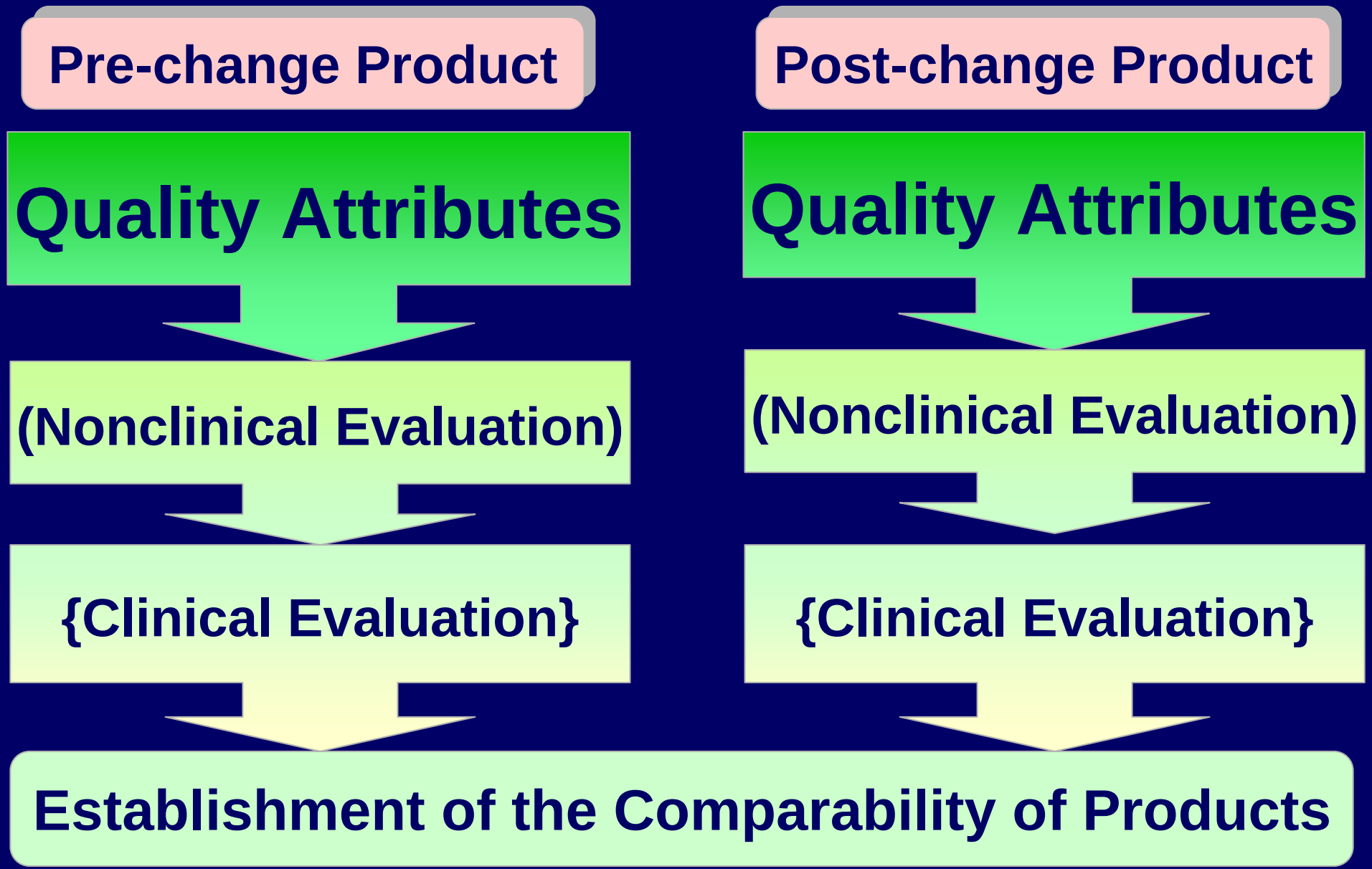

Cell Substrate for Drug Production
Manufacturing Process
Biotechnology Protein Product
Desired Product +
Product-related Substances
Active Ingredient
+
Process-related Impurities +
Product-related Impurities
Degradation Products
(Product-related Impurities)
Impurities

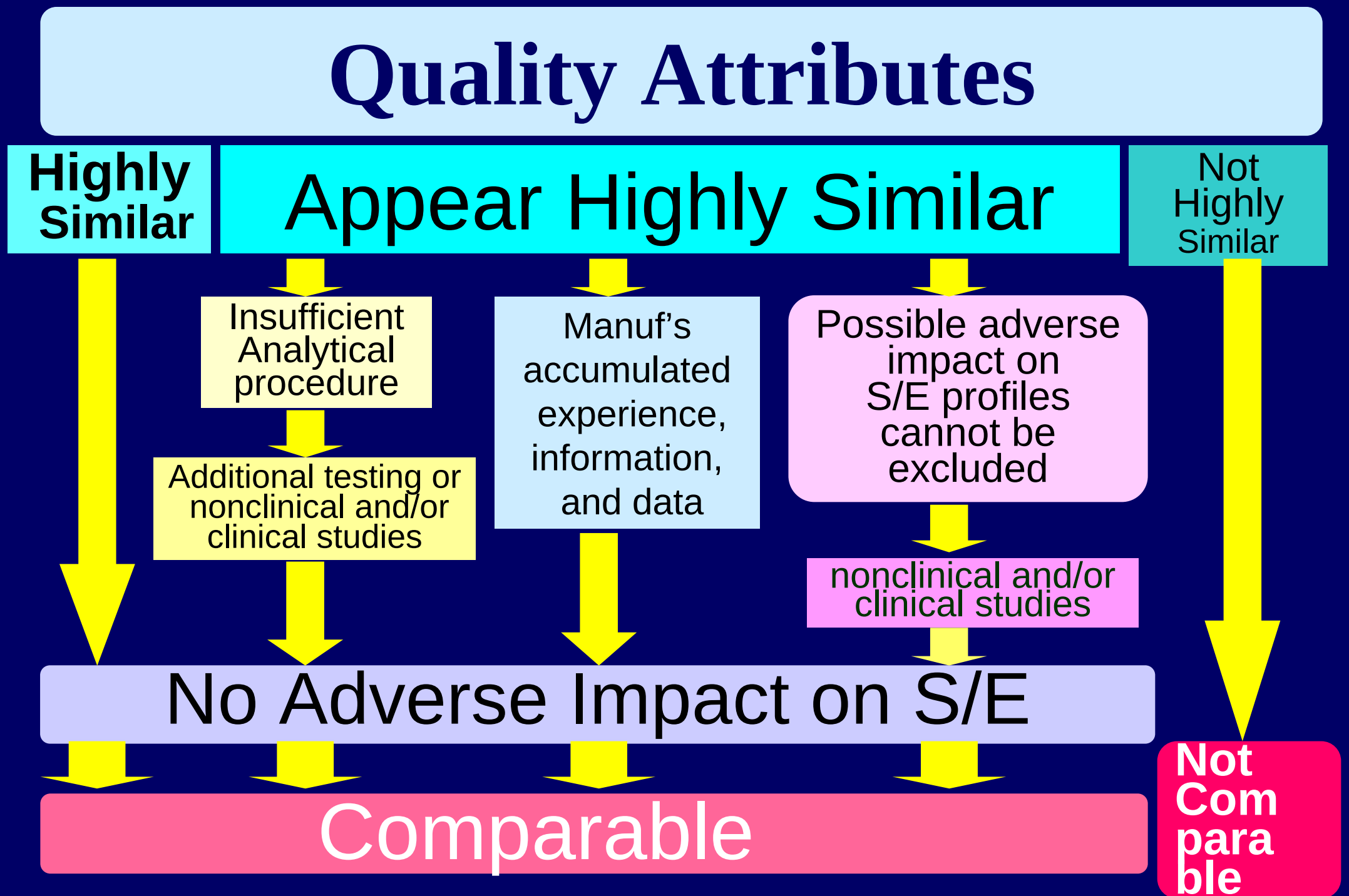

PRODUCT
Follow-on biosimilar
Compara-bility at post-approval stage
Existing PRODUCT
Licensed
Under development
Compara-Bility at various stages
PRODUCT
Manufacturing variation
Process Y-B
Process Y-C
Process Y-D
Manufacturer B
Manufacturer C
Manufacturer D
Process X
Manufacturer A
Innovator
Process Y
Manufacturer A
Innovator

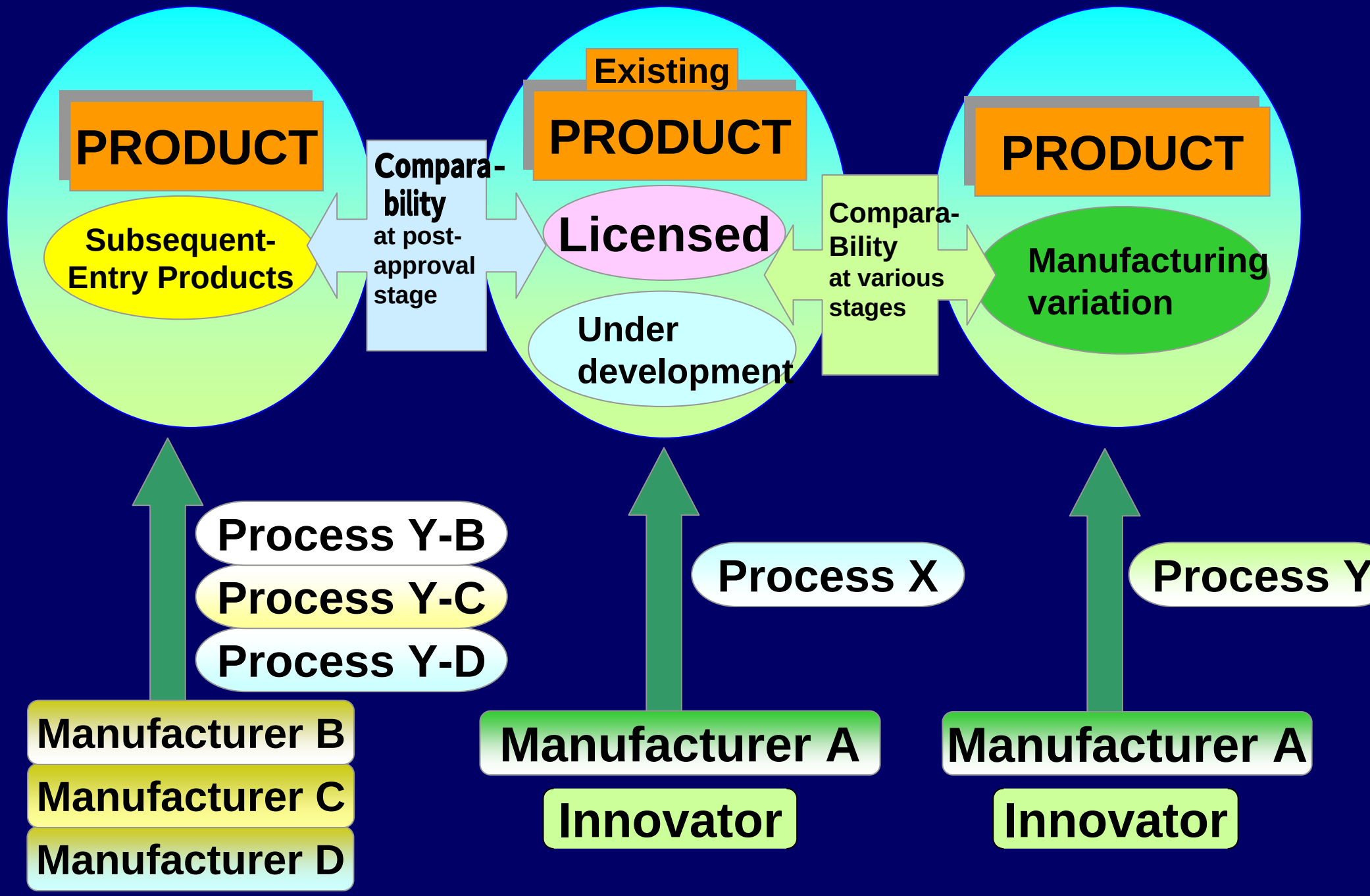
Comparable

A conclusion that products have highly similar "quality attributes" before and after manufacturing process changes and that no adverse impact on the safety, or efficacy, including immunogenicity of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.

Strategies for Comparability Exercise: Product Aspects




Quality Attributes
Highly Similar
Appear Highly Similar
Not Highly Similar
Insufficient Analytical procedure
Additional testing or nonclinical and/or clinical studies
Manuf's accumulated experience, information, and data
Possible adverse impact on S/E profiles cannot be excluded
nonclinical and/or clinical studies
No Adverse Impact on S/E
Comparable
Not Com para ble


PRODUCT
Subsequent-Entry Products
Compara-bility at post-approval stage
Existing PRODUCT
Licensed
Under development
Compara-Bility at various stages
PRODUCT
Manufacturing variation
Process Y-B
Process Y-C
Process Y-D
Manufacturer B
Manufacturer C
Manufacturer D
Process X
Manufacturer A
Innovator
Process Y
Manufacturer A
Innovator

A View regarding Subsequent-Entry Protein Products (1)

- Theoretically, "Comparable Subsequent-Entry Protein Products" can be developed by using comparability approach for any kind of products, but, in practice, the success of such a development approach will depend on the product characteristics, availability of relevant analytical methods and reference product, intended clinical use and so on.

A View regarding Subsequent-Entry on Protein Products (2)

- In some cases, “Comparability Concepts and Approaches” can lead to a reduced burden of testing for data submission for approval, and result in more rational, effective or economical drug development.

A View regarding Subsequent-Entry Protein Products (3)

- However, comparability study alone may not always suffice for ensuring Quality, Safety and Efficacy of certain "Subsequent-Entry Protein Products".
- In such a case, the combination of "Comparability Assessments" and "Conventional Assessments" may be appropriate to ensure Q/S/E of the "Subsequent-Entry Protein Products".

A View regarding Subsequent-Entry Protein Products (4)

- Also, there may be the case where “Conventional Approaches and Evaluation” is rather appropriate to ensure quality, safety and efficacy of “Subsequent-Entry Protein Products” in question.

General Considerations: Product Aspects (1)

- The better one knows the product characteristics and intended clinical use, the more rational approaches can be taken
- Therefore, first of all, extensive identification and characterization studies should be performed using state of the art analytical methods to reveal the molecular and quality attributes of the "Subsequent-Entry Product".

Collectively, the quality attributes define the adventitious agent safety, purity, potency, identity, and stability of the product. Specifications measure a selected subset of the quality attributes.

General Considerations：Product Aspects (2)

- DRUG SUBSTANCE: in practice, "Comparable Subsequent-Entry Drug Substance" may be developed for nonconjugated protein products but not for many of conjugated proteins in terms of quality attributes.
- *Examples of nonconjugated proteins are Insulin, Somatoropin (hGH), Filgrastim (non-glycosylated met-G-CSF), Teceleukin (met-IL-2), Celmoleukin(IL-2), Interferon alfa 2a, Interferon alfa 2b and so on*

General Considerations: Product Aspects (3)

- DRUG PRODUCT: In case where the innovator's drug product has more than one indication, the efficacy and safety of the subsequent-entry product clamed to be comparable have to be justified or, if appropriate, demonstrated separately for each of the clamed indications.
- Any new dosage forms and/or new clinical indications of a subsequent-entry product should be the subjects of extensive "Conventional Exercise".

Special Concerns on Product Safety(1)

- Subsequent-entry protein products may exhibit their own safety profile in terms of nature, seriousness, or incidence of adverse reactions including immunogenicity.
- Data from pre-approval non-clinical and clinical studies may be insufficient to identify all safety profiles.

Special Concerns on Product Safety(2)

- Therefore, clinical safety of subsequent-entry products should be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment.

Special Concerns on Product Safety(3)

- The applicant should present a pharmacovigilance plan to address immunogenicity and potential rare serious adverse event.
- A specific risk management plan is required in situations when there is a safety signal in pre-approval non-clinical or clinical studies or when safety problems have been encountered with other products of the same class.

A View regarding Subsequent-Entry Protein Products: Summary

- In principle, any "Subsequent-Entry Protein Products" can be accepted for marketing authorization
- Whatever the Product is, ensuring its Quality, Safety and Efficacy is a crucial element for a product intended for therapeutic use

A View regarding Subsequent-Entry Protein Products: Summary

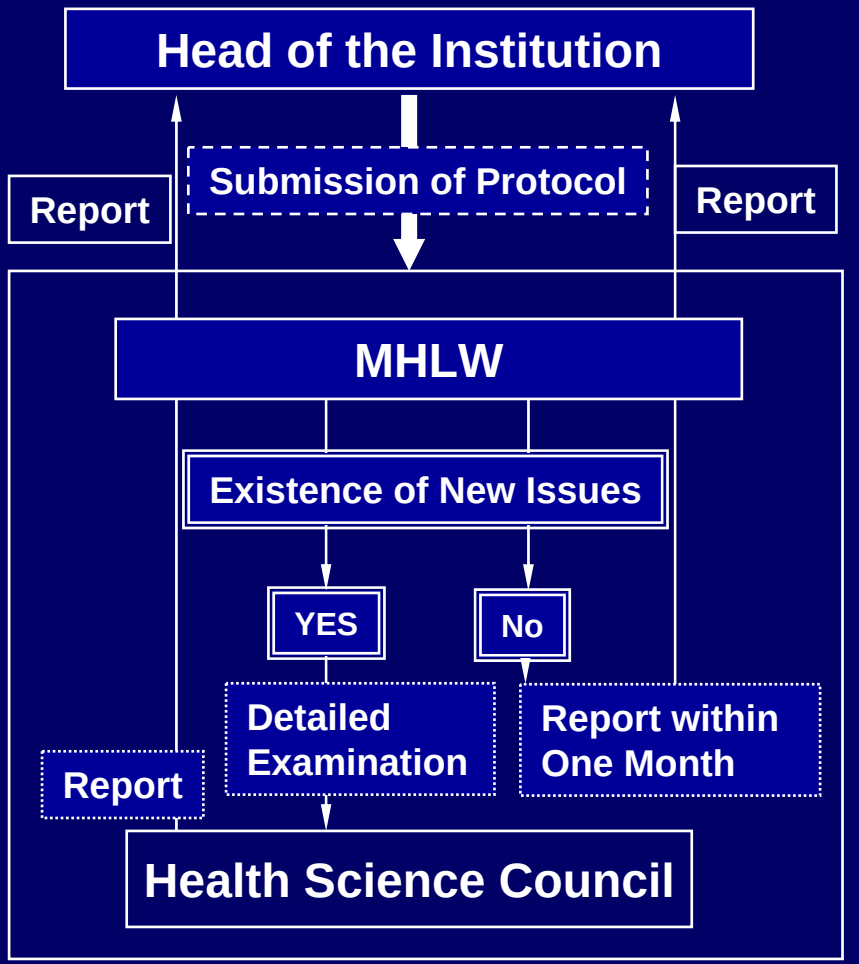
- Whatever the product is, establishment of a well-defined manufacturing process with its associated process controls is one of the critical elements for assurance of consistent drug production
- Improvement of product Quality, Safety and/or Efficacy is always desirable and encouraged. If the results of the relevant studies on "Subsequent-Entry Products" indicate an improved Q/S/E and no comparability, the product would be acceptable.

Outline of the History of Gene Therapy in Japan

1991.10	Establishment of “Expert Committee on Gene Therapy”
1993. 4	“Guideline for Gene Therapy Clinical Research” (Health Science Council Report, MHW)
1994. 2	“Guideline for Gene Therapy Clinical Research” (MHW Notice No.23)
1994. 8	First Gene Therapy Protocol Was Proposed for Approval
1995. 8	Start of Gene Therapy Clinical Research for ADA Deficiency
1995. 11	“Guideline for Assuring the Quality and Safety of the Gene Therapy Products” (MHW PAB Notice No.1062)
1998. 12	Start of Gene Therapy Clinical Research for Renal Cell Cancer
	…
2002. 4	Amendments of Guidelines and Evaluation System on Gene Therapy Clinical Study
2004. 4	Minor Change of Evaluation System on Gene Therapy Clinical Trial (Establishment of PMDA)
2004. 12	Amendment of Guideline for Gene Therapy Clinical Research (on Privacy protection)
~2007. 1	Total of Submitted Clinical Study Protocols in Japan : 27 (Approved : 22)

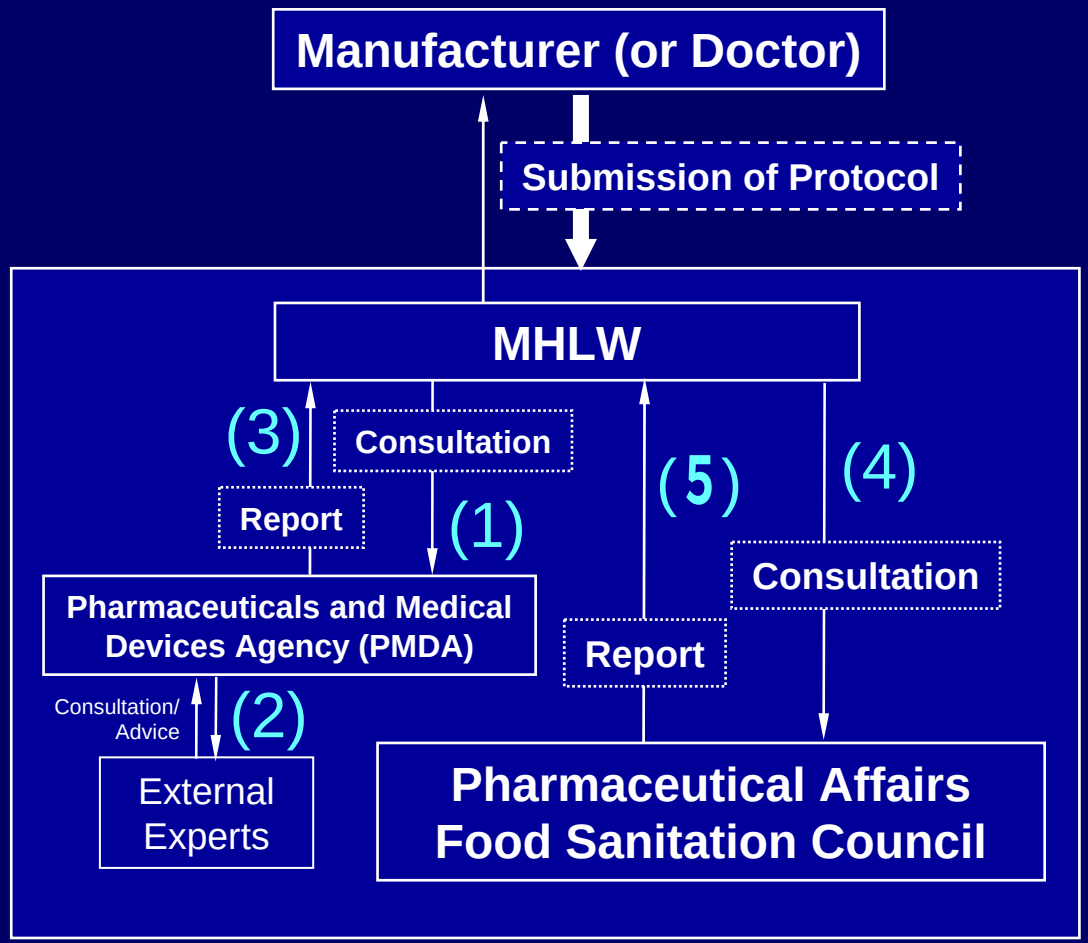
Evaluation of Clinical Study of Gene Therapy in Japan

Clinical Research



Guidelines for Gene Therapy Clinical Research

Clinical Trial under the Regulation by Pharmaceutical Law



Guidelines for Assuring the Quality and Safety of Gene Therapy Products

Summary of the Guideline for Gene Therapy Clinical Research (1)

- **Chapter 1 : General Rules**
  - **Target diseases**
    - **Serious genetic diseases or life-threatening diseases such as cancer**
    - **Diseases which seriously damage the physical function of the patients**
  - **Confirmation of Quality**
    - **Genes and related materials transferred to the patients should be manufactured in accordance with GMP**
  - **Genetical modification of human germ cells (including fertilized ovum and embryo) is prohibited**
  - **Effectiveness and safety of the research can be predicted based on sufficient scientific knowledge**

Summary of the Guideline for Gene Therapy Clinical Research (2)

- Chapter 2 : Protection of the Human Rights of Patients
  - Informed consent by document
- Chapter 3 : System of Research and Review
  - Tasks of the researchers, director, institution head, IRB
- Chapter 4 : Procedures for Conducting Clinical Research

  The director of the research should prepare a project protocol including,

  (1) The purpose, (2) Theoretical basis for the selection of the disease
  (3) Genes involved and the methods of transferring genes
  (4) Non-clinical research findings currently available
  (5) Safety evaluation from non-clinical studies
  (6) Basis for the conclusion that the research is feasible
  (7) Plan, (8) Suitability of institutions where the planned research will be conducted
  (9) Current situations of research related to the planned research
  (10) Professional records and list of publications of researchers
- Chapter 5 : Opinion of the Minister of MHLW
  - Responsibility of the Minister of MHLW
- Chapter 6 : Acts for Protection of Personal Information
- Chapter 7 : Miscellaneous Provisions

Guideline for Assuring the Quality and Safety of Gene Therapy Products

This guideline describes the major issues concerning the assurance of quality and safety of the gene therapy products and outlines the data and information to be addressed by manufacturers when filing an application with respect to the quality and safety of gene therapy products intended for clinical use.

- **Chapter 1 General provisions**
- **Chapter 2 Manufacturing process**
- **Chapter 3 Specifications and formulation**
- **Chapter 4 Stability**
- **Chapter 5 Preclinical safety studies**
- **Chapter 6 Tests for effectiveness**
- **Chapter 7 Pharmacokinetics and pharmacodynamics**
- **Chapter 8 Manufacturing facilities and equipment**
- **Chapter 9 Ethical consideration**
- **Chapter 10 Miscellaneous provisions**

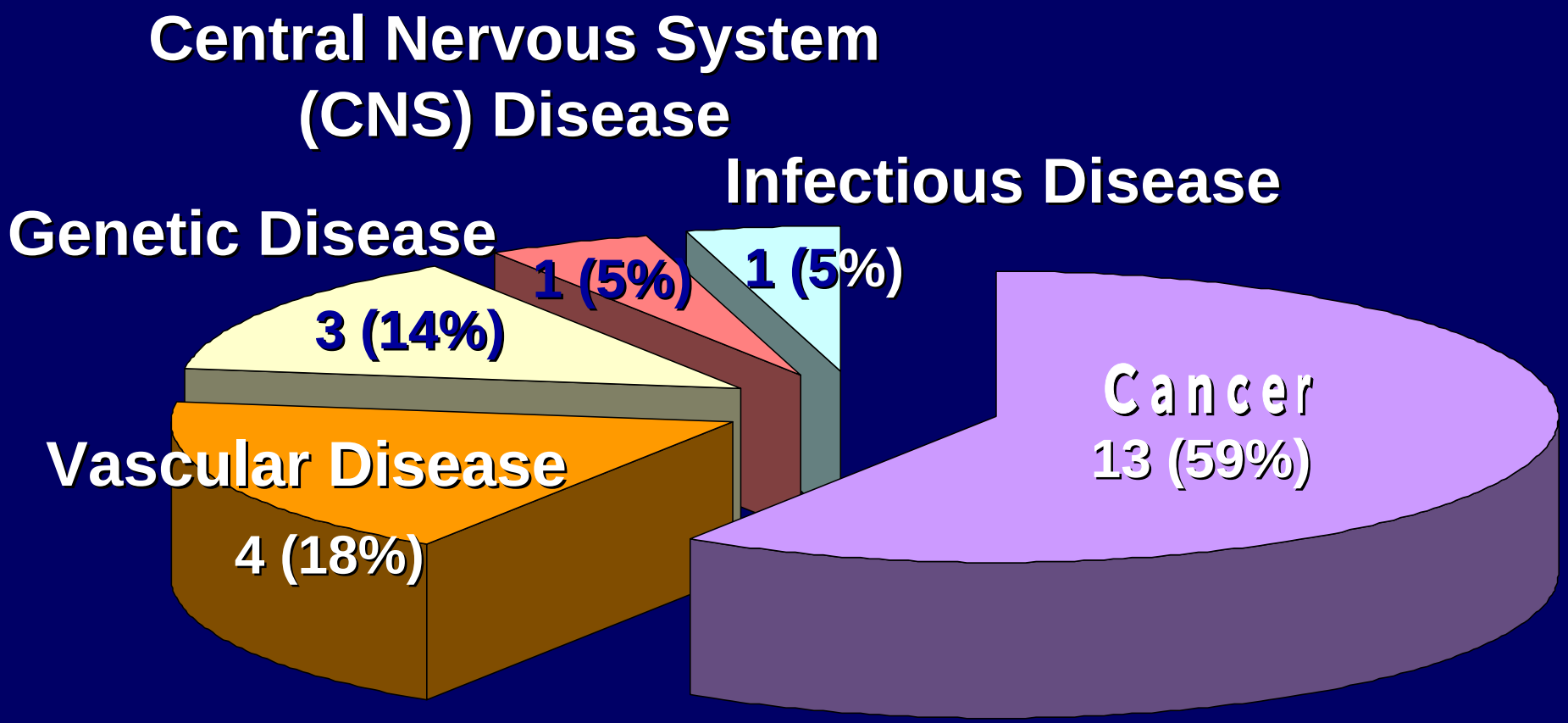
Summary of Non-clinical Test Results and Justification of the Clinical Study

- **Data from the manufacturing process to pharmacokinetics and pharmacodynamics described so far, should be summarized.**
- **It should be demonstrated that the safety of gene therapy products is adequately guaranteed based on current knowledge, and conducting the clinical study is justified from the viewpoints of quality, safety, and expected efficacy.**

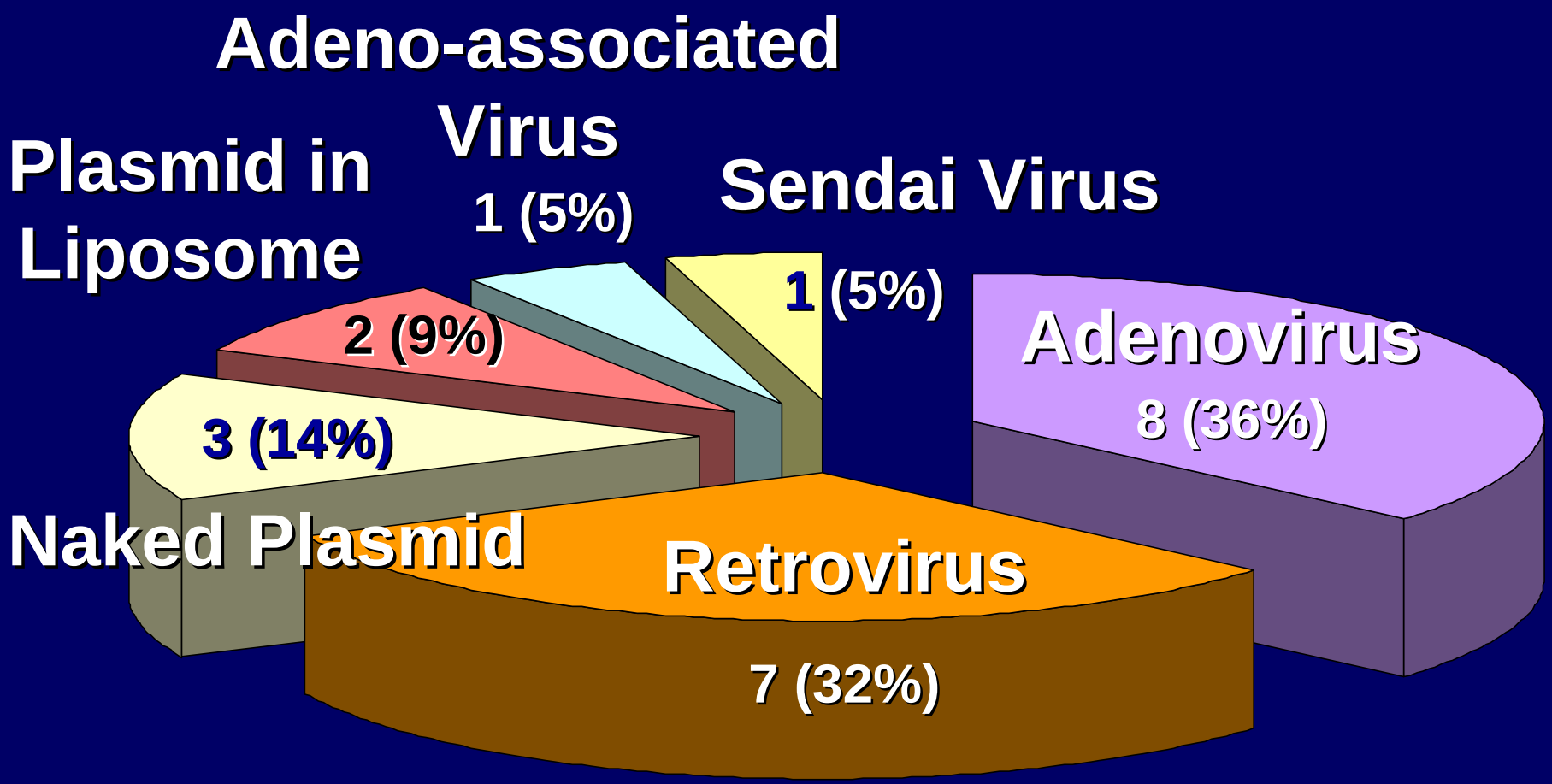
Outline of Clinical Study

- **Current knowledge about the diseases selected as indications**
- **Plan for the clinical study on gene therapy**
- **Justification of conducting gene therapy clinical study**
- **Patient selection and exclusion criteria**
- **Method of obtaining patients' consent**
- **The number of patients required for clinical evaluation and the terms of clinical study, and their rationales**
- **Methods used in the gene therapy clinical study**
- **Schedule for follow-up of patients**
- **Potential for gene transfer to persons who are not patients**

Target Diseases



Gene Delivery Systems

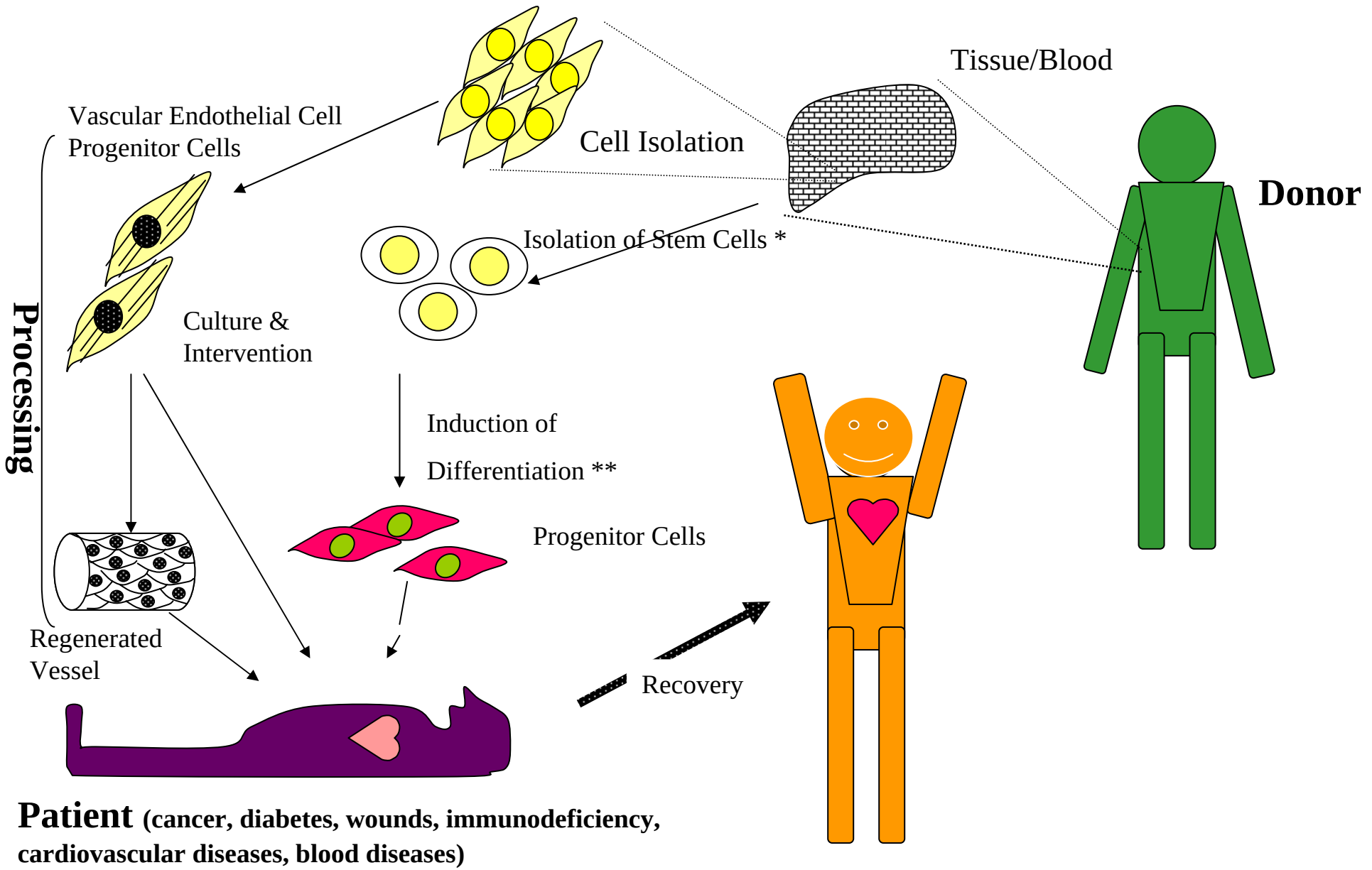


How to Promote and Move Forward

- Efficacy -

- **Development of Vector with More Efficient, Stable, and Regulatable Expression**
- **Development of Vector with Targeted Delivery**
- **Identification and Selection of Suitable Gene of Interest (GOI)**
- **Selection of Appropriate Administration Method**

Cell and Tissue-based Products



Patient **(cancer, diabetes, wounds, immunodeficiency, cardiovascular diseases, blood diseases)**

General Principles for the Handling and Use of Cell/Tissue-Based Products

- MHLW Notification No.266 (28 March 2001)

Guideline on Ensuring Quality and Safety of Products Derived from Processed Human Cell and Tissues

- MHLW Notification No.1314 (26 November 2000)

MHLW homepage
http://www.mhlw.go.jp/english/index.html

Background and Objective of “General Principles GL.”

- Concern on the spread of infectious diseases from cell/tissue-based products (to use raw materials free of infectious agents and to prevent contamination during Manufacturing Process)
- To prevent problems arising from defective products not properly manufactured or from inappropriate handling and use of products
- The objective of the guideline is to show basic requirements in handling cells/tissues and to ensure scientific and ethical validity in handling cells/tissues.

Major Elements addressed in “General Principles GL.”

- Technological requirements for securing the quality and safety of the products
- Requirements to be met by medical institutions at the cells/tissues collection stage
- Review by the IRB
- Explanation to and informed consent by the donor
- Matters relating to selection criteria and eligibility of the donor
- Ensuring the appropriateness of the cells/tissues collection process

Major Elements addressed in “General Principles GL.”

- Preparation of the cells/tissues collection record and the record storage (at least 10years)
- Storage of appropriate samples including part of the collected cells/tissues for an appropriate period
- Appropriate information supply on the products in the stage of their use
- Explanation to and consent from the patient as to product application
- Storage of samples including patients’
- Matters relating to grasping information including blood sample of patients
- Matters relating to protection of personal data

Cellar Therapy Products Evaluation Prior to Clinical Studies (by #1314 GL)

1. Qualification, Collection, Characterization and Processing of Cells/Tissues
2. Control of Manufacturing Process
3. Characteristics, Quality, and Control of Products
4. Stability of Products
5. Non-Clinical Safety Studies
6. Non-Clinical Pharmacology Studies
7. Information of Clinical Studies

Cell Therapy Products Evaluation Prior to Clinical Studies (by #1314 GL)

6. Information of Clinical Studies

- Summary of Clinical Experience if Available
- Information Regarding Target Disease
- Justification of the clinical use of the product
- Selection of Subjects
- Informed Consent
- Number of Subjects
- Treatment Procedure
- Primary and Secondary Endpoints Including Infection
- Plans for Analyses
- Records of Investigational Products
- Records of Subjects

Development of Cell Therapy Products in Japan

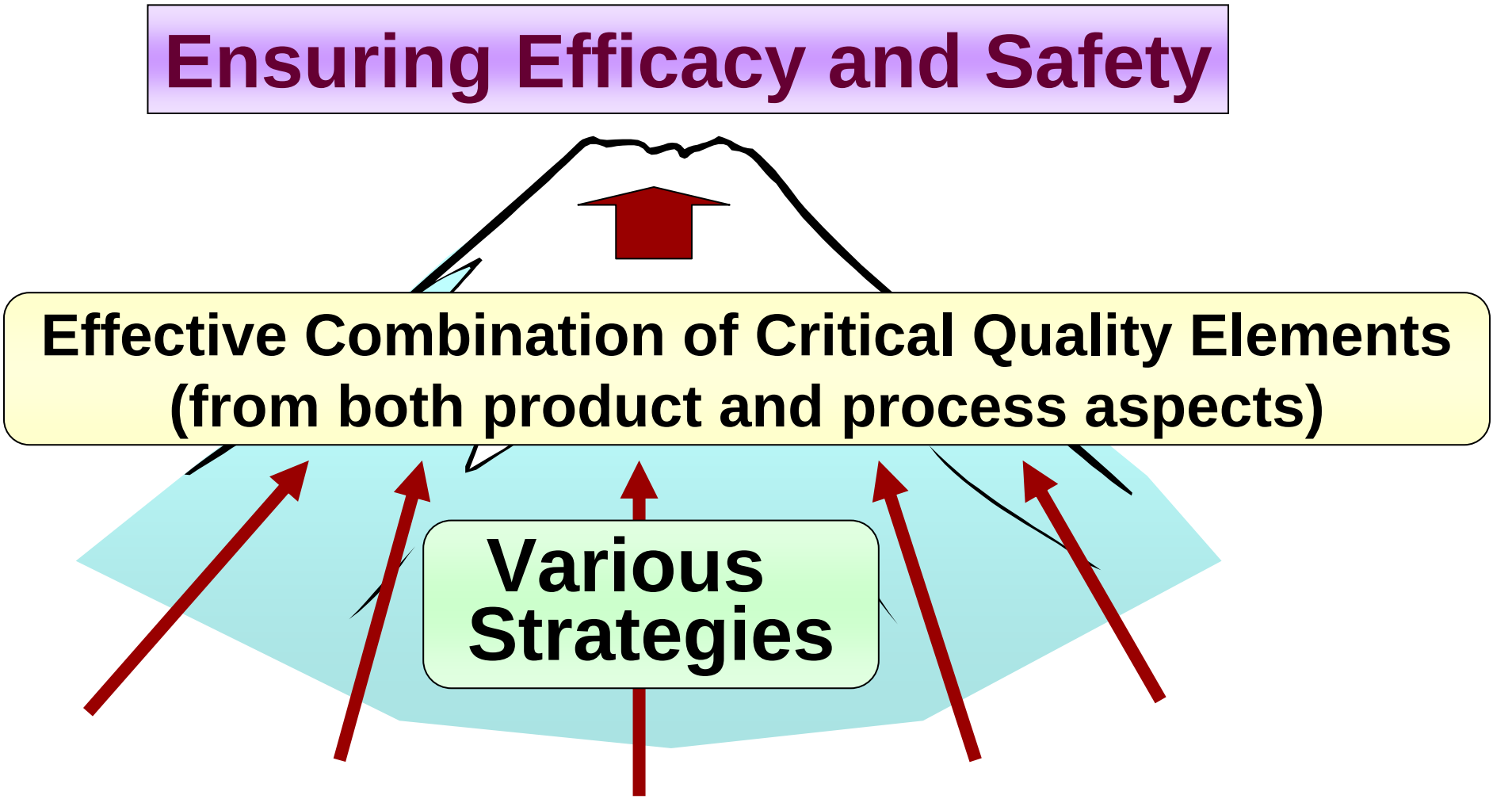
- Products have been developed
  - On review; 2
  - Evaluated; 5 (2 are discontinued)

- Products planned for clinical research; more than 200

Toward the Future

- Effective/Efficient/Flexible/Scientific Regulation depending on the Characteristics of the Product and Intended Clinical Use
- Up-dating and/or New Development of GLs
- Promotion of Novel Product Development and Application through Frequent Dialog among Regulatory Agency, Industry and Academia
- Acceleration of Review

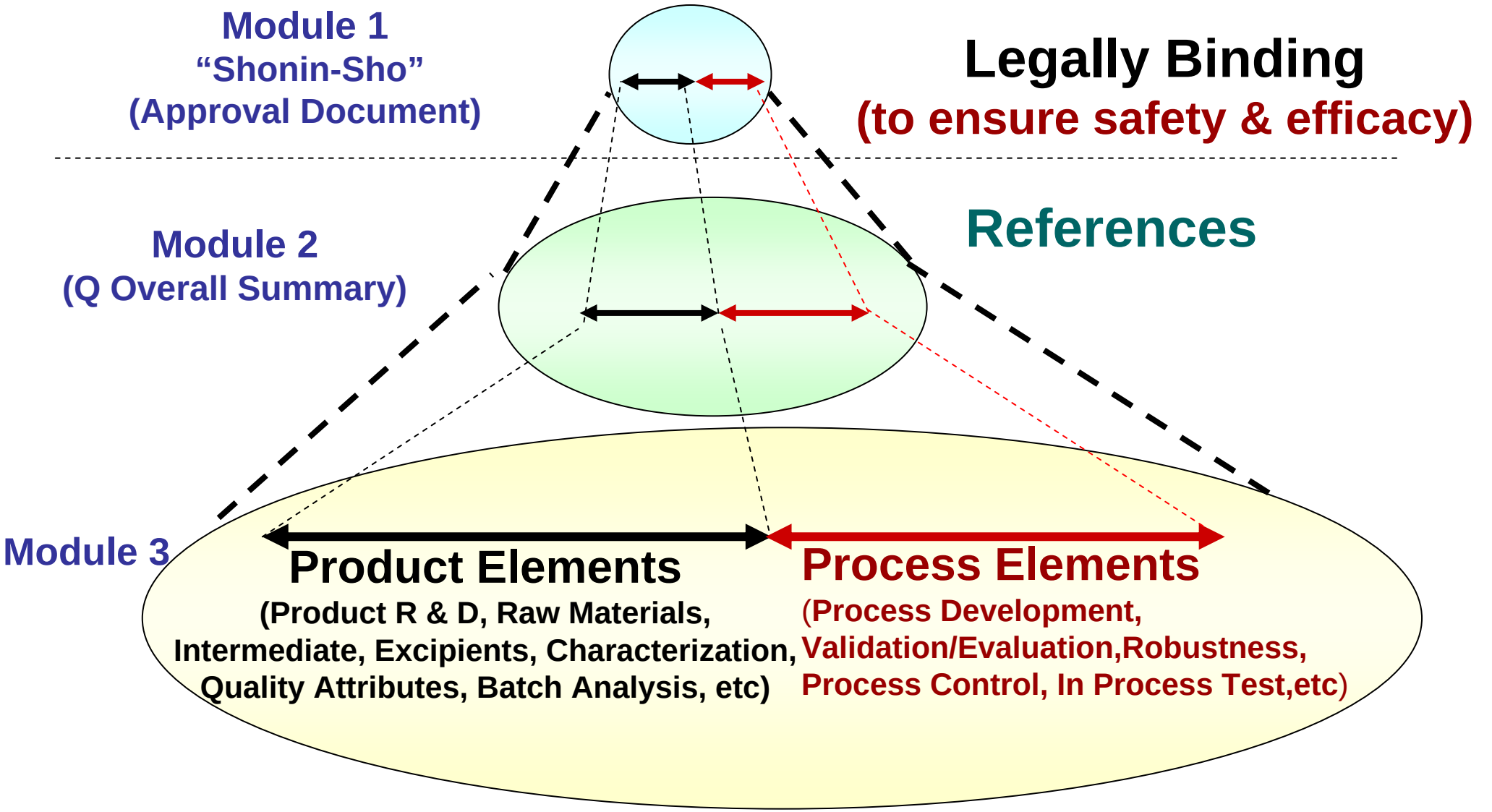
Drug's Quality is NOT for itself, but for Efficacy and Safety



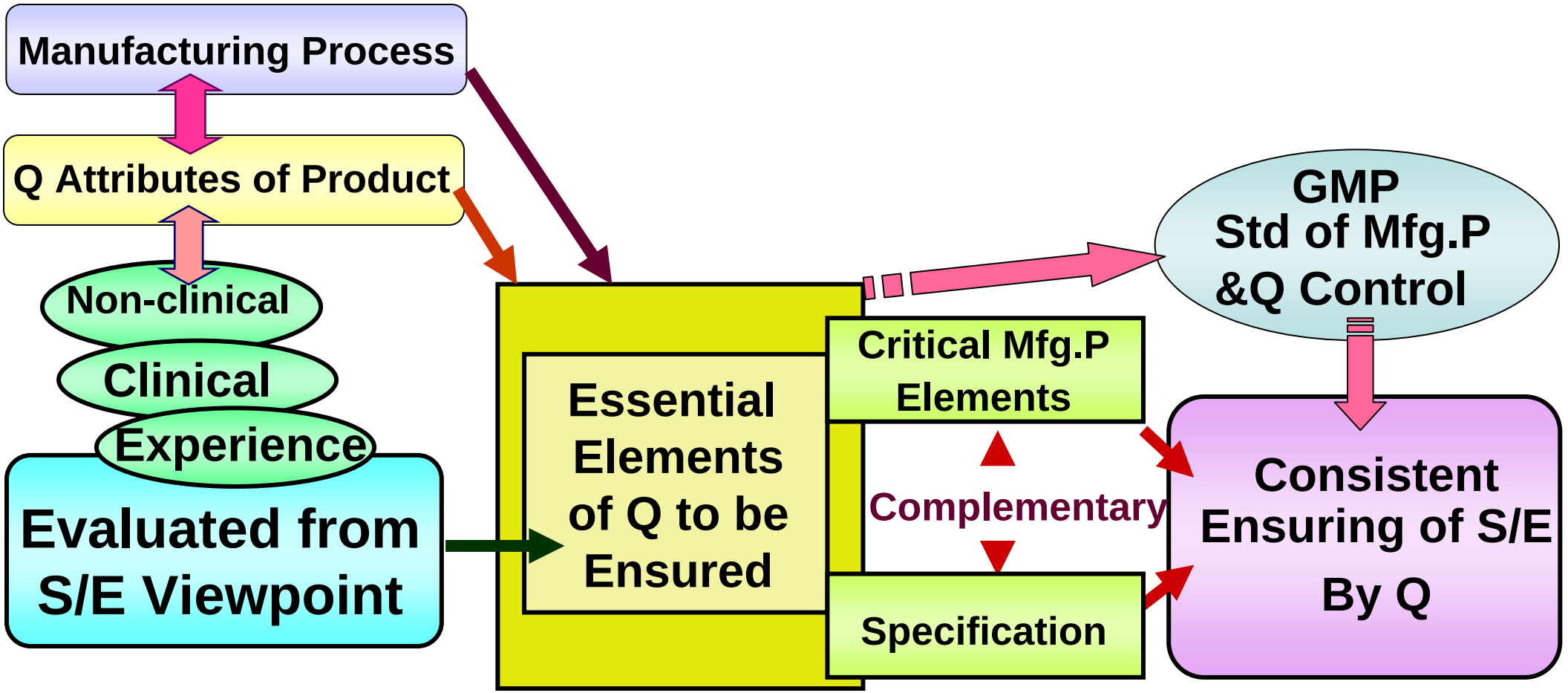
The Approach need not be a Single Path

To meet Products of different properties and to ensure their quality & consistency, the more the approaches/tools and their effective combinations are for Regulators and Manufacturers to choose from, the better.

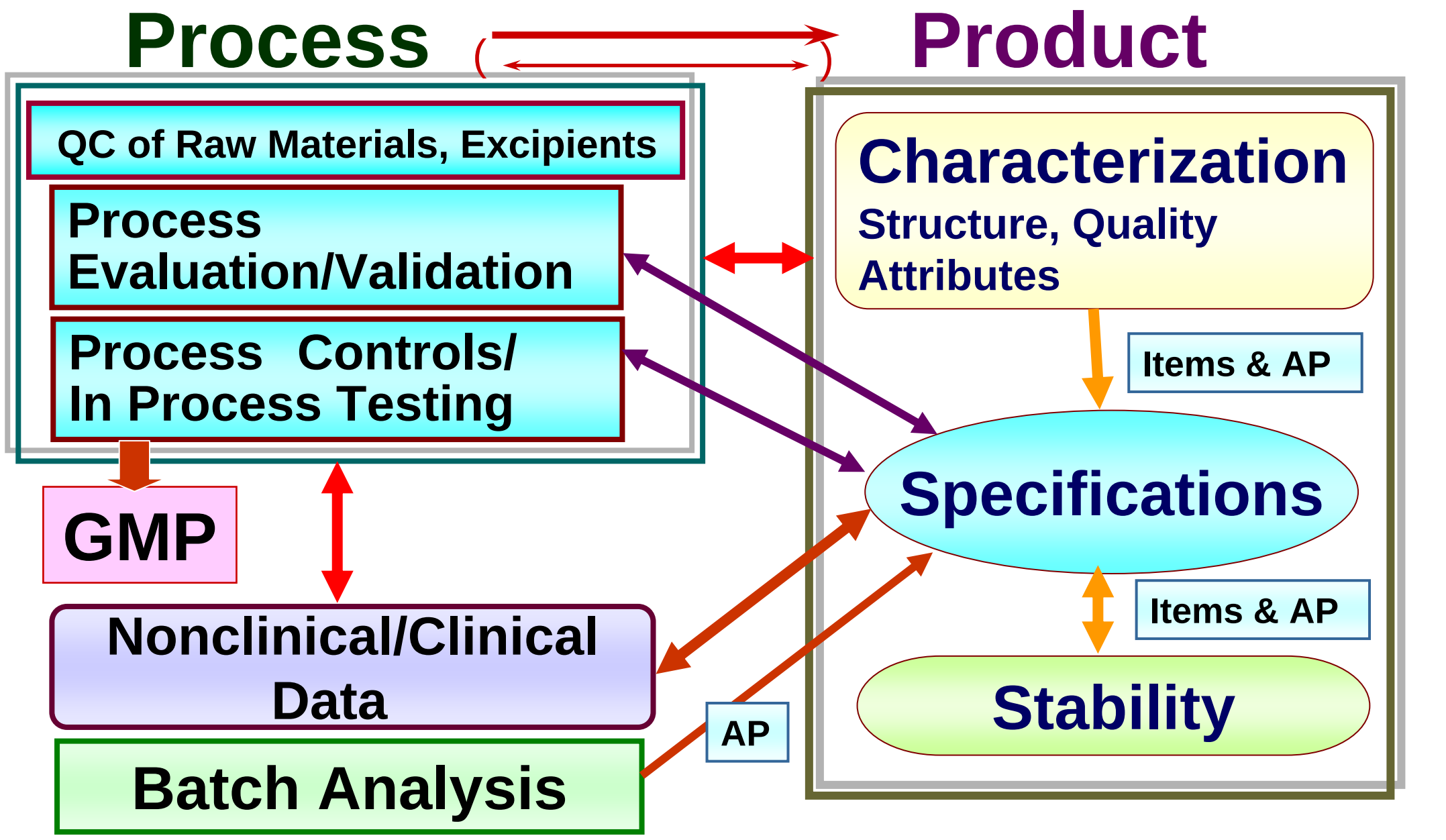
Japan's Science-Based Effective/Efficient/Flexible Quality Regulation

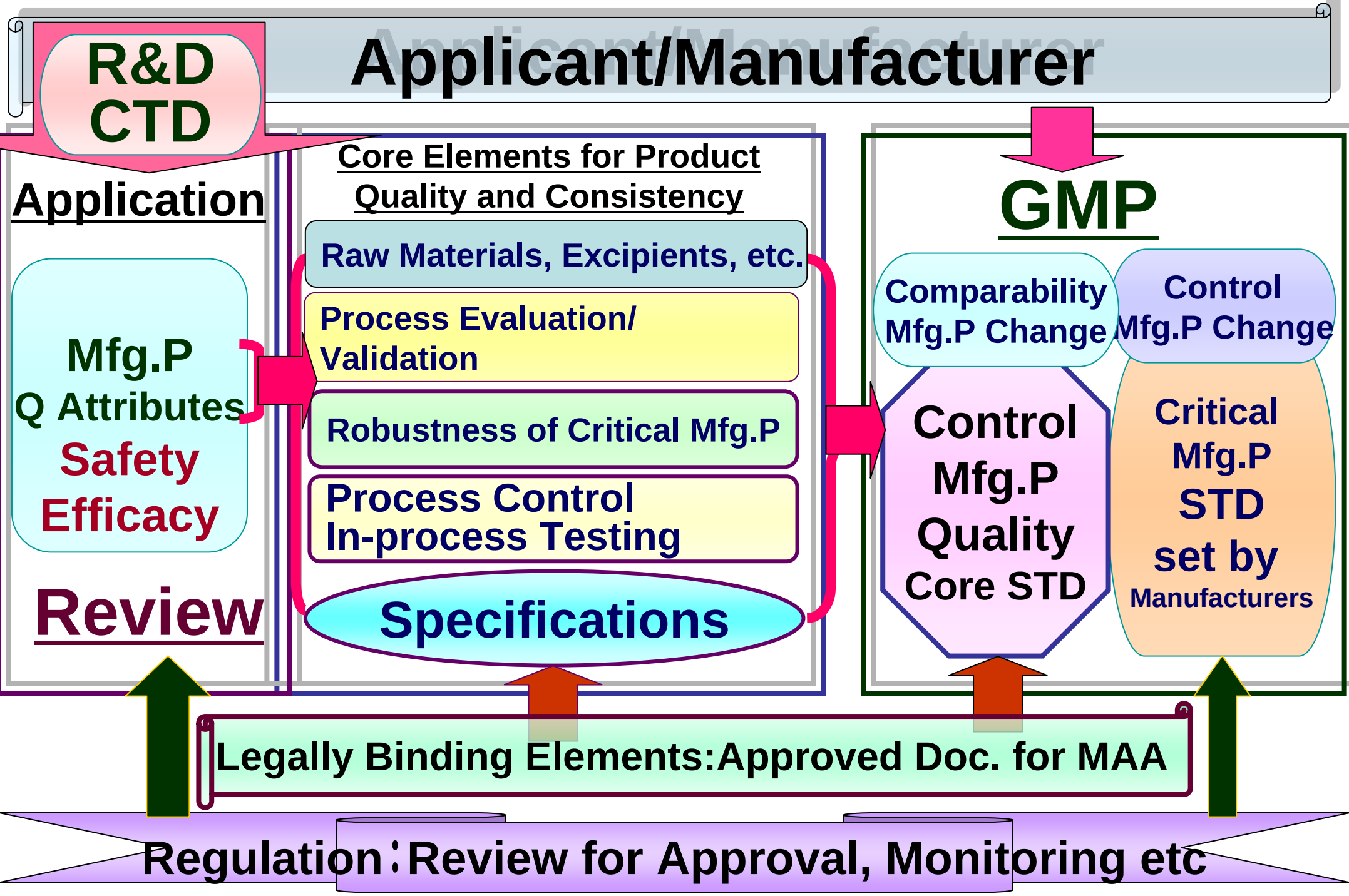


Japan's Science-Based Effective/Efficient/Flexible Quality Regulation

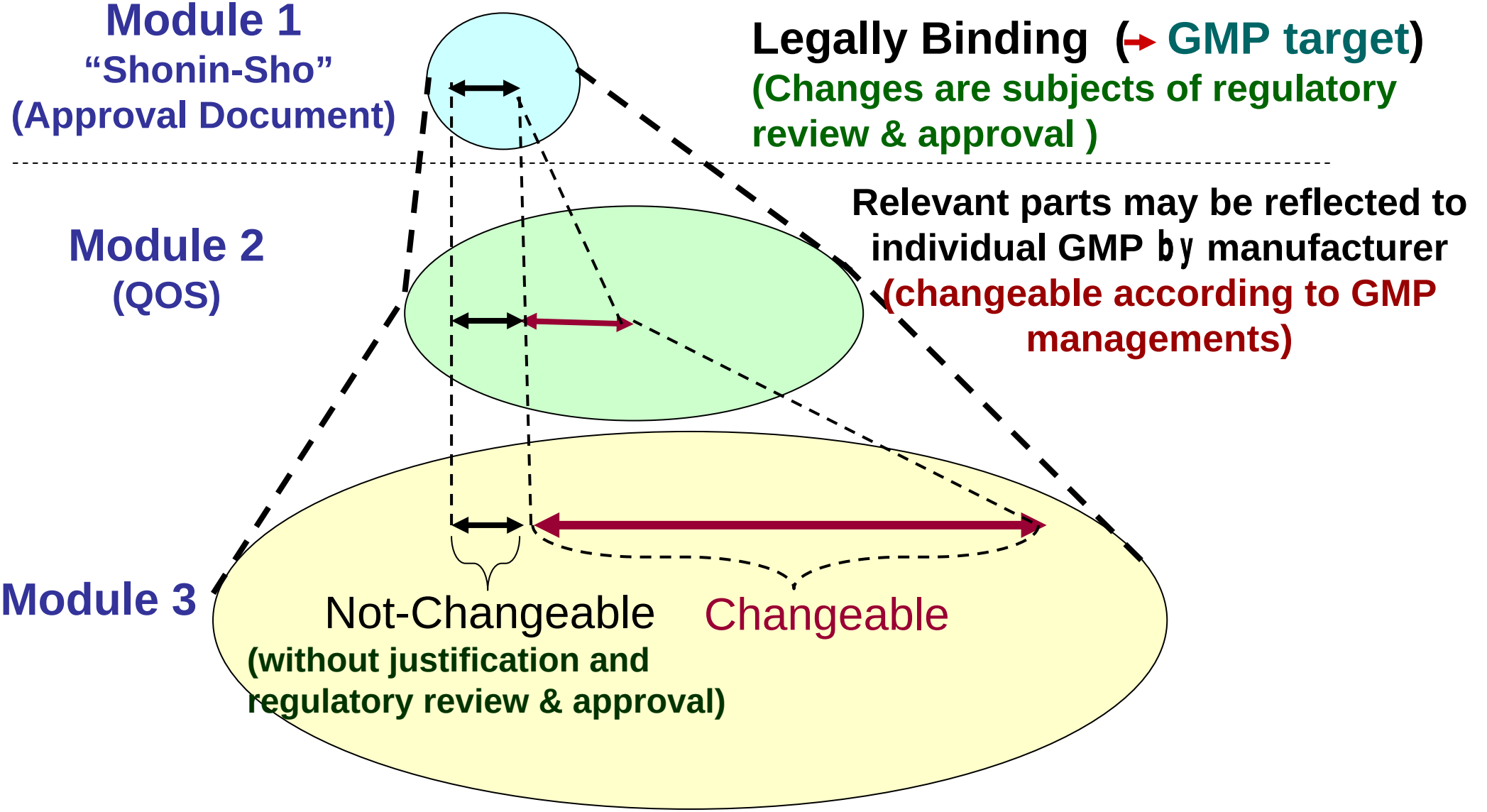


Elements for Ensuring Product Quality and Consistency

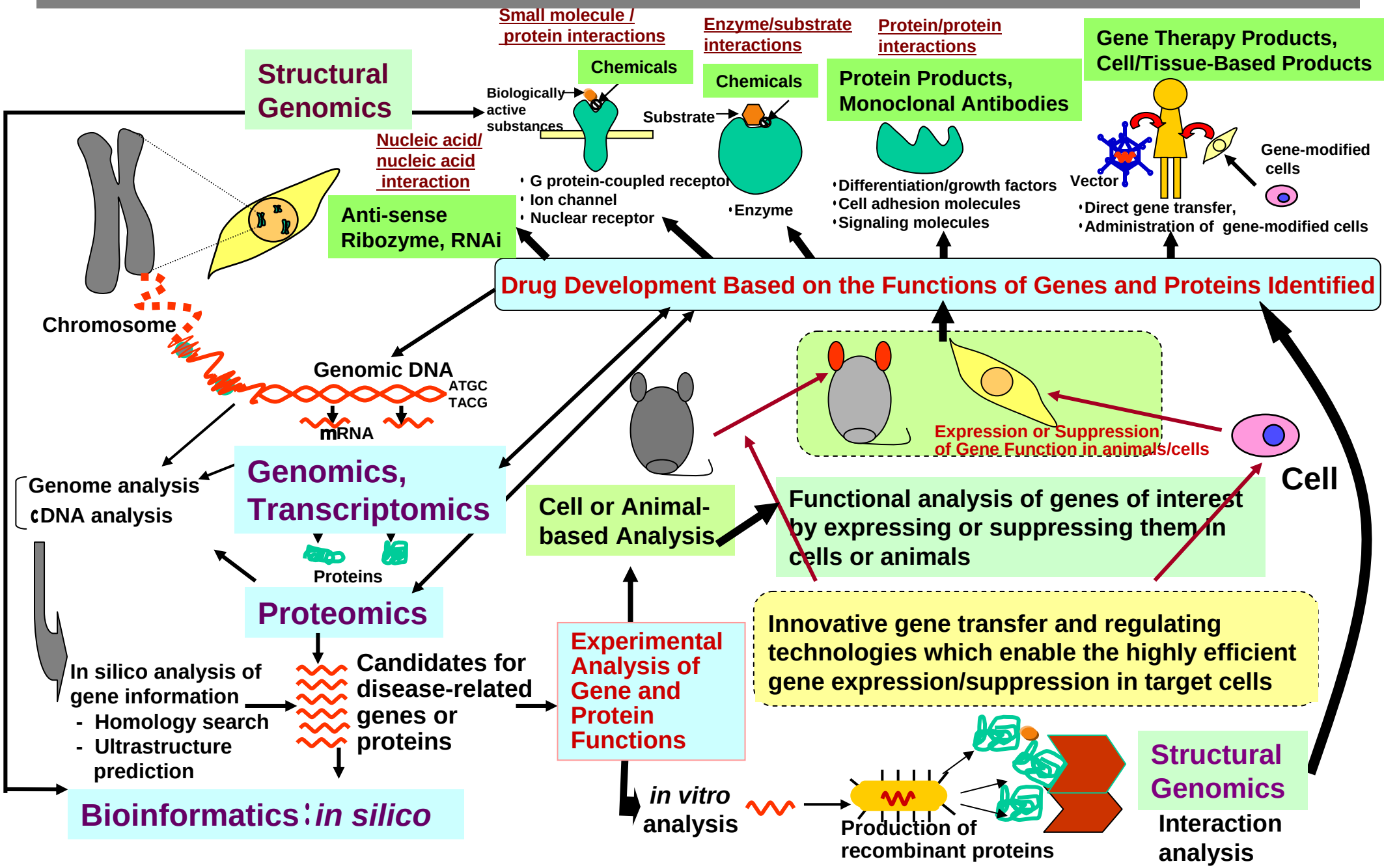



R&D
CTD
Applicant/Manufacturer
Application
Mfg.P
Q Attributes
Safety
Efficacy
Review
Core Elements for Product
Quality and Consistency
Raw Materials, Excipients, etc.
Process Evaluation/
Validation
Robustness of Critical Mfg.P
Process Control
In-process Testing
Specifications
GMP
Comparability
Mfg.P Change
Control
Mfg.P Change
Control
Mfg.P
Quality
Core STD
Critical
Mfg.P
STD
set by
Manufacturers
Legally Binding Elements:Approved Doc. for MAA
Regulation：Review for Approval, Monitoring etc

Japan's Science-Based Effective/Efficient/Flexible Quality Regulation



Development of Innovative Therapeutics and Therapies in Post-Genome Era

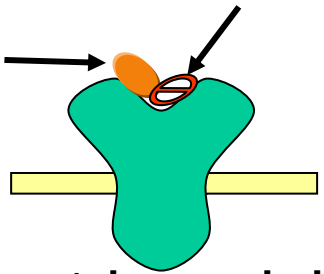


Application of Genome Information to Development of Innovative Therapeutics and Therapies

Small molecule / protein interactions

Chemicals

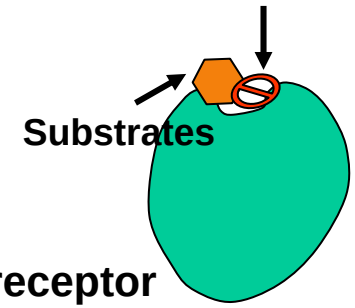
Biologically active substances



- G protein-coupled receptor
- Ion channel
- Nuclear receptor

Enzyme/substrate interactions

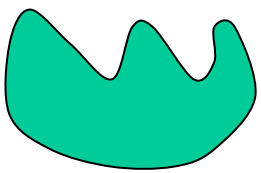
Chemicals



- Enzyme

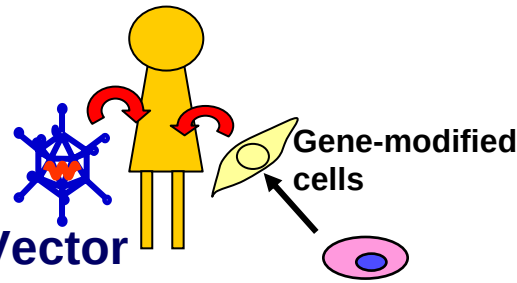
Protein/protein interactions

Protein Products, Monoclonal Antibodies



- Differentiation/ growth factors
- Cell adhesion molecules
- Signaling molecules

Gene Therapy Products, Cell/Tissue-Based Products



- Direct gene transfer,
- Administration of gene-modified cells

Nucleic acid/ nucleic acid interactions

Antisense, Ribozyme, siRNA, μRNA

Drug Development Based on the Functions of Genes and Proteins Identified

1st Stage

Exploration of new functional genes and proteins and identification/elucidation of their functions

Human full-length cDNA library

Genomics/Transcriptomics

- DNA Microarray

Proteomics

- 2D-EP, HPLC, BIAcore, MS

Bioinformatics

- *In Silico* Analysis

Structural Genomics

- NMR, X-ray, MS, *In Silico* Analysis

Experimental analysis of Gene and Protein Functions (Target Validation)

- Innovative gene transfer vectors, Gene regulation system (on/off system, siRNA, ribozyme)
- Evaluation systems based on specific cell and animal models

2nd Stage

Drug development based on the functions of genes and proteins identified

Screening, selection and optimization of drug candidates

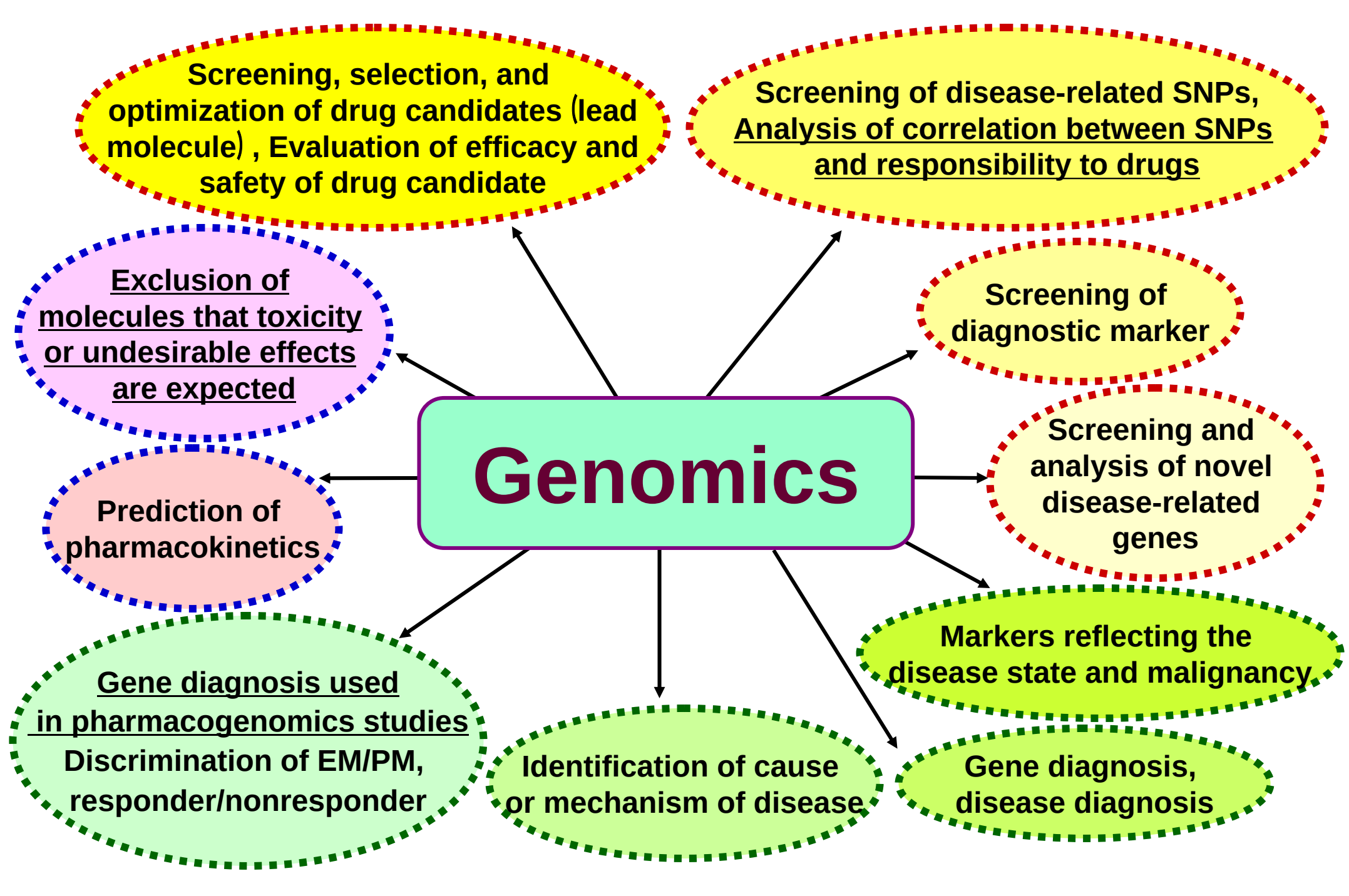
- Proteins, Genes, Cells, Nucleic acids, Small

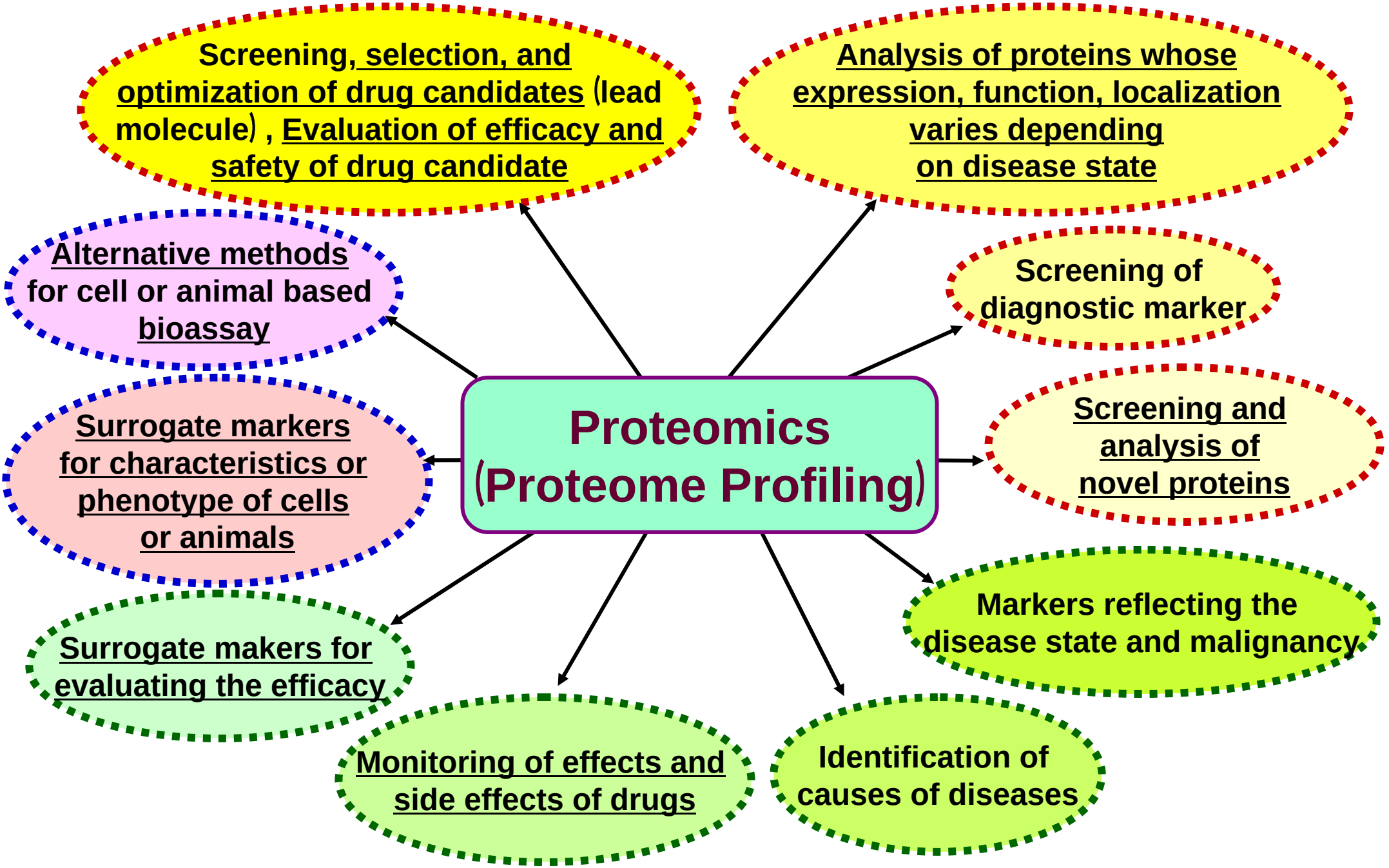
Validation of manufacturing methods of drug candidates

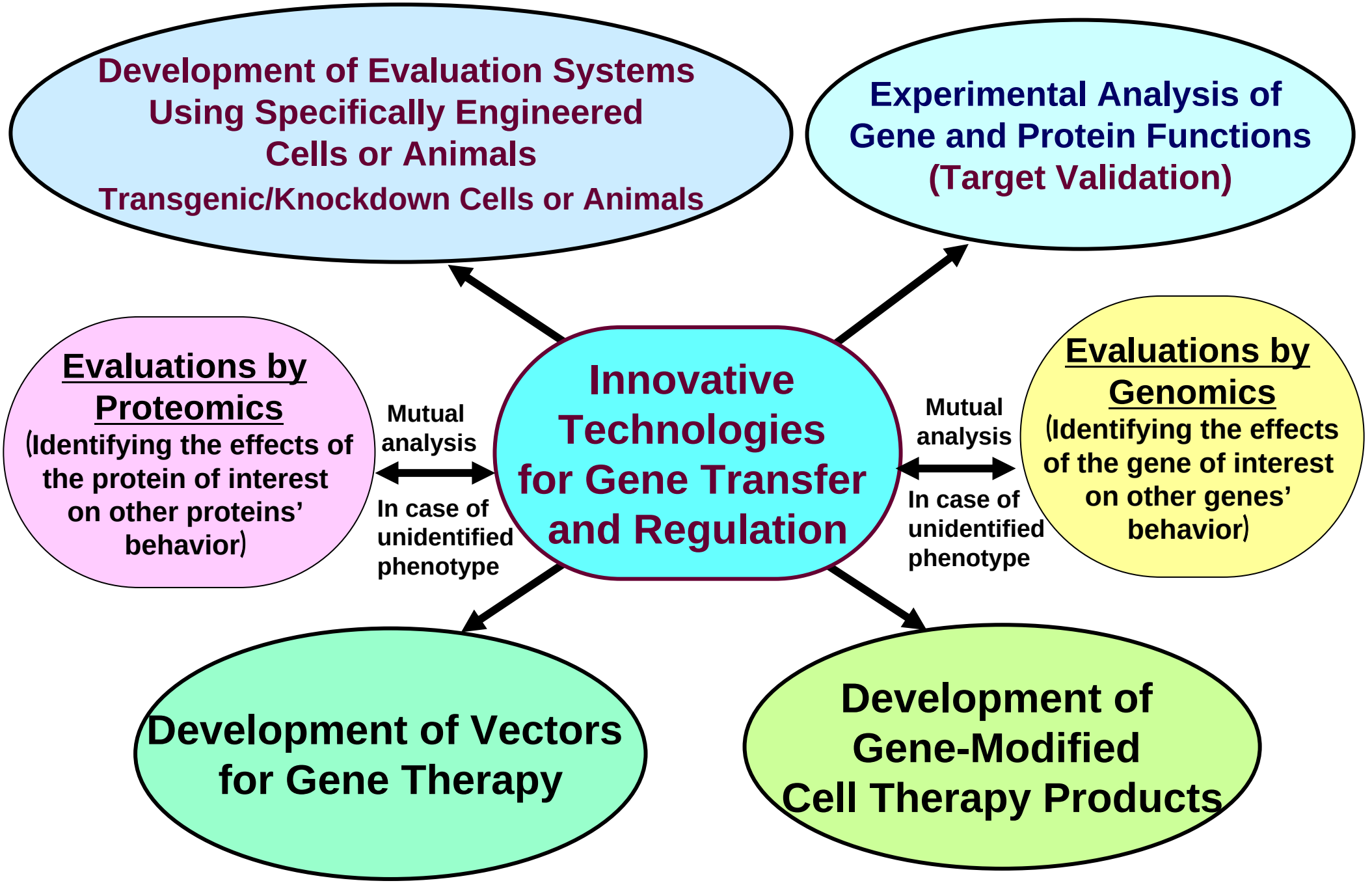
Evaluation of quality, efficacy and safety of drug candidates

- Characterization and quality evaluation of drug candidates
- General non-clinical studies (Toxicity, Pharmacodynamics, ADME)
- **Experimental analysis of functions, quality and safety of drug candidates, by using specific cell or animal models**
- **Structural Genomics**
- **Toxicogenomics, Toxicoproteomics**
- **Bioinformatics**
- **Pharmacogenomics, Pharmacoproteomics**
- Clinical Studies (including TR and Clinical Researches)

Two Stages in Development of Therapeutics in Post-Genome Era:Exploration of Target Molecules in and Procedures for Drug Development


Screening, selection, and optimization of drug candidates (lead molecule) , Evaluation of efficacy and safety of drug candidate
Screening of disease-related SNPs, Analysis of correlation between SNPs and responsibility to drugs
Exclusion of molecules that toxicity or undesirable effects are expected
Screening of diagnostic marker
Genomics
Prediction of pharmacokinetics
Screening and analysis of novel disease-related genes
Markers reflecting the disease state and malignancy
Gene diagnosis used in pharmacogenomics studies
Discrimination of EM/PM, responder/nonresponder
Identification of cause or mechanism of disease
Gene diagnosis, disease diagnosis


Proteomics
(Proteome Profiling)
Screening, selection, and optimization of drug candidates (lead molecule) , Evaluation of efficacy and safety of drug candidate
Analysis of proteins whose expression, function, localization varies depending on disease state
Alternative methods for cell or animal based bioassay
Screening of diagnostic marker
Surrogate markers for characteristics or phenotype of cells or animals
Screening and analysis of novel proteins
Surrogate makers for evaluating the efficacy
Markers reflecting the disease state and malignancy
Monitoring of effects and side effects of drugs
Identification of causes of diseases


Development of Evaluation Systems Using Specifically Engineered Cells or Animals
Transgenic/Knockdown Cells or Animals
Experimental Analysis of Gene and Protein Functions (Target Validation)
Evaluations by Proteomics
(Identifying the effects of the protein of interest on other proteins' behavior)
Mutual analysis
In case of unidentified phenotype
Innovative Technologies for Gene Transfer and Regulation
Mutual analysis
In case of unidentified phenotype
Evaluations by Genomics
(Identifying the effects of the gene of interest on other genes' behavior)
Development of Vectors for Gene Therapy
Development of Gene-Modified Cell Therapy Products

Other Approaches for Producing Novel Types of Biologicals

- Combination products (a biological used with either a therapeutic agent, or a device, or both)
- Some engineered proteins made by the combination of functional domains
- Cell/Tissue-based products derived from stem cells, committed progenitor cells, and tissues "engineered" *ex vivo*
- Cancer vaccines
- New dosage forms of biologicals including nanotechnology-based delivery systems

Combination Products

Typical combination products are various hybrids of physical and biological components, that is biological-device combination products.

Combination products areas will require new research approaches on:

- how to develop and apply regulatory standards.

Key challenging points are:

- how to characterize and evaluate each component and end product with respect to quality, safety and efficacy,
- how to evaluate or validate manufacturing processes, and
- how to ensure the consistency of processes and end products.

To make novel biologicals contribute more significantly to human health care, it is essential that suitable measures based on sound scientific principles and approaches at the time be taken by the manufacturers and control authorities to assure the quality, safety, and efficacy of these products.

Relevant aspects with respect to

- Emerging technologies
- Public concerns
- Protection of individual rights

are essential elements that must be taken into account.

- The better one understands and employs new technologies, the better one can characterize, evaluate, and control a biological product

- Understanding public concerns about novel products before they are used for human therapy could help guide the collection of specific safety data and increase the likelihood of public acceptance of an important new product

Continuous Research and Discussion are needed to develop or improve methodologies and publicly acceptable standards for characterizing, evaluating and controlling various types of biological, so that each specific type of product can be characterized, evaluated and controlled properly to correspond to its specific features, scientific progress and public concerns at the time.

Another Challenge

is the need for nondestructive techniques or techniques that use limited amounts of material as many current tests cannot be applied to precious samples (due to amount - cell therapies or type - organs) .

Infectious Contaminants

There will be significant concern about how to develop assay methodology with high sensitivity and specificity to detect infectious contaminants, and how to apply regulatory standards to manage and reduce the risks of application of biological products.

Infectious Contaminants Detection(1)

It is expected that emerging novel technologies can wipe away major safety concerns of biologicals with respect to infectious agents.

Challenges to meet for such an expectation may include:

1) rapid development of novel tests to sensitively and accurately detect new, emerging and re-emerging infectious diseases.

2) reduction of the amount of products destroyed by sampling for the ever-expanding number of individual tests.

Infectious Contaminants Detection(2)

- Detection of the genetic material of infectious pathogens in a multiplex format, using a microarray technology, would allow combined (multiplex) screening that only requires a single product sample for multiple tests viruses, transmissible spongiform encephalopathies (TSEs), and many other pathogens.

- In addition, using a multiplex microarray format, the addition of new tests for emerging infectious diseases may be simplified and licensed in an expedited fashion.

Infectious Contaminants Detection(3)

Quantitative infectivity PCR with high sensitivity can be a powerful method for detecting trace amounts of specific infectious agent.

Infectious Contaminants Detection(4)

- Proteomics: proteomic profiles can be developed to detect abnormalities in products, including the presence of known or suspected infectious agents.
- Nanotechnology: “flow through” assays can be developed to sensitively and rapidly detect the presence of low numbers of infectious virus, bacterial or fungal particles in products in “real time” without destroying product samples.

Infectious Pathogens Inactivation

The development of novel technological approaches, including methods to inactivate pathogens using chemical or physical means of selective inactivation/destruction in order to protect all biologicals from infectious pathogens, are being anticipated.

How and Where New Techniques can be utilized

It is a challenge to decide how and where new techniques such as genomics, proteomics and bioinformatics can be utilized suitably as the characterization, evaluation, control methodologies of biologicals, at various stages of research and development, during the regulatory review and approval process, or for postmarketing quality control.

For more technologically advanced regulation (1)

- More technologically advanced regulatory standards for these and other new assays need to be developed.

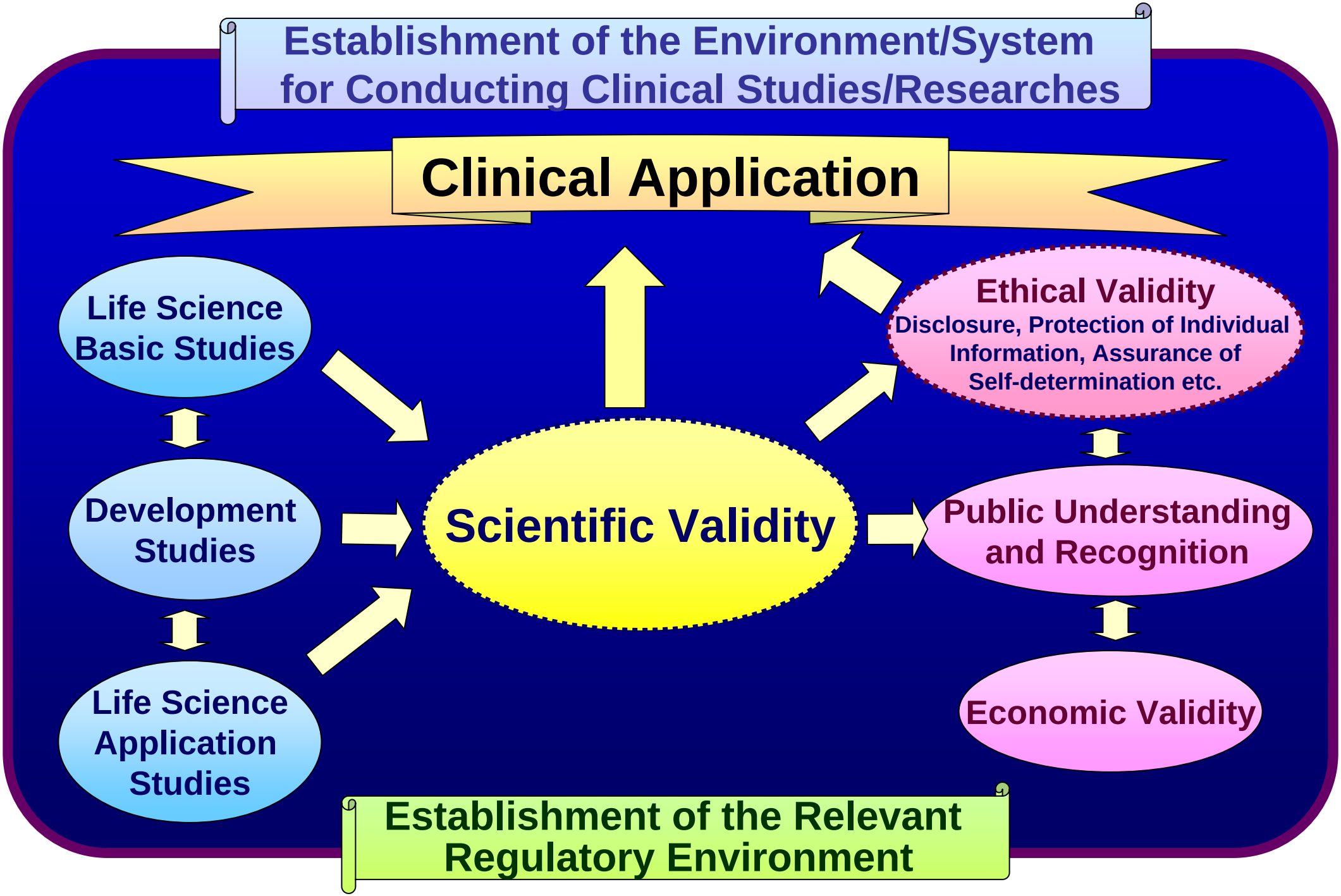
-The transition from animal models of testing to biochemical, genomic and proteomic based safety and efficacy models is also a challenging subject.

For more technologically advanced regulation (2)

In order to facilitate entry of new technology, especially, to perform science-based review for biological products developed from novel technologies, the regulatory agencies need to understand these technologies.

Translational Research：TR
（Exploratory Clinical Studies）

With many candidates for drugs obtained through exploration of new genes and proteins and their functions identified, a rapid increase is expected in the future in the number of medicinal products developed. Then, from those many candidates of medicinal products, more promising ones should be picked out more quickly and more adequately to promote efficient drug development. Here, it is very important to provide proper bridging between the basic study and the clinical study, especially an exploratory clinical study (translational research: TR).


Establishment of the Environment/System for Conducting Clinical Studies/Researches
Clinical Application
Life Science Basic Studies
Development Studies
Life Science Application Studies
Scientific Validity
Ethical Validity
Disclosure, Protection of Individual Information, Assurance of Self-determination etc.
Public Understanding and Recognition
Economic Validity
Establishment of the Relevant Regulatory Environment

Proper Way of Conducting Clinical Studies of Novel Biologics

Consider the characteristics and uniqueness in type/nature, manufacturing method, structure/composition and other molecular/quality attributes, stability, toxicity, pharmacodynamics and pharmacokinetics of each individual product

Set up objectives of the clinical study, validity of conducting the clinical study and the rationale, inclusion/exclusion criteria of subjects, procedure for explaining and obtaining informed consent, target efficacy/effects and endpoints/decision criteria, number of subjects, clinical dose and dose regimen, and route, frequency, and duration of administration

Appropriate clinical study planning according to characteristics and uniqueness of each individual product, conducting, monitoring, auditing, recording, data analysis, reporting, long-term follow-up study on incidence of infectious diseases, storage of clinical record, product record, product, and samples derived from donors and subjects, active collection of related information

Elements for Appropriate and Effective Advance in Biologics Development

- Advance in Life Science
- Development and Application of Innovative Technologies
- Establishment of System for Providing Research Sources
- Cooperation of Basic, Application, and Development Studies
- Assurance of Scientific Validity, Ethical Validity, Public Understanding and Recognition, Economic Validity, and Establishment of Relevant Regulatory Environment
- Cooperation of Industry, Academia, and Regulatory Agency
- International Collaboration and Harmonization of Relevant Regulations
- Assurance of Quality, Efficacy, and Safety
- Promotion of Translational Research
- Proper Use of Products

In Post-Genome Era, Appropriate and Effective Advance in Biologics Development Depends on How These Factors are Advanced and Applied.

There will be more products produced one after another and medical technologies that are new to medical application.

They will challenge economic validity, social understanding and recognition, and ethical validity, but there will be no answers readily available.

Therefore it will be very important for all concerned to concentrate their knowledge and efforts on the progress of medical treatment and solution of problems, unanimously aiming at prompt supply of excellent products and proper medical technologies for patients.

Though the difficulties will be enormous when challenging these issues, our endeavors should not be lessened in order to better serve the public interest and health.

Thank you very much for your attention!