Global Regulatory Considerations in the Development of Oncology Biologics Products for the Treatment of Cancer

October 29, 2008
Westin Gaslamp Quarter Hotel
San Diego, CA

www.isbtc.org

Schedule at a Glance

Wednesday, October 29

1:00 pm – 1:20 pm	**Welcome and Introductions**
1:20 pm – 2:50 pm	**US: Regulatory Considerations in Oncology Biologics Product Development**
2:50 pm – 3:15 pm	*Break*
3:15 pm – 4:25 pm	**European: Regulatory Considerations in Oncology Biologics Product Development**
4:25 pm – 5:00 pm	**Japan: Regulatory Considerations in Oncology Biologics Product Development**
5:00 pm – 5:30 pm	**Global Regulatory Considerations in Oncology Biologics Product Development**
5:30 pm – 6:30 pm	**Roundtable Discussion**
6:30 pm – 8:00 pm	*Reception*

Table of Contents

General Information

OVERVIEW

The Global Regulatory Summit was developed by the International Society for Biological Therapy of Cancer (iSBTc) to bring together the knowledge and insight of thought leaders at regulatory agencies from around the world to give a global perspective on regulatory considerations in the development of oncology biologics products for the treatment of cancer. iSBTc as a society, and in particular through its educational programming, has evolved into a premier venue for scientific exchange and collaborative interaction among investigators from academia, industry, and regulatory agencies in the U.S. and abroad with a specific focus on tumor immunology and the biological therapy of cancer.

The purpose of the Global Regulatory Summit is to provide the audience with key information from regulatory agencies from various regions of the world in oncology biologics product development. The attendees of this program will learn about and participate in the discussion of a variety of specific regulatory considerations and requirements. The presentations will address those requirements and considerations especially pertaining to product, pre-clinical and clinical trial issues for oncology biologics products.

INTENDED AUDIENCE

Attendees will include clinicians, industry representatives, government representatives, translational and basic scientists, graduate students, post-doctoral fellows, as well as other allied health professionals who are involved in clinical trials in the area of oncology biologics product development.

PROGRAM OBJECTIVES

- Discuss current regulatory requirements and guidences that are available in different regions of the world for product development for oncology
- Discuss global regulatory considerations for product, pre-clinical and clinical trial design and analysis issues for oncology biologics
- Discuss the latest clinical developments regarding application of biologic approaches and establish dialogue between academia, various government regulatory bodies, and industry regarding global implications and future direction of oncology biologics development
- Promote scientific exchange of most recent advances and data in the biological treatment of cancer, as well as advances in basic cancer biology with relevance for anti-tumor immunity

EXPECTED OUTCOMES

- Learn about regulatory oversight in different parts of the world including the differences and similarities in regulatory approach in various countries
- Learn key regulatory and scientific issues related to product, pre-clinical and clinical design and analysis in oncology product development
- Learn about the new and existing polices and guidelines from various World Regulatory Agencies
- Learn about opportunities to participate in U.S. government's oncology biomarker qualification initiative

General Information (continued)

PROGRAM CONTENT

- US FDA will discuss 1) key regulatory considerations for product development for oncology biologics and how to avoid clinical holds of IND; 2) regulatory considerations for pre-clinical studies; and 3) clinical trial design and analysis for oncology biologics
- European Medicines Agency (EMEA) will address 1) how the EMEA and National Authorities cooperate; 2)new regulations for Advanced therapy Medicinal Products; and 3) how the Advanced Therapy Regulation will be implemented in the EMEA
- Paul-Ehrlich-Institute will address 1) the latest EU guideline developments for Advanced Therapies; 2) risk-based approach for product development; and 3) clinical trials with Advanced Therapies and cancer vaccines in Germany
- Canada, Japan, India, China and Switzerland will address regulatory pathways for oncology biologics product development in their countries. In addition, representatives will answer any specific questions pertaining to existing or new regulatory polices from their region
- Panel discussion with organizers, faculty, program organizers and other invited representatives for international regulatory agencies. This will include questions posed by the faculty, brief statements from invited representatives and time for audience questions

EVALUATION FORM

Please take a moment to fill out an evaluation form and return to one of the marked Survey Return boxes or to iSBTc Staff at the Registration Desk. Your feedback is important to us.

Program Schedule

Wednesday, October 29

1:00 pm – 1:20 pm **Welcome and Introductions** (Program Organizers)
Raj K. Puri, MD, PhD – US Food and Drug Administration, CBER
Ulrich Kalinke, PhD – Paul-Ehrlich-Institut; TWINCORE – Centre for Experimental and Clinical Infection Research, Germany

1:20 pm – 2:50 pm **United States: Regulatory Considerations in Oncology Biologics Product Development**

1:20 pm FDA: Chemistry, Manufacturing, and Controls (CMC) Issues for Investigational New Drugs (IND)
Keith Wonnacott, PhD – US Food and Drug Administration, CBER

1:50 pm FDA: Perspectives on the Preclinical Evaluation of Biological Therapies for Cancer
Yongjie Zhou, MD, PhD – US Food and Drug Administration, CBER

2:20 pm Introduction to FDA Drug and Biologic Review Process
Ke Liu, MD, PhD – US Food and Drug Administration, CBER

2:50 pm – 3:15 pm *Refreshment Break*

3:15 pm – 4:25 pm **European Regulatory Considerations in Oncology Biologics Product Development**

3:15 pm European Medicines Agency: New Regulation for Advanced Therapies Including Oncology Biological Products
Patrick Celis, PhD – European Medicines Agency

3:50 pm Paul-Ehrlich-Institut: Considerations in Product Development with Advanced Therapies and Cancer Vaccines
Thomas Hinz, PhD – Paul-Ehrlich-Institut, Germany

4:25 pm – 5:00 pm **Japan: Regulatory Considerations in Oncology Biologics Product Development**
Cancer Vaccines and Immunotherapy Regulation
Masatoshi Narita – Pharmaceuticals and Medical Devices Agency, Japan

5:00 pm – 5:30 pm **Global Regulatory Considerations in Oncology Biologics Product Development**

5:00 pm *Gina Coleman, MD – Health Canada*
5:06 pm *Bindu Dey, PhD – Department of Biotechnology, Government of India*
5:12 pm *Luo Jianhui, MD – Center for Drug Evaluation, SFDA, P.R. China*
5:18 pm *Andreas Marti, PD, PhD – Swissmedic, Swiss Agency for Therapeutic Products*
5:24 pm *Samir Khleif, MD – National Cancer Institute*

5:30 pm – 6:30 pm **Roundtable Discussion**
Moderators:
Raj K. Puri, MD, PhD
Ulrich Kalinke, PhD

Panelists:

Ashok M. Batra, MD	*Luo Jianhui, MD*	*Masatoshi Narita*
Patrick Celis, PhD	*Koji Kawakami, MD, PhD*	*Keith Wonnacott, PhD*
Gina Coleman, MD	*Samir Khleif, MD*	*Yongjie Zhou, MD, PhD*
Bindu Dey, PhD	*Ke Liu, MD, PhD*	
Thomas Hinz, PhD	*Andreas Marti, PD, PhD*	

6:30 pm – 8:00 pm **Reception**
Open to all program faculty and registered attendees

Faculty

Organizing Committee

Ulrich Kalinke, PhD
Paul-Ehrlich-Institute
TWINCORE – Centre for Experimental and Clinical Infection Research

Raj Puri, MD, PhD
US Food and Drug Administration, CBER

Faculty

Ashok M. Batra, MD
US Food and Drug Administration, CBER

Patrick Celis, PhD
European Medicines Agency

Gina Coleman, MD
Health Canada

Bindu Dey, PhD
Department of Biotechnology, Government of India

Thomas Hinz, PhD
Paul-Ehrlich-Institut, Germany

Luo Jianhui, MD
Center for Drug Evaluation, SFDA, P.R. China

Koji Kawakami, MD, PhD
Japan Science and Technology Agency

Samir Khleif, MD
National Cancer Institute

Ke Liu, MD, PhD
US Food and Drug Administration, CBER

Andreas Marti, PD, PhD
Swissmedic, Swiss Agency for Therapeutic Products

Masatoshi Narita
Pharmaceuticals and Medical Devices Agency, Japan

Keith Wonnacott, PhD
US Food and Drug Administration, CBER

Yongjie Zhou, MD, PhD
US Food and Drug Administration, CBER

Presentation Abstracts

FDA: Chemistry, Manufacturing and Controls (CMC) Issues for Investigational New Drugs (IND)
Keith Wonnacott, PhD
Chief, Cellular Therapies Branch, CBER, FDA

In the United States, biological therapies for cancer are medical products regulated by the U.S. Food and Drug Administration. Clinical research using these therapies in the United States must be conducted under an Investigational New Drug (IND) application. The IND process is guided by Federal regulations, primarily published in the Code of Federal Regulations (CFR) Title 21 Part 312. The major objectives of the FDA during the review of an IND application for early phase clinical studies are to assure the safety and rights of the subjects who participate in the clinical trials. In addition, for later phase studies, FDA must ensure that the clinical trials are adequately designed and controlled to allow an evaluation of the product's safety and effectiveness [21 CFR 312.22 (a)].

One element of any IND review by FDA is the chemistry, manufacturing and controls. This talk will introduce some of the essential elements of CMC expectations as outlined in the US regulations. It will provide an overview of regulations referred to collectively as good manufacturing practices (GMPs) as well as related guidance provided by the FDA. This talk will also discuss potential challenges of and provide insight into developing a clinical manufacturing process for cancer vaccines and immunotherapies.

Presentation Abstracts

FDA Perspective on the Preclinical Evaluation of Biological Therapies for Cancer

Yongjie Zhou MD, PhD
Pharmacology/Toxicology Reviewer, Division of Clinical Evaluation and Pharmacology/Toxicology, Office of Cellular, Tissue & Gene Therapies, Center for Biologics Evaluation and Research, The United States Food and Drug Administration (US FDA)

The administration of investigational biological therapies in clinical trials for cancer must be conducted under an Investigational New Drug (IND) application. The conduct of these trials is guided by the Code of Federal Regulations (CFR) Title 21, Part 312. According to 21 CFR 312.23 (a)(8), adequate information derived from pharmacology and toxicology studies is needed in order to support a conclusion that the trial is reasonably safe and scientifically feasible to conduct. Biological therapies for the treatment of cancer include diverse and complex products such as antigen-based, cell-based and gene-based products. In addition, many of these therapies are administered in combination with other therapeutic modalities, such as adjuvants, immunomodulators, chemotherapeutic agents, and radiation. The design of preclinical pharmacology and toxicology studies that are sufficiently adequate to guide in the design of the clinical trial can thus be challenging. In addition, toxicology studies intended to support licensure of an investigational product should be conducted in compliance with Good Laboratory Practice (GLP), as defined in 21 CFR 58. This presentation will provide an overview of FDA's current practice in the preclinical development of oncology biologics, as well as discuss potential regulatory and scientific challenges in designing preclinical studies to assess the safety and activity of these diverse products.

Presentation Abstracts

Introduction to US FDA Review and Approval Process for Oncologic Biologics

Ke Liu, MD, PhD
Clinical Oncology Team Leader, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA)

Oncologic biologics are reviewed and approved according to US laws and regulations. Biological products are approved under the authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. § 262). Licensing of biological products is regulated under 21 CFR 600-601 and requires that the products meet standards designed to ensure "continued safety, purity, and potency" of the products. *Potency* is interpreted to include effectiveness (21 CFR 600.3(s)). Development of Investigational oncologic biologics is regulated under 21 CFR 312 (IND regulations) as well.

There are two types of approval: regular (full) approval and accelerated approval, based on the primary endpoint for which the biologic has demonstrated the treatment effect on direct clinical benefits to patients such as prolongation of life or alleviation of symptoms. Accelerated approvals are granted, among other criteria, if the product has a treatment effect on a surrogate endpoint (other than survival or irreversible morbidity) that is reasonably likely to predict clinical benefit; and fulfils post-marketing commitment to verify and describe its clinical benefit. In both types of approvals, there usually are other post marketing commitments to further demonstrate the safety of the products.

Presentation Abstracts

EMEA: New Regulations for "Advanced Therapies" including Oncology Biological Products
Patrick Celis, PhD
Scientific Administrator, European Medicines Agency (EMEA), UK

The European Medicines Agency (EMEA) is responsible for the evaluation of applications for marketing authorisation for medicinal products, resulting in license which is valid for the entire European Union (EU). EMEA is not responsible for the authorisation of clinical trial applications: this remains the responsibility of the EU member state where the trial is conducted.

For some medicines, such as biotechnology derived products and cell/gene therapies, the centralised authorisation procedure via the EMEA is mandatory, for other products the centralised procedure is optional. Since November 2005, the centralised procedure has become mandatory for all new medicines indicated for the treatment of cancer.

Within the centralised procedure, applicants of medicines for the treatment of seriously debilitating or life-treating diseases (such as cancer treatment) can apply for a conditional marketing authorisation. This will allow for flexibility at the level of clinical package to be included in the application. Additionally, accelerated assessment could be granted for medicinal products expected to be of major public health interest.

New legislation has recently been put in place in the EU for Advanced Therapy Medicinal Products (Regulation 1394/2007), setting the requirements and standards for the authorisation gene and cell based medicinal products and tissue engineered products, and establishing a new scientific committee within the EMEA, the Committee for Advanced Therapy Medicinal Products. This new legislation, which will come in force on 30 December 2008, will offer further incentives and opportunity for companies developing Cell- and Gene therapy based cancer therapeutics.

Presentation Abstracts

Paul-Ehrlich-Institute: Considerations in Product Development with Advanced Therapies and Cancer Vaccines

Thomas Hinz, PhD
Head of Section Therapeutic Vaccines, Paul Ehrlich Institute, Germany

Many of the currently developed oncology biological products fall into the group of Advanced Therapies that have to be licensed by the European Medicines Agency (EMEA). After EMEA licensing these products can be marketed in all EU Member States. Nevertheless, clinical trial authorization of Advanced Therapies and of medicinal products in general is the sole responsibility of individual EU Member States where the trials are being conducted.

Advanced Therapies constitute cell-based products, gene therapy and tissue engineered products. Cell-based cancer therapeutics such as adoptive T cell transfer, dendritic cells, modified PBMC, NK cells as well as gene therapy approaches are therefore classified as Advanced Therapies in the EU.

A new guideline has been developed in the EU that addresses manufacturing and quality control, preclinical and clinical aspects for the development of Advanced Therapies. An overarching principle of this "Guideline on human cell-based medicinal products" is the development of cell-based products along a risk-based approach. Moreover, a scientific guideline on "Potency testing of cell based immunotherapy medicinal products for the treatment of cancer" has been developed.

The principles of potency testing of cell-based cancer vaccines and dedicated manufacturing/quality issues and preclinical topics of the above mentioned guidance documents will be discussed.

Presentation Abstracts

Japan: Regulatory Considerations in Oncology Biologics Product Development

Masatoshi Narita
Pharmaceuticals and Medical Devices Agency

Several types of biological products for cancer are eventually being developed in Japan. Some monoclonal antibodies and immunotherapy products have been approved in last several years. Some gene therapy products, cell therapy products and cancer vaccines are now in the process of pre-clinical and clinical development. Cancer vaccines may include DNA vaccines, peptide vaccines, attenuated viral vaccines, genetically modified viral vaccines and so on. Currently there are no guidelines for cancer vaccines or immunotherapy. However, there are general guidelines for biological products in Japan. For instance, in order to initiate clinical trials with genetically modified viral vaccines and cell based therapy products, pre-INDs should be submitted according to "Guidelines for Assuring the Quality and Safety of Gene Therapy Products" and "Guidelines for Assuring the Quality and Safety of Cell/Tissue based Products". Clinical evaluation of medicines for cancer therapy will be reviewed under "Guidelines for Clinical Evaluation of Anti-cancer Drugs" which was revised in 2005. However, we are concerned that we need some sort of viewpoints (PTC) when we assess the efficacy and safety of new types of biological products, specifically for cancer vaccines and immunotherapy products. In this session, I will like to explain Japanese review system of medicines and the developments of biological products for cancer.

Presentation Abstracts

Regulatory Considerations for Oncology Biologics Development in Canada
Gina Coleman, MD
Health Canada

In Canada biologics are regulated under the Food and Drugs Act and Regulations. The Biologics and Genetic Therapies Directorate, a part of Health Canada, is the regulatory authority responsible for working to ensure the safety, efficacy, and quality of all biologics for human use marketed in Canada.

To market a biologic in Canada, a manufacturer requires an establishment licence as well as a product authorization (Notice of Compliance). To receive an NOC the sponsor must submit scientific evidence that its product is safe, efficacious and of suitable quality. This information can be obtained through human clinical trials in other countries, or in Canada. Reviews of clinical and chemistry & manufacturing data are carried out by a team review process involving practicing physicians, scientists as well as technical staff. Regulatory review of oncology biologics is unique in Canada because emphasis is placed equally on not just paper review but also on laboratory lot testing as well as on-site evaluations to inform more completely regulatory decision making.

If the conclusion is that the benefits of the product outweigh its risks and the risks can be mitigated, then the biologic is issued a Drug Identification Number (DIN) and a Notice of Compliance (NOC) indicating approval for sale in Canada.

Biologics are placed on a lot release schedule tailored to their potential risk and manufacturing, testing and inspection history to date.

Health Canada monitors biologic adverse events, investigates complaints and problem reports, maintains post approval surveillance, manages recalls as required, and conducts regular inspections of certain biologic production sites.

Health Canada's Special Access Programme allows access to drugs that are unavailable for sale in Canada. This access is limited to patients with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable, or are unavailable.

Presentation Abstracts

Regulatory scene on Cancer Biologics in India

Bindu Dey, Ph.D
Adviser, DBT, India

There are several drivers to development, clinical testing and licensing of bio-pharmaceuticals in India. Though there are no specific regulations on "Cancer Biologics" per se in India, most bio-pharmaceutical industrial Research & Development is oriented towards: **either** making cost-effective treatments for domestic use **or** for meeting the requirements of the regulated and non-regulated markets abroad. The Patent Act, India, 1970 followed **process patent** encouraging domestic industry towards generics boom. The biotechnology product and processes developments necessitated incorporation of bio-safety regulations. The Environmental Protection Act, 1989 introduced a three-tier system: firstly at the institutional level (R & D); secondly at the Department of Biotechnology level (Pre-clinical) and thirdly at the level of the Ministry of Environment (Clinical and commercialization). The clinical trials approval and licensing rights rest with the Drugs Controller General of India (DCGI). Hence, **multiple approvals** are required. The archival Drugs and Cosmetics Act, 1940 regulated the approval system, both for indigenous as well as imported drugs promulgating the essential data required for doing various phases of the clinical trials and/or introducing a product. However, global trials and the expiring patents on biotechnological products resulted into modification in Schedule Y of the Drugs and Cosmetic Act, so as to meet global requirements on quality of the product. While, there are only a few Investigational New Drugs in "biologics sector" in the India, most Indian Pharmaceutical and Bio-pharmaceutical companies are following "USFDA guidelines for IND" for generating pre-clinical and clinical data for bio-similars, with a hope that US would soon follow EMEA for having the guidelines on bio-similars. Progress is evident on stem-cell and DC-based immuno-therapy but there are no distinct guidelines. Recently, the political wisdom has insisted on single-window approvals for biologics. Hence, a National Bio-technology Regulatory Authority (NBRA) is on anvil.

Presentation Abstracts

Center for Drug Evaluation, SFDA
Luo Jianhui, MD
Office for Biological Products, Division V, Center for Drug Evaluation, SFDA, P.R.China

Advanced therapy such as gene therapy, cell therapy are regulated by SFDA in China according to drug registration regulation. Therapeutical vaccine, oncolytical virus, cell therapy give rise new hope to cancer patient and yet arise great challenge to regulatory agency. We would like to take this opportunity to discuss on Clinical efficacy and safety evaluation issues, giving the cancer vaccine for example, immune response usually takes time before showing reaction, not to say the clinical efficacy, should we wait and see? Can we afford the disease progress and lost treatment opportunity? How to consider individual variation of immune response in cancer patient?

In addition, cancer patient is a very special population because death threat exists, many issues including disease progress and treatments changes may arise due to different clinical practice, confronted with such uncertainty or inconsistency, how to evaluate individual factor and their contribution to the final results?

As reviewer and evaluator of clinical trail and BLA application, CDE is closely following up the progress of this new field, we received several clinical trail application of such products both from domestic and internationally recent years, each application is dealt with case by case and go through meeting discussion by expert committee. We hope to have paradigm or draft guideline available international on development of biologics for cancer therapy.

Presentation Abstracts

Regulation of Oncology Biologics in Switzerland

Andreas Marti, PD, PhD
Swissmedic, The Swiss Agency for Therapeutic Products

Based on The Swiss Law on Therapeutic Products that came into force January 2002, Swissmedic approves all therapeutic products in Switzerland ranging from synthetically synthesized molecules and biologically produced medicinal products to medical devices. Marketing approvals of oncology biologics include products consisting of recombinant proteins and monoclonal antibodies. No cancer vaccine, gene therapy product or cell-based product has so far been approved for the market in Switzerland. Oncology Biologics can often profit from an accelerated review procedure, based on the severity of the indication and the innovative nature of the product. Swissmedic procedures and activities supporting the development of therapeutic products include the development of national guidelines (e. g. with respect to orphan indications), the participation in expert groups drafting globally relevant guidelines (e. g. ICH Guidelines), the arrangement of pre-submission meetings and scientific advice meetings with applicants and the organization of scientific/regulatory meetings at the national and international level. Since July 2007 a new Swiss Law on Transplantation came into force regulating cell- and tissue-based products, now collectively defined as transplantation products. The requirements for the approval of transplantation products will be very similar to the requirements for advanced therapy products as described in the EU.

FDA: Chemistry, Manufacturing, and Controls (CMC) Issues for Investigational New Drugs (IND)

Keith Wonnacott, PhD

U.S. Food and Drug Administration
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

ISBTC Global Regulatory Summit October 29, 2008

US FDA: CMC Issues for INDs

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US Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Cellular, Tissue, and Gene Therapies

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Basis for regulation of INDs

- **Statutes: THE LAW --- passed by Congress and signed by the President**
  - 42 USC 262 (United States Code)
- **Regulations: details of the law --- written by the Agency and approved by the Executive Branch**
  - 21 CFR 312 (Code of Federal Regulations)
- **Guidance: the Agency's interpretation of the Regulations --- written and approved within the Agency**
  - 68 FR 49488 (Federal Register)

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Drug and Biologics Law

1902 Biologics Control Act authorizes regulations to ensure purity and safety of serums, vaccines, and similar products

1938 Food, Drug, and Cosmetic Act required new drugs to be shown safe before marketing. It also authorized factory inspections and other provisions.

1944 PHS Act incorporates provisions for biologics regulation. Outlines licensing requirements that are independent from pre-marketing requirements for drugs.

1962 FD&C Act Amendments required drug manufacturers to prove the effectiveness of their products before marketing them and allowed FDA to regulate investigational studies.

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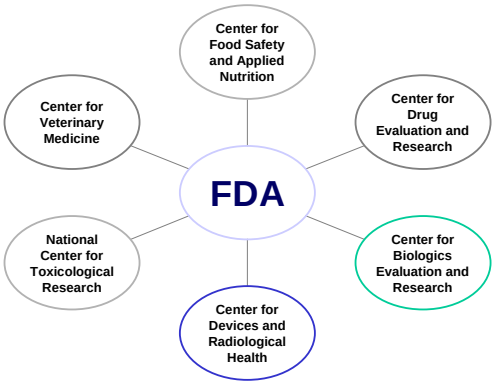

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Premarket approval pathways

- **Biologics**
  - BLA – Biologics License Application
- **Drugs**
  - NDA – New Drug Application
  - ANDA – Abbreviated New Drug Application
- **Devices**
  - PMA – Premarketing Application
  - HDE – Humanitarian Device Exemption
- **Combination products**

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Drug and Biologics Marketing Regulations

- **21 CFR parts 210, 211, 225, & 226**
  - Good manufacturing practices for drugs and biologics
- **21 CFR parts 600, 601, & 610**
  - Biological products regulations
- **21 CFR parts 201, 202, 203, 314**
  - Prescription drug regulations
- **21 CFR part 25**
  - Environmental impact considerations

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Investigational studies

- **Biologics**
  - IND – Investigational New Drug application
- **Drugs**
  - IND – Investigational New Drug application
- **Devices**
  - IDE – Investigational Device Exemption
- **Combination products**

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Regulations For INDs

21 CFR 312
Investigational New Drug Application

National Archives and Records Administration
code of federal regulations

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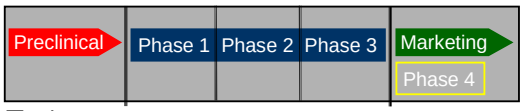
What are the phases of investigation?



- ☒ Phase I: Designed to evaluate safety and side effects
- ☒ Phase II: Designed to evaluate safety and explore efficacy and dose ranging
- ☒ Phase III: Expanded study designed to obtain efficacy and safety data for approval
- ☒ Phase IV: Post marketing commitments to monitor safety and efficacy

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What are the elements of an IND application?

☐	Form FDA 1571	21 CFR 312.23(a)(1)
☐	Table of Contents	21 CFR 312.23(a)(2)
☐	Introductory statement and general investigational plan	21 CFR 312.23(a)(3)
☐	Investigator's brochure	21 CFR 312.23(a)(5)
☐	Protocols	21 CFR 312.23(a)(6)
☐	Chemistry, manufacturing, and control data	21 CFR 312.23(a)(7)
☐	Pharmacology and toxicology data	21 CFR 312.23(a)(8)
☐	Previous human experience	21 CFR 312.23(a)(9)
☐	Additional information	21 CFR 312.23(a)(10)

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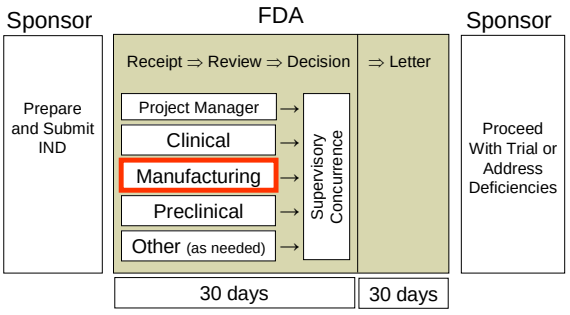
Initial IND Review Process



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IND Review criteria

- **Clinical Hold Criteria (21 CFR 312.42)**
  - Risks are unreasonable and significant
  - Investigators not qualified
  - Investigator brochure false or misleading
  - Insufficient information to assess risk
  - Gender exclusion for a condition that occurs in both men and women

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CMC Information for INDs: Starting material

- **Choose an appropriate starting material**
  - Appropriate screening and testing of donors
    - See DE rule and guidance
  - Perform all required testing on your cell bank
    - Sterility, mycoplasma, viral testing (in vivo, in vitro, specific viruses)
    - Identity testing (species origin, markers, activity, purity, etc)
    - Stability (maintain desired activity upon thaw and passage)
    - Propagation, containers, labeling, storage
- **Ensure that your starting material is consistent**
  - Make sure your cell line is stable
  - Account for and determine how to control individual patient variability

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CMC Information for INDs: Manufacturing

- **Choose and qualify your reagents**
  - Ensure that reagents will perform as desired in the manufacturing process
  - Ensure clinical quality reagents (safety, purity, potency/activity)
  - Document reagent quality (in-house testing or COA)
- **Establish adequate facility and equipment performance standards and monitoring plans**

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CMC Information for INDs:
Manufacturing process

- **Choose a robust manufacturing process**
  - Establish standard operating procedures (SOPs)
  - Establish batch records
- **Qualify your facilities**
- **Do performance runs to ensure process consistency**
- **Establish procedures to prevent:**
  - Product mix-ups
  - Product cross-contamination
- **Ensure process safety**
  - Qualify procedure for killing of tumorigenic cells
  - Validate viral clearance methods

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CMC Information for INDs:
Product quality testing

- **In-process testing**
  - Design to assess process and product quality
- **Final product testing**
  - Perform on the final product, not intermediate
  - Establish proper specifications
    - Ensure the safety and consistency of product lots
    - Base acceptance criteria on experience
    - Determine the criteria for acceptable product
    - Should agree with current FDA standards

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CMC Information for INDs:
Other

- **Include a plan for post infusion sterility failure:**
  - Notification of physician and patient.
  - Identification and sensitivity testing of the microbial contaminant.
  - Description of additional patient monitoring that will be conducted as a result of the event.
  - Investigation and potential corrective action
  - Reporting of the incident to the IRB and FDA
- **Have a quality assurance program**
- **Provide stability data to justify storage and holding times**
- **Make sure cross-references are accurate and relevant**

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Common Cell and Gene Therapy IND Deficiencies

- **Analysis of FDA comments in ~100 Clinical Hold Letters issued 2002-2005**
- **Cytotherapy. 2008;10(3):312-6**
  - INDs Submitted To FDA That Are Placed On Clinical Hold: Experience of the Office of Cellular, Tissue, and Gene Therapies. Keith Wonnacott, Deborah Lavoie, Robert Fiorentino, Maritza McIntyre, Ying Huang, Steven Hirschfeld.

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Summary

- **FDA regulates both investigational and marketing applications**
- **Information about the process in US is contained in regulations and guidance documents**
- **Detailed manufacturing information is needed during product development**
- **Communicate with the FDA throughout your product development**

U.S. Food and Drug Administration
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Contact Information

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FDA: Perspective on the Preclinical Evaluation of Biological Therapies for Cancer

Yongjie Zhou, MD, PhD

Slides available on page 134 as part of the addendum

NOTES

NOTES

NOTES

Introduction to FDA Drug and Biologic Review Process

Ke Liu, MD, PhD

Introduction to FDA Drug and Biologic Review Process

Ke Liu, MD, PhD

Office of Cellular, Tissue and Gene Therapies
CBER, FDA

iSBTc Global Regulatory Summit
October 29, 2008

1

Outline

- **Regulatory background**
  - US Laws and FDA Regulations
  - History of Regulation
- **Review and Approval process**
- **Clinical Trial Review Process**

2

Basis for Regulation

- Statutes: **THE LAW (Act) --- passed by Congress and signed by the President**
  - USC (United States Code)
- Regulations: **Detail interpretation of the law --- written by the Agency and approved by the Executive Branch**
  - CFR (Code of Federal Regulations)
- Guidance: **Issued by individual agencies to reflect current thinking, not binding**.

3

Legal Requirement for Approval

- **Accurate and adequate label**
  - **Food and Drug Act (1906)**
- **Safety**
  - **Food, Drug and Cosmetic Act (FDC Act) (1938)**
- **Effectiveness**
  - **FDC Act amended 1968**

4

History of US Drug and Biologic Regulations

5

Biologics Control Act

1901 13 children in St. Louis died of tetanus after receiving diphtheria antitoxin from a horse named Jim.

9 children die of tetanus from contaminated smallpox vaccine

1902 Biologics Control Act authorizes Hygienic Laboratory to issue regulations to ensure purity and safety of serums, vaccines, and similar products

1944 PHS Act incorporates provisions for biologics regulation. Outlines licensing requirements that are independent from pre-marketing requirements for drugs.

1973 Blood, blood products, and allergenics included in the PHS Act

7

Food and Drug Act

1905 Samuel Hopkins Adams published "The Great American Fraud," a commentary on the patent medicine industry exposing cure-all claims for worthless and dangerous patent medicines.

Upton Sinclair publishes "The Jungle" with shocking disclosures of insanitary conditions in meat-packing plants.

1906 Food and Drug Act prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs.

8

Food, Drug, and Cosmetic Act

1937 **Sulfanilamide elixir containing diethylene glycol killed 107 people**

1938 Food, Drug, and Cosmetic Act required new drugs to be shown safe before marketing **— starting a new system of drug regulation. It also authorized factory inspections and other provisions.**

9

Kefauver-Harris Amendments

1962 Thalidomide, a new sleeping pill, was found to have caused birth defects in thousands of babies born in western Europe. Over two million pills distributed in the United States for investigational studies.

1962 Kefauver-Harris Drug Amendments passed to ensure drug **efficacy** and greater drug safety. It required drug manufacturers to prove the **effectiveness** of their products before marketing them, gave FDA control over drug advertising, and allowed FDA to regulate investigational studies.

10

A new biologic, drug, or device may not be entered into interstate commerce unless:

- **It is approved by the FDA as safe and effective**
  (biological license application [BLA], new drug application [NDA], pre-market approval [PMA], or other marketing approval)

OR …

- **An IND (Investigational New Drug Application) is in effect**
  (exempting the study from the premarketing approval requirements that are otherwise applicable)

11

Laws affecting FDA

- More than 20 Statutes affecting FDA
- Two main Laws concerning human drugs and biologicals
  - Food, Drug, and Cosmetic Act (FD&C Act), United States Code (U.S.C.) Title 21, Chapter 9 (enacted in 1938)
  - Public Health Service Act (enacted in 1944), United States Code (U.S.C.) Title 42, Chapter 6A Part F - Licensing of Biological Products and Clinical Laboratories

12

Food, Drug, and Cosmetic Act (FD&C Act)

- Enacted in 1938 and amended in 1968
  - foods are pure and wholesome, safe to eat, and produced under sanitary conditions
  - drugs and medical devices are **safe and effective** for their intended uses. This includes drugs used in medicated feeds for animals.
  - cosmetics are safe and properly labeled.
  - packaging and **labeling** of these products is truthful and informative.
- Amended 20 times (latest: August, 2004)

13

Major amendments for FD&C Act

- Orphan Drug Act (Jan. 4, 1983)
- Prescription Drug User Fee Act (PDUFA) of 1992
- Safe Medical Devices Act of 1990
- Food and Drug Administration Modernization Act (FDAMA) of 1997
- Medical Device User Fee and Modernization Act

14

Public Health Service Act

- United States Code (U.S.C.) Title 42, Chapter 6A Part F - Licensing of Biological Products and Clinical Laboratories
  - The Secretary shall approve a biologics license application on the basis of a demonstration that the **biological product** that is the subject of the application is **safe, pure, and potent**

15

Public Health Service Act

• "Biological product" defined in this section, the term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, 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.

16

Regulations on Drug Approval

- 21 CFR 314.126
  - –Determination of **substantial evidence** to support the claims of **effectiveness** for new drugs.
  - –Primary basis: **Adequate and well-controlled investigations**
- 21 CFR 314.126
  - –Acceptable safety
- 21 CFR 201
  - –Product label
    - Defines an appropriate patient population
    - Provides adequate information to enable safe and effective use

17

Two Types of Approvals

- Regular (Full) Approval or
- Accelerated Approval

18

Regular (full) Approval

- Direct clinical benefits
  - Prolongation of overall survival (live longer)
  - Improvement of symptoms (live better)
  - Favorable effect on established surrogate
  - Composite endpoints

19

Accelerated Approval

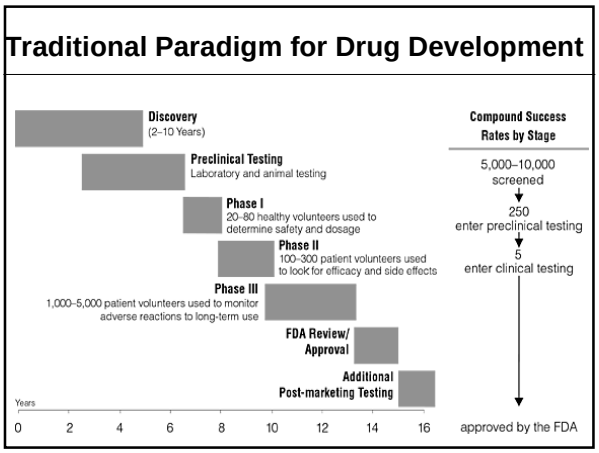
- 21 CFR 314.510 for drugs (subpart H)
- 21 CFR 691.41 for biologics (subpart E)
- The product
  - Treats serious or life-threatening illnesses
  - Provides meaningful therapeutic benefit to patients over existing treatments
  - Is tested in adequate and well-controlled clinical trials
  - Has an effect on a **surrogate endpoint** that is **reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity
  - Fulfils post-marketing commitment to verify and describe its clinical benefit

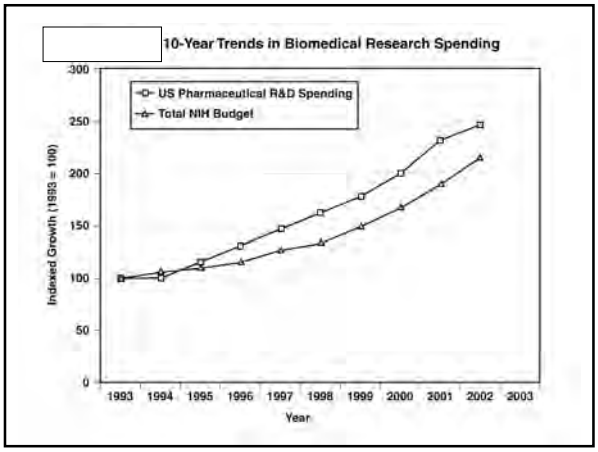
20

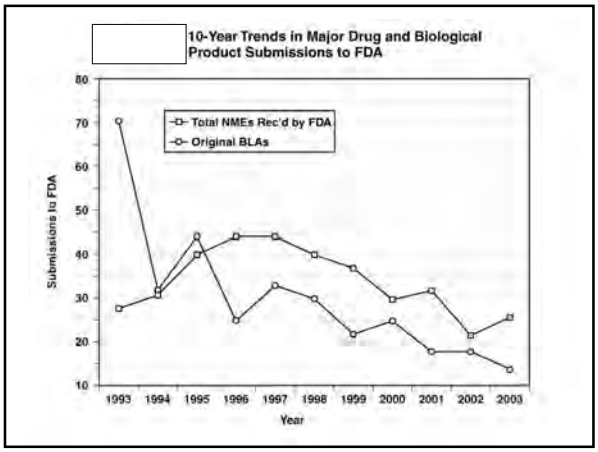
Drug/Biological Development

- An orderly process starting from scientific discovery
- Multiple components involving critical decision making
- Time and cost

21


Traditional Paradigm for Drug Development
Discovery
(2–10 Years)
Preclinical Testing
Laboratory and animal testing
Phase I
20–80 healthy volunteers used to determine safety and dosage
Phase II
100–300 patient volunteers used to look for efficacy and side effects
Phase III
1,000–5,000 patient volunteers used to monitor adverse reactions to long-term use
FDA Review/ Approval
Additional Post-marketing Testing
Years
0 2 4 6 8 10 12 14 16
Compound Success Rates by Stage
5,000–10,000 screened
250 enter preclinical testing
5 enter clinical testing
approved by the FDA


10-Year Trends in Biomedical Research Spending
US Pharmaceutical R&D Spending
Total NIH Budget
Indexed Growth (1993 = 100)
300
250
200
150
100
50
0
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003
Year


10-Year Trends in Major Drug and Biological Product Submissions to FDA
Total NMEs Rec'd by FDA
Original BLAs
Submissions to FDA
80
70
60
50
40
30
20
10
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003
Year

Review Process

- **Starts with the sponsor's application**
- **NDA: New Drug Application**
  - **Mainly in the Center for Drugs**
- **BLA: Biological Licensure Application**
  - **Mainly in the Center for Biologics and some in Center for Drugs**

25

Review Process

- **Team approach**
  - **Clinical reviewer in collaboration with biostatistician: clinical data to determine the efficacy and safety**
  - **Other disciplines reviewers:**
    - **Clinical pharmacologist**
    - **Toxicologist**
    - **Chemistry, Manufacturing and Control (CMC) reviewer (chemist or biologist)**

26

Application status

- **Regular: 10 month**
- **Priority: 6 month**
- **Mid-cycle Review Team Meeting**

27

FDA Advisory Committee Meeting (1)

- **Advisors**
  - **Special Government Employees (SGEs)**
  - **Pre-screened for Conflict of Interests (COI)**
- **Meeting agenda and dates announced in advance in Federal Register**
- **Briefing Package**
  - **From Sponsor**
  - **From FDA**
  - **Made public prior to the meeting**

28

FDA Advisory Committee Meeting (2)

- **Presentations**
  - **Sponsor**
  - **FDA**
  - **Public (need to pre-register)**
- **Committee discussion of questions posed by FDA**
- **Committee Votes if there are voting questions**

29

FDA Advisory Committee Meeting (3)

- **FDA makes its own decision whether to approve a product or not after AC meeting**

30

Public Information after Approval

- **For approved drugs and biologics, information (letters, labeling, reviews) is accessible**
  - **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
  - **http://www.fda.gov/cber/products.htm**
- **Food and Drug Administration Amendments Act of 2007 (FDAAA) requires internet web posting after approval**
  - **Immediate publication of summary review, no later than 48 hours**
  - **Action Package no later than 30 days**
    - **Review memos**
    - **Action letters**

31

The IND Process

- **Preclinical testing/investigation**
  - ***In vitro* tests/animal testing**
    - **"reasonably safe" determination (21 C.F.R. § 312.23)**
  - **Pharmacological data**
  - **Toxicity testing**
- **"Good Laboratory Practice" (GLP) (21 C.F.R. Part 58)**
  - **Governs preclinical testing conduct**
    - **Organization, personnel, facilities, study conduct, and records retention**

32

The IND Process

- **Clinical testing/investigation and "Good Clinical Practice" (GCP)**
  - **Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.**
  - **See Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance (April 1996)**
    - **Details GCP principles**

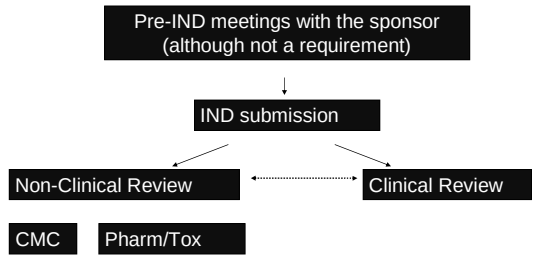
33

Regulatory Considerations in reviewing 1st in-human use of investigational agents (phase I)

- **The product manufacturing and characterization?**
- **The level of safety assurance needed for beginning clinical trials**
- **Clinical study design**

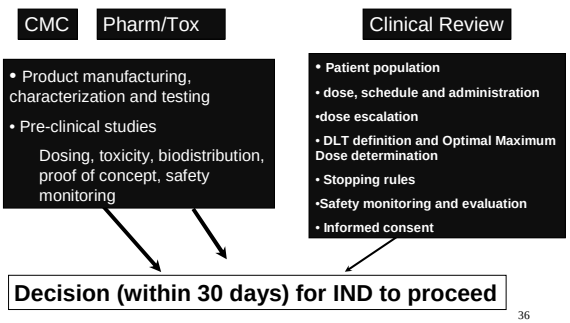
34

Review Process for Phase 1 Trials



35

Review process for phase I trials --- continued



36

Review process for phase II, III trials

CMC | Pharm/Tox

- Product manufacturing, characterization and testing and **Potency**
- Pre-clinical studies

Clinical Review

Proposed clinical trials may proceed

37

Phase 2 studies

- Begin if Phase 1 studies do not reveal unacceptable toxicity.
- Primarily focus on collection of preliminary data on
  - – whether the drug has effect in a defined patient population
  - –the relationship between dose and effectiveness.
- Continue to evaluate safety and short-term side effects.
- For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment -- usually a placebo or a different drug.

38

Phase 3 studies

- **Begin if preliminary evidence of effectiveness is shown during phase 2.**
- **Gather more information about safety and effectiveness in a defined population.**
- **May form the primary basis of an efficacy claim**

39

Some considerations of phase II and phase III studies

- **Protocol design**
  - Patient population
  - Choice of endpoints
  - Choice of control (placebo vs. active control)
  - Evaluation
- **Study conduct and execution**
  - Study sites
  - Investigator's brochure
  - DSMB
  - CRF
- **Protocol design**
  - Data collection and Evaluation
  - Statistical analytic plan
  - Assumption of effect size, power and sample size
- **Implications for labeling.**
  - Currently available therapies for the indication sought
  - possibility of the study to generate data to support the claim

40

Special protocol assessment

[Section 505(b)(4)(c) of the FDA Modernization Act].

- **Agreement between the sponsor and FDA documented in writing**
  - Protocol design
  - Primary efficacy endpoints
  - Study conduct
  - Data analyses
  - Clearly described labeling statements one could expect if the data are supportive and the product is approved
  - whether the design and planned analysis of a study adequately address objectives in support of a regulatory submission.
- **The sponsor submits protocols with specific questions**
  - Animal carcinogenicity protocols,
  - Final product stability protocols or
  - clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim
- **FDA documents in writing within 45 days any agreement or disagreement to the sponsor**

41

Interactions with FDA

- Early interactions with FDA are critical
- Know your guidance documents
- Consider early in translational research the questions that will be asked at the clinical trial phase
- Phone, face to face; formal or informal: dialogue is encouraged

42

Interactions with FDA

- **Scientific meetings, conferences, workshops**
- **Pre-Pre-IND**
- **Pre-IND meetings**
- **End of Phase 1 meeting**
- **End of Phase 2 meeting**
- **Special Protocol Assessment review**
- **Fast Track program application**
- **New protocol submission under existing IND**

43

Conclusion

- **Drug and biologic development is an orderly process involving multiple components**
- **Academia, industry and regulatory bodies are integral parts of this process**
- **Many challenges exist for product characterization as well as testing the safety and effectiveness in humans throughout the life cycle of the product development**
- **FDA critical path and other initiatives aim to help the development of drugs and biologics**
- **Frequent and early engagement with FDA are strongly encouraged**

44

Contact Information

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45

European Medicines Agency: New Regulation for Advanced Therapies Including Oncology Biological Products

Patrick Celis, PhD

New Regulation for Advanced Therapies including Oncology Biological Products

iSBTc Global Regulatory Summit

Patrick Celis, PhD
European Medicines Agency (EMEA)

Presentation Overview

- EMEA and the European network
- Centralised authorisation procedure
  – Additional regulatory tools
- Regulation on Advanced Therapies
- Concluding remarks

Presentation Overview

- EMEA and the European network
- Centralised authorisation procedure
  – Additional regulatory tools
- Regulation on Advanced Therapies
- Concluding remarks

The EMEA

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  Canary Wharf
  London E14 4HB
  United Kingdom

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- Fax: +44 (0) 20 7418 8416

- www.emea.europa.eu

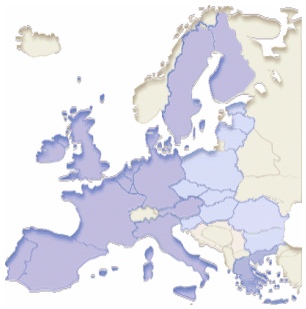
Overview of EMEA

- EUROPEAN MEDICINES AGENCY — Responsibilities and administrative structure
  - **Title IV: REGULATION (EC) No 726/2004**
- The EMEA is the European Union body responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.
- Responsible for the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

Evolution of the EU Network

- EMEA Established 1993
- Centralised procedure
  - European Marketing Authorisation
- Expansion – 27 Member States
- Development of Legislation, e.g.
  - Pharmacovigilance, Paediatric, Advanced therapies
- Increased scope, e.g.
  - e.g. Biosimilars, viral / immune diseases

Europe from 1 Jan 2007



Austria	Latvia
Belgium	Lithuania
Bulgaria	Luxembourg
Cyprus	Netherlands
Czech Republic	Malta
Denmark	Poland
Estonia	Portugal
Finland	Romania
France	Slovak Republic
Germany	Slovenia
Greece	Spain
Hungary	Sweden
Ireland	UK
Italy	

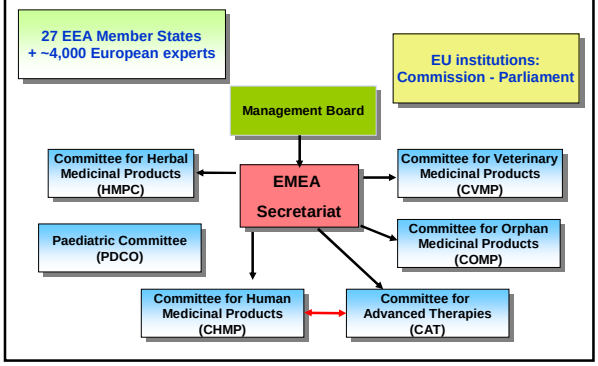
Role of the EMEA

- The Agency provides the Member States and the institutions of the EU the best-possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use referred to it in accordance with the provisions of EU legislation relating to medicinal products
- Mission Statement = to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

Objectives of the EMEA

- To complete the single EU market for pharmaceuticals
- To protect and promote public and animal health
- To facilitate access by patients to new & better medicines
- To allow further development of European based R&D pharmaceutical industry
- To provide a platform for discussion of public health issues at European level

EMEA Organisation and Partners



Presentation Overview

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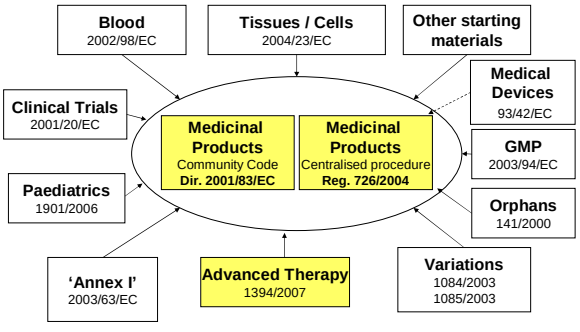
EU regulatory framework

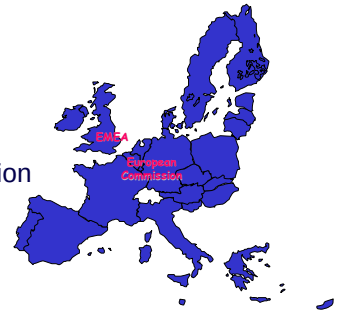


Centralised Procedure

Rapid (277 days)

EU-wide (27 MSs)

Marketing authorisation (license)



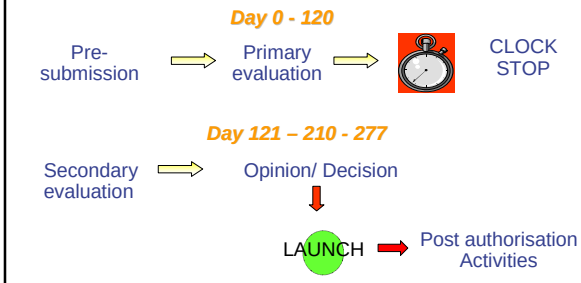
Centralised procedure

- **1 Assessment**
- **Scientific Committee:**
  - CHMP - Committee for Medicinal Products for Human Use
  - CAT – Committee for Advanced Therapies
- **Maximum time limit**
  210 days evaluation to CHMP Opinion → Decision (MA)
- **1 Marketing Authorisation** valid whole EU
- **1 Invented name**
- **1 Common Labelling** (all EU languages identical)
  Summary of Product Characteristics
  User Package Leaflet & Package Labelling

Centralised procedure

- Scope (mandatory)
  - Biotechnology products / ATMP
  - Orphan drugs
  - Medicines for treatment of:
    - AIDS, Cancer, Neurdegenerative disorders, Diabetes, auto-immune diseases/immune disfunctions, Viral diseases
- Scope (optional)
  - New chemical entity
  - Significant therapeutic, scientific or technical innovation

Centralised Procedure - TIMETABLE



New regulatory tools – Conditional marketing authorisation

- **Authorisation** valid for 1 year**, renewable**
- **Allows for** increased flexibility **when granting a MA**
- **Conditions:** unmet medical need **and benefit to public health of** immediate availability **overweighs risks inherent that additional data is required.**
- **Limited to medicinal products:**
  - Aimed at preventing, treating or for medical diagnosis of **seriously debilitating or life-threatening diseases**,
  - **Emergency threats** (WHO, EC)
  - **Orphan** medicinal products

New regulatory tools – Accelerated review

- Accelerated review
  - **150 days** instead of 210 days
    - Possibility to revert back to normal timetable during the procedure
  - For products with **major public health interest – therapeutic innovation**

New regulatory tools – Risk management plans

- Risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including risk communication and assessment of risk minimisation interventions.
- Risk Management Plan: to be submitted with all new MAA (legal requirement).
  1. Safety Specification
  2. Pharmacovigilance Plan (Routine – Additional PhVig activities)
  3. Evaluation of the need for risk minimisation measures
  4. Risk Minimisation Plan (if needed)
  5. PM Efficacy follow-up (for ATMP only)

New regulatory tools – Paediatric Investigation Plan (PIP)

- **System of both** obligations and Rewards **for all med. prod.:**
  - **Med. products under development** and yet to be authorised
    - Have to submit results of PIP (agreed by **PDCO**) at time of marketing authorisation application (unless waiver or deferral)
    - 6-month extension of the Supplementary Protection Certificate
  - **Med. products still covered by property rights**
    - Have to submit results of agreed PIP at time of change (variation/extension) for new indication, route of administration, or pharmaceutical form
    - 6-month extension of the Supplementary Protection Certificate
  - **Authorised medicinal products no longer covered by IP rights**
    - new *Paediatric Use Marketing Authorisation* covering exclusively paediatric indication(s) and formulation(s)
    - 10 years data protection

Clinical trial applications

- In EU, authorisation of clinical trials remain the responsibility of the member states where the trial in conducted
- Harmonised procedure (based on same legislation) and requirements for clinical trial applications
- EMEA is hosting the 'Clinical trials coordination group'
  - Discussion on common principles and processes to be applied throughout the European medicines regulatory network

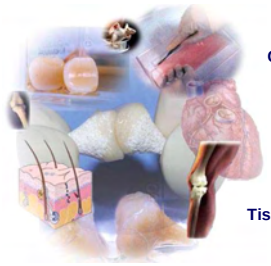
Presentation Overview

- EMEA and the European network
- Centralised authorisation procedure
  - Additional regulatory tools
- Regulation on Advanced Therapies
- Concluding remarks

Advanced Therapy Medicinal Products ATMP

Regulation (EC) No 1394/2007

Effective 30 December 2008



Cell Products

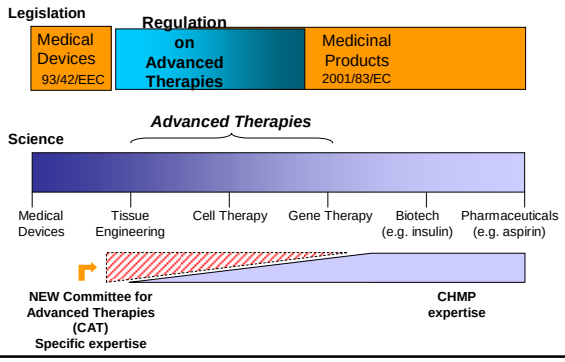
Gene Therapy

Tissue Engineered

Evaluation procedure for ATMP

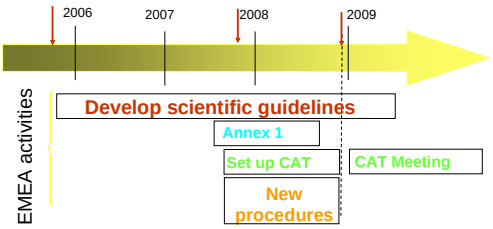
- New Committee for Advanced Therapies (CAT)
  - Legislation defines composition / expertise
  - Main tasks: To evaluate & prepare draft opinions on ATMP
    - For final approval by CHMP
  - Involvement in Scientific Advice on ATMP
  - Additional (new) tasks such as:
    - Certification of Quality / Non-clinical data (for SMEs)
    - Scientific recommendation on classification as ATMP
    - Evaluation of products already on the market

Bridging the gap



EMEA Implementation of ATMP Regulation

Nov 2005	December 2007	End Dec. 2008
ATMP Regulation Proposal	Publication ATMP Reg. 1394/2007	Application of Reg. 1394/2007



1. Development of Guidelines

- A lot of Scientific guidelines already in place:
  - Overaching GL on gene transfer medicinal products
  - Overaching GL on cell-based medicinal products (somatic cell therapy + tissue engineered products)
  - Specific guidelines e.g.
    - Quality/manufacture of lentivirus vectors (GT),
    - Non-clinical testing before first use of GT product in man
    - Xenogeneic cell therapy products
- Guidelines under development, for example:
  - GL on clinical monitoring and follow-up of patients expose to GTMP
  - GL on the application of the risk analysis approach for cell-based medicinal products in pre- and post-authorisation phase

2. Development of technical requirements

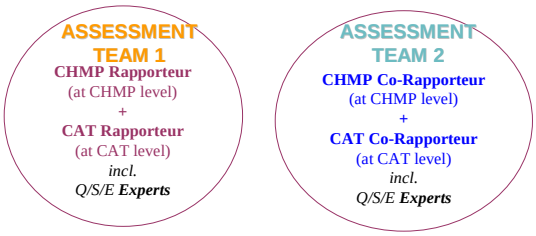
- Scientific input by EMEA/CHMP & Working Parties in revision, by the Commission, of Annex I to Dir. 2001/83
  - Legal document describing the technical requirements for ATMP
  - Published by European Commission
- 'Dossier requirements' for gene therapy MP (revision), somatic cell-therapy MP (revision) and Tissue engineered product (new)
  - Requirements specific for / adapted to ATMP
  - Additional flexibility where needed for new class of ATMPs

3. Setting up of the CAT

- Development of CAT Rule of Procedures **(ongoing)**
  - Includes CAT-CHMP interactions, appointment of Rapporteurs, etc.
- Appointment of CAT members **(ongoing)**
  - From CHMP (5 + 5 alternates),
  - From Member States (1 + 1 alternate per MS),
  - From Patients' & Doctors' associations (each 2 + 2 alternates)
- Appointment of CAT Chairperson
- First meeting**: scheduled for 15-16 January 2009**

CAT-CHMP interactions - Principles

- **Two <u>extended</u> assessment teams** responsible for the review of ATMP MAA



CAT-CHMP interactions - Principles

- **Roles** in the two assessment teams of:
  - **CAT (Co)Rapp** will coordinate the procedure & discussions at CAT + prepares assessment reports
  - **CHMP (Co)Rapp** responsible for flow of information between CAT & CHMP + discussion/adoption of opinion
- **Product discussions** (up to adoption of draft opinion) take place at CAT
- **Peer review** by 1 CHMP member + 1 (or more) CAT member(s)
- CAT will ensure full **transparency** of the evaluation towards CHMP

4. Development of new procedures

- Related to the tasks of CAT
  - Evaluation of MAA for ATMP
    - Interactions with Notified Bodies (combined ATMP = engineered cells + medical devices)
  - Re-examination procedure
  - Scientific classification of ATMP
  - Post-authorisation applications (variations, Annex II applications)
  - Scientific advice Certification of Quality /Non-clinical dossier for SMEs
    - Development of procedural & scientific guidelines
  - Procedure to bring products legally on the market in line with new Regulation

5. Additional implementation activities

- Support to the Commission on the development of:
  - Guideline on GMP for ATMP
  - Guideline on GCP for ATMP
  - Guideline on Traceability of ATMP
    - Systems to be in place to ensure complete traceability from donor to patient & vice versa
- Development of a Guideline on Post-marketing Safety & Efficacy follow-up and RMP of ATMP
  - EMEA Guideline, out for consultation May 2008

More information on Advanced Therapy Medicinal products

- EMEA

http://www.emea.europa.eu/htms/human/mes/advancedtherapies.htm

- Commission

http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/advanced_en.htm

Presentation Overview

- EMEA and the European network
- Centralised authorisation procedure
  – Additional regulatory tools
- Regulation on Advanced Therapies
- Concluding remarks

Concluding remarks

EMEA and Oncology Biological Products

- EMEA is responsible for the licensing of medicinal products via the centralised procedure
- Responsibility for the approval of clinical trials is with the EU Member State where the trial in conducted

Concluding remarks

- Oncology (Biological) Products will all be authorised via the centralised procedure:
  - Recombinant products
  - Biological products (e.g. cell lysates)
  - Advanced therapy products:
    - Cell therapy products: dendritic cells loaded with cancer antigens
    - Gene therapy products
  - Also: New chemical entities

Concluding remarks

- All companies developing oncology (biological) products should contact EMEA for assistance:
  - SME status
  - Orphan drug status
  - Scientific advice
  - Marketing authorisation application

How to contact EMEA

- General queries, Request for briefing meetings or Request for regulatory Classification
  http://www.emea.europa.eu/htms/human/mes/itf.htm
- SME Office
  http://www.emea.europa.eu/SME/SMEoverview.htm
- EMEA Scientific advice procedure
  http://www.emea.europa.eu/htms/human/sciadvice/Scientific.htm
- EMEA Orphan drug designation
  http://www.emea.europa.eu/htms/human/orphans/intro.htm

Thank you

Dr Patrick Celis

Scientific Administrator,

Quality of Medicines Sector

0044 20 7418 8656
Patrick.celis@emea.europa.eu

Paul-Ehrlich-Institut: Considerations in Product Development with Advanced Therapies and Cancer Vaccines

Thomas Hinz, PhD

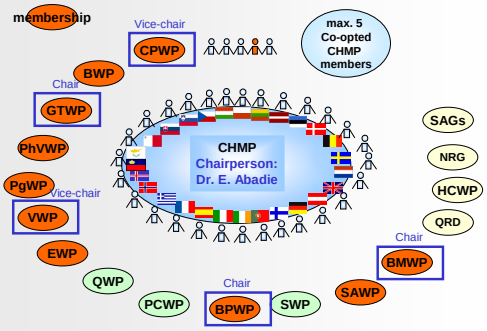
Considerations in Product Development with Advanced Therapies and Cancer Vaccines

Thomas Hinz
Head of Section Therapeutic Vaccines
Paul-Ehrlich-Institut
hinth@pei.de

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines

- Responsibility for sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, allergens, gene transfer medicinal products, somatic cell therapy products, xenogenic cell therapy products and blood components manufactured using genetic engineering
- Marketing authorization (national and EU)
- Clinical trial authorization (pure national responsibility)
- Batch control
- Pharmacovigilance
- Inspections (EMEA-GCP/GMP), support of regional authorities (manufacturing license, routine GMP inspections)
- Research in the fields of immunology, biotechnology, virology

Membership of Paul-Ehrlich-Institut in EMEA Working Parties



Guidance for Advanced Therapy Products Including Cell-Based Cancer Vaccines

- Draft Guideline on GCP for ATMPs available from the European Commission (traceability, patient follow up, licensed tissue establishments)
- EMEA Guideline on Human Cell-Based Medicinal Products available since September 2008 (CMC, preclinical, clinical)
- No Guidance available for Cancer Vaccines in general
- EMEA Guideline on Potency Testing of Cell Based Immunotherapy Medicinal Products for the Treatment of Cancer

Diversity of Substances Used for Therapeutic Cancer Vaccination

Only some of the following are Advanced Therapy Products

- RNA (possibly defined as ATMP in the future)
- **DNA**
- Synthetic peptides
- Virus-like particles (e.g. Bacteriophage Q_{beta})
- Recombinant proteins
- Cell lysates
- **Somatic cells**

Products are often used together with novel adjuvants and formulations such as MPL, TLR, and liposomal formulations, respectively.

Definition of Somatic Cells Therapy Medicinal Products in the EU

L 159/46 EN Official Journal of the European Union 27.6.2003

COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

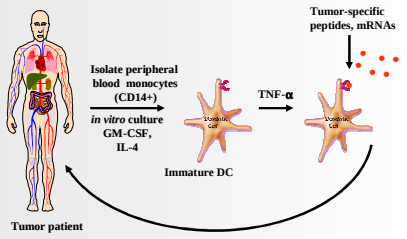
amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

... somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy)...

Substantial Manipulation of Cells According to Advanced Therapy Regulation 1394/2007/EC

- Manipulations not considered substantial:
  - — cutting
  - — grinding
  - — shaping
  - — centrifugation
  - — soaking in antibiotic or antimicrobial solutions
  - — sterilization,
  - — irradiation,
  - — cell separation, concentration or purification,
  - — filtering
  - — lyophilization
  - — freezing
  - — cryopreservation
  - — vitrification
- The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

Cell-Based Cancer Vaccine Using Substantially Manipulated Cells



Eligibility of Dendritic Cell-Based Cancer Vaccines to EMEA Procedure

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Mandate of the EMEA Innovation Task Force (ITF)

EMEA/CHMP Conclusion for dendritic cell-based cancer vaccine:

"…falls into the class of advanced therapy medicinal products (Part IV of the annex to Directive 2001/83/EC as amended), and more specifically into the class of somatic cell therapy medicinal products."

How to Develop Cell-Based Medicinal Products?

Human Cell-Based Guideline

- Cell-Based Products should be developed on the basis of a risk analysis
- The results of the risk analysis should be used
  - to identify risk factors associated with the quality and safety of the product
  - determine the extent and focus of non-clinical and clinical studies

Some Risk Factors of Cell-Based Products

Human Cell-Based Guideline

- Origin (autologous vs. allogeneic)
- Ability to proliferate and differentiate
- Ability to initiate an immune response
- Level of cell manipulation (in vitro/ex vivo expansion/activation/genetic manipulation)
- Mode of administration (ex vivo perfusion, local, systemic)
- Duration of exposure (short to permanent)
- Combination product (cells + bioactive molecules or structural materials)
- Availability of clinical data on or experience with similar products

Reflection Paper on the practical application of the risk-based approach for cell-based products will be published by EMEA

Quality of Cell-Based Medicinal Product at Release

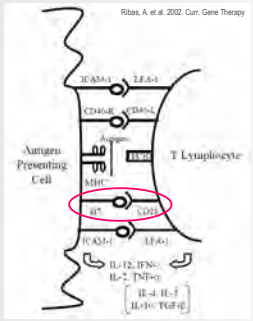
Human Cell-Based Guideline

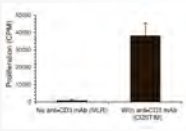
- Identity (CD marker by FACS etc.)
- Purity (consider contaminating cells, control consistency of complex cellular preparations)
- Cell number
- Sterility
- Viability
- Potency

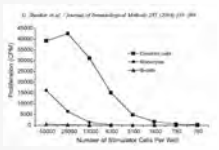
Guideline on Potency Testing of Cell Based Immunotherapy Medicinal Products for the Treatment of Cancer

- Acknowledges that complex and laborious potency assays are not suitable for release testing of product. Such potency testing rather to be used for product characterization
- Surrogates can be tested such as co-stimulatory molecule expression in case of dendritic cells
- Correlation of surrogate with real biological activity has to be shown

Measure Expression of Costimulatory Molecules as Surrogate for Potency of Dendritic Cells







Principles of Preclinical Development for Cell-Based Medicinal Products

Human Cell-based Guideline

- Conventional requirements as detailed in Directive 2001/83/EC may not always be appropriate
- Deviations from these requirements need to be justified
- The scrutiny applied during non-clinical testing should be proportional to the risk expected to be associated with clinical use

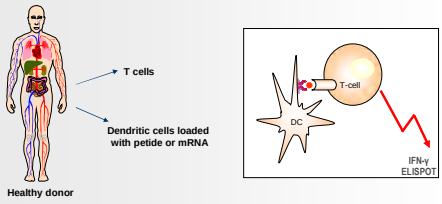
Non Clinical Development - General Aspects

Human Cell-Based Guideline

- Objectives of the non-clinical studies are to
  - demonstrate proof-of-principle
  - define the pharmacological & toxicological effects predictive of the human response.
- The goal of non-clinical studies include:
  - to provide information on safe dose for clinical trials
  - to support the route of administration & application schedule
  - to support duration of exposure
  - to identify target organs for toxicity

In Vitro Preclinical Testing can Contribute to Proof of Concept

- Reasonable when using self antigens for tumor vaccination, e.g. peptides or mRNA
- Test for presence of antigen-specific T cells in peripheral blood of healthy donors
- Verify absence of central tolerance

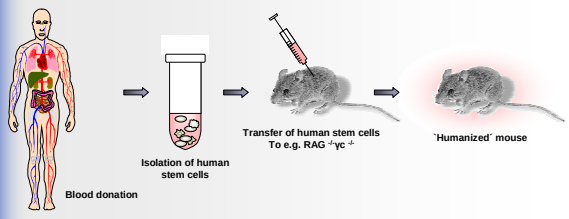


Animal Models

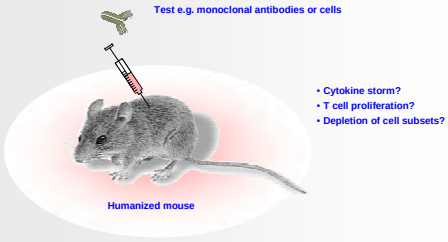
Human Cell-Based Guideline

- Relevant animal models should be used
- The chosen animal model may include immuno-compromised, knockout or transgenic animals
- Homologous models may be useful (mouse cells in mice)

Several Preclinical Animal Models Could be Envisaged



Use of Humanized Mice for Preclinical Analyses



- Cytokine storm?
- T cell proliferation?
- Depletion of cell subsets?

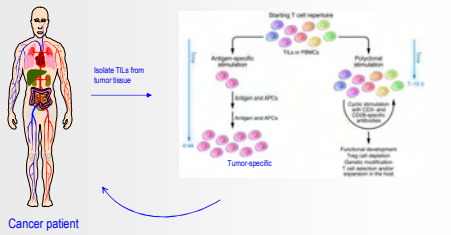
Toxicology
Human Cell-Based Guideline

Toxicity might emerge for example from
- Altered in vivo behaviour (proliferation, differentiation)
- Materials used during manufacturing
- Use of combination therapies (e.g. cell product plus adjuvants, cytokines etc.)
- **Auto immunity** especially in case of immune therapies

Local tolerance studies
- May be performed in single or repeated dose toxicity studies

Other toxicity studies
- Conventional carcinogenicity/genotoxicity normally not be required
- Tumourigenicity studies might be required (stem cells, tumour cells)

Risk for Auto Immunity after e.g. Adoptive Transfer of Tumor-Specific T Cells



Case of Autoimmunity After Adoptive T cell Transfer

- Carbonic Anhydrase IX (CAIX)-specific T cells expressing scFv adoptively transferred to treat renal cell carcinoma
- Stop of clinical trial due to grade 2-4 liver toxicities
- T cell infiltration around bile ducts
- CAIX expression found on bile duct epithelial cells
- Lamers, C.H. et al. (2006). Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against Anhydrase IX: First clinical experience. J. Clin. Oncol. 24: e20

Estimate Risk Of Autoimmunity

- Tissue expression of some self antigens is well known, and sometimes restricted to only a few tissues, e.g. MAGE
  The risk for autoimmunity thus can be estimated and is probably low
- In case of new antigens their expression in tissues and organs should carefully be evaluated before going into clinical trials (in **vitro analyses**, such as RT-PCR, chip technology, histology etc.)
- Risk for autoimmunity is part of overall benefit/risk estimation

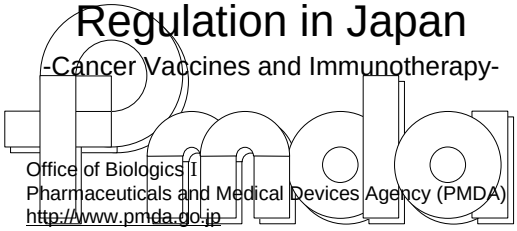

Thank you for your attention !
1. KKSN-Symposium October 29, 2008, San Diego
Martina Schüßler-Lenz
Thomas Hinz,
25

Biological Products Regulation in Japan Cancer Vaccines and Immunotherapy

Masatoshi Narita

Biological Products Regulation in Japan

-Cancer Vaccines and Immunotherapy-



Office of Biologics I
Pharmaceuticals and Medical Devices Agency (PMDA)
http://www.pmda.go.jp
Associate Executive Director Center for Product Evaluation

Masatoshi Narita

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Disclaimer Notice

- These views expressed are my personal opinions and not necessarily represent the views or findings of the PMDA

Outline today

- About PMDA（Pharmaceuticals and Medical Devices Agency）
  - PMDA and MHLW（Ministry of Health, Labour and Welfare)
- Approval processes for pharmaceuticals in Japan
- Regulation of biological products in Japan
  - Differences between biological products and small molecule NCEs
- Regulation of Gene-therapy or Cell/Tissue-derived Products
- Development of biological products for cancer

3

Introduction of PMDA

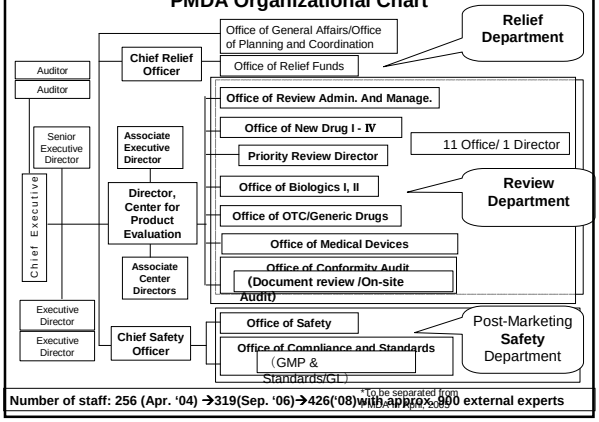
- NAME: Pharmaceuticals and Medical Devices Agency
- Date of Establishment : April 2004

  Established as an Incorporated Administrative Agency (IAA) in April, 2004 by integrating 3 review-related organizations.
- Effective operation under "Medium Term Plan" for 5 years' activities (04' -08')
- PMDA submits performance report to MHLW annually, and that is evaluated by the "IAA Evaluation Committee" for necessary improvement.

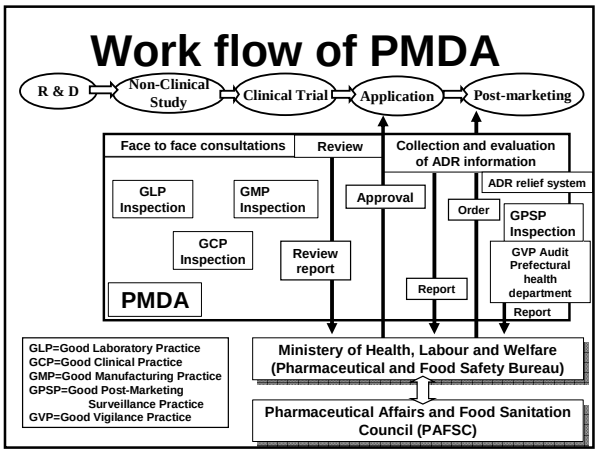
3 major work areas of PMDA

Review and Audit for Drugs/ Medical Devices	**Face-to-face Advice (Clinical Trial etc.)**
	Approval reviews for Pharmaceuticals and Medical Devices
	Conformity Audits for Application Materials of GLP,GCP and GMP
Post-marketing Safety Operations for Drugs/ Medical Devices	**Reinforce Safety Information (Database)**
	Scientific Review and Research for Safety Information
	Provision of Information (via the Internet), Telephone Consultation Services for Consumers
Relief Service for ADR and Other Infections derived from biological products	**Provision of Medical Expenses, Disability Pensions etc.**
	Relief Service for SMON, HIV-positive and AIDS patients, and HCV-positive and HC patients

PMDA Organizational Chart



Number of staff: 256 (Apr. '04) →319(Sep. '06)→426('08)with approx. 800 external experts



Responsibilities of MHLW and PMDA

[MHLW]

Planning basic policy, enforcement of administrative measures, such as approval, administrative order, etc which are based on the law

ex.
- **Final judgment on approval**
- **Directions of withdrawal and issuance of emergency safety information**
- **Safety measures for emergent and significant cases**

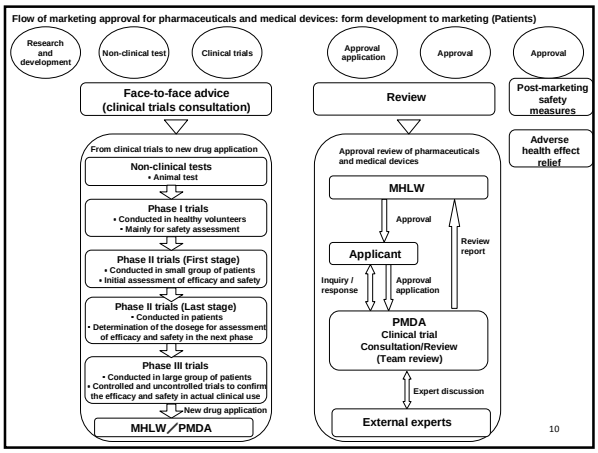
[PMDA]

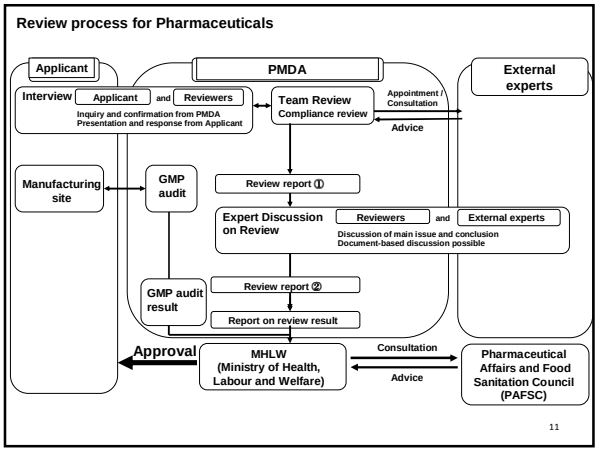
Implementation of work, such as review, examination, data analysis, etc before administrative measures

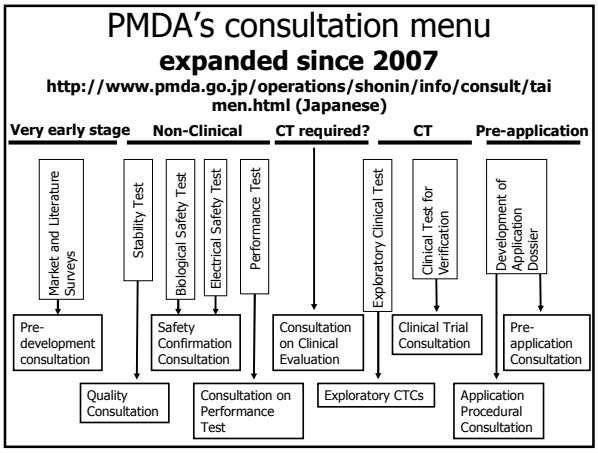
ex.
- **Review of Pharmaceuticals and Medical Devices GMP/GLP/GCP inspection, Clinical trial consultation**
- **Collection, examination, analysis, assessment and provision of ADR information**

Approval processes for pharmaceuticals in Japan

9


Flow of marketing approval for pharmaceuticals and medical devices: form development to marketing (Patients)
Research and development
Non-clinical test
Clinical trials
Face-to-face advice (clinical trials consultation)
From clinical trials to new drug application
Non-clinical tests
• Animal test
Phase I trials
• Conducted in healthy volunteers
• Mainly for safety assessment
Phase II trials (First stage)
• Conducted in small group of patients
• Initial assessment of efficacy and safety
Phase II trials (Last stage)
• Conducted in patients
• Determination of the dosege for assessment of efficacy and safety in the next phase
Phase III trials
• Conducted in large group of patients
• Controlled and uncontrolled trials to confirm the efficacy and safety in actual clinical use
New drug application
MHLW／PMDA
Approval application
Approval
Review
Approval review of pharmaceuticals and medical devices
MHLW
Approval
Applicant
Review report
Inquiry / response
Approval application
PMDA
Clinical trial Consultation/Review (Team review)
Expert discussion
External experts
Approval
Post-marketing safety measures
Adverse health effect relief
10


Review process for Pharmaceuticals
Applicant
PMDA
External experts
Interview
Applicant
and
Reviewers
Inquiry and confirmation from PMDA
Presentation and response from Applicant
Team Review
Compliance review
Appointment / Consultation
Advice
Manufacturing site
GMP audit
Review report ①
Expert Discussion on Review
Reviewers
and
External experts
Discussion of main issue and conclusion
Document-based discussion possible
GMP audit result
Review report ②
Report on review result
Approval
MHLW (Ministry of Health, Labour and Welfare)
Consultation
Advice
Pharmaceutical Affairs and Food Sanitation Council (PAFSC)
11


PMDA's consultation menu
expanded since 2007
http://www.pmda.go.jp/operations/shonin/info/consult/taimen.html (Japanese)
Very early stage
Non-Clinical
CT required?
CT
Pre-application
Market and Literature Surveys
Stability Test
Biological Safety Test
Electrical Safety Test
Performance Test
Exploratory Clinical Test
Clinical Test for Verification
Development of Application Dossier
Pre-development consultation
Safety Confirmation Consultation
Consultation on Clinical Evaluation
Clinical Trial Consultation
Pre-application Consultation
Quality Consultation
Consultation on Performance Test
Exploratory CTCs
Application Procedural Consultation

- Regulation of biological products in Japan

13

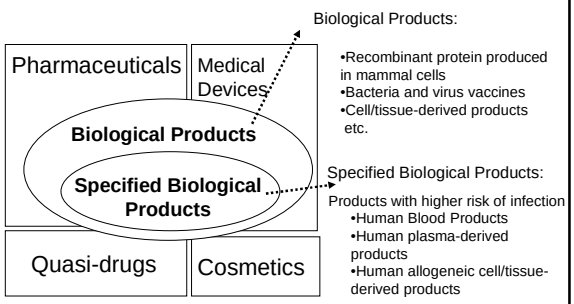
Definition of the "biological products"

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

14

Products Defined in PAL



Biological Products:

- Recombinant protein produced in mammal cells
- Bacteria and virus vaccines
- Cell/tissue-derived products etc.

Specified Biological Products:

Products with higher risk of infection

- Human Blood Products
- Human plasma-derived products
- Human allogeneic cell/tissue-derived products

The Requirements for Biological Source Materials

1. General Notices and Requirements
2. Requirements for Human Blood
   1. Source for blood products for transfusion
   2. Source for plasma-derived products
3. Requirements for human-derived materials
   1. Cell and Tissue-derived materials
   2. Urine-derived materials
   3. Other human-derived materials
4. Requirements for animal-derived source materials
   1. Ruminant-derived materials
   2. Cell and Tissue-derived materials
   3. Other animal-derived materials

4．1 The Requirements for Ruminant-derived materials

- Materials treated with high-temperature or alkaline condition, such as fatty acids or amino acids are out of scope.
- Tissues with high risk of prion are prohibited to use as source materials; pituitary, brain, spinal cord, dura matter, placenta, spleen, thymus, lymph node, etc.
- Ruminant-derived materials should be originated from area not affected with TSE; limited to 20 countries such as Australia and New Zealand. US, Canada and Japan are designated as TSE-affected area in Japan.
- When unaccepted ruminant-derived source materials are inevitably used and benefit of the product overcomes the risk of TSE, appropriateness and justification should be described in application form.

The Minimum Requirements for Vaccines & Blood Products

- MRBP provides critical matters of quality control of vaccines and blood products such as test method and acceptance criteria, control of raw materials, manufacturing process control, storage condition and shelf-life.
- MRBP contents;
  - General notices and requirements
  - Official Monographs
  - Methods of analysis
  - Standard materials
  - Reagents

Major points to consider when registering biological products in Japan

Biological products are reviewed scientifically in PMDA.

If there are some ICH guidelines, PMDA reviews the application based on these guidelines. (ICH-Q5A, Q5B, Q5C, Q5D, Q6B, S6)

In case of making changes to manufacturing processes of products both during development and after approval, PMDA evaluates the changes based on ICH-Q5E.

ICH: International Conference on Harmonization (Japan-US-EU)

- Regulation of

Gene-therapy Products or Cell/Tissue-derived Products

20

Important MHLW Notification for Gene therapy Products

Assuring the Quality and Safety of Gene therapy Products

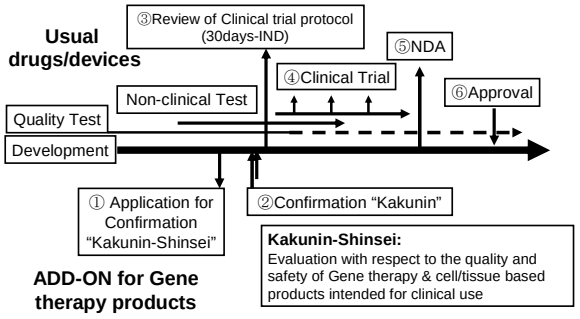
-MHLW Notification No.1062 (15 Nov. 1995)
Rev1. 29 Mar. 2002
Rev2. 28 Dec. 2004

⇨ **Application for confirmation prior to the first clinical trial : "Kakunin Shinsei"**

Kakunin Shinsei = pre IND

21

Development Process of Gene therapy in Japan under the PAL.



Regenerative Medicine 5 (2):172-215, 22

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**

23

Recently Confirmed Gene Therapy Protocols (2003～)

Year	Institution	Target	Vector	Gene	Pts/Cases (Planed)
2003	Anges MG Inc.	ASO	Plasmid	HGF	41 (100) *
2003	Anges MG Inc.	Buerger's disease	Plasmid	HGF	On going (15) *
2007	Takara-bio Inc.	GVHD	Retro	HSV-TK	Planed *
2007	Sanofi-aventis K.K.	ASO	Plasmid	FGF1	More than 10 *

* Reproduced with permission from National Institute of Health Sciences web site http:www.nihs.go.jp/cgtp/cgtp/sec1/gt_prtcl/prtcl-j3.html

As of Dec. 2007

24

Important MHLW Notifications for Cell/Tissue based Products

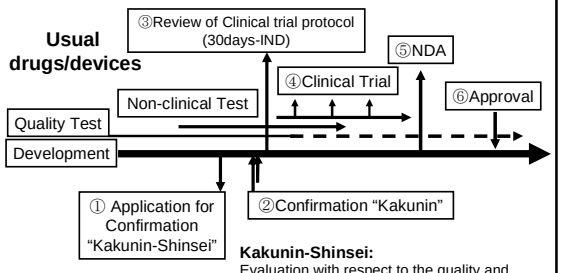
Assuring the Quality and Safety of Cell/Tissue Based Products
-MHLW Notification No.906 (30 Jul. 1999)
Rev. 30 Mar. 2007

⇨ **Application for confirmation prior to the first clinical trial: "Kakunin Shinsei"**

Guideline on Ensuring Quality and Safety of Products Derived from Processed Human Cell and Tissues
-MHLW Notification No.1314 (26 November 2000)

25

Development Process of Cell/Tissue based Products in Japan under PAL.



ADD-ON for Cell/Tissue based products

Kakunin-Shinsei:
Evaluation with respect to the quality and safety of Gene therapy & cell/tissue based products intended for clinical use

Regenerative Medicine 5 (2):172-215, 26

Guideline for Assuring the Quality and Safety of Cell/Tissue based products

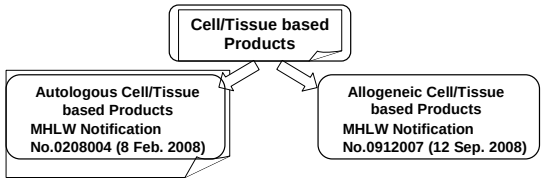
This guideline describes the major issues concerning the assurance of quality and safety of the Cell/Tissue based products and outlines the data and information to be addressed by manufacturers when filing an application with respect to the quality and safety of the products intended for clinical use.

- **Chapter 1 General provisions**
- **Chapter 2 Manufacturing process**
- **Chapter 3 Specifications and formulation**
- **Chapter 4 Stability**
- **Chapter 5 Preclinical safety studies**
- **Chapter 6 Summary of preclinical study (evaluation of risk/benefit)**
- **Chapter 9 Ethical consideration**
- **Chapter 10 Miscellaneous provisions**

27

Revision of Application for Confirmation "Kakunin-Shinsei"

- Revision of the Guideline on Ensuring Quality and Safety of Products Derived from Manipulated Human Cell and Tissues (#1314 GL app.2)



- The GMP/QMS for human autologous cell/tissue manipulated products ⇨ **MHLW Notification No.0327025 (27 Mar. 2008)**

28

Confirmed Cell/Tissue based product Protocols

Year	Sponsor	Disease	Cell/Tissue	Auto/Allo
2001	Kirin	Prostate Cancer	Dendritic Cell	Autologous Cell
2001	Kirin	Multiple Myeloma	Dendritic Cell	Autologous Cell
2002	J-TEC	Sever Burns	Epidermis Cell	Autologous Cell *
2004	J-TEC	Osteoarhtritis etc.	Cartilage	Autologous Cell
2006	Terumo	Coronary Infraction	Skeletal Myoblast	Autologous Cell
2007	JCR	GVHD	Mesenchymal Stem Cell	Allogeneic Cell
2007	BCS	Severe Burns	Epidermis and Fibroblast Cell	Autologous Cell

* Approved on 29th Oct. 2007

As of Dec. 2007

Development of

Biological Products for Cancer

30

Cancer Vaccines and Immunotherapy Regulation

- Cancer vaccines and immunotherapy should be regulated as Biological Products.
- In case of Gene-therapy or Cell/Tissue-derived Products, there are add-on regulation respectively.
- The efficacy will be reviewed as anti-cancer agents.

What's "cancer vaccine"?

- Antigen/adjuvant vaccines
- Whole cell cancer vaccines
- Dendritic cell (DC) vaccines
- Viral vectors
- DNA vaccines
- Idiotype vaccines

- HPV vaccine???
- HBV vaccine???

Japanese Regulation of Cancer Vaccines and Immunotherapy

- **Peptide/adjuvant vaccines**
- **Whole cell immunotherapy**
  ex. BCG for intravesical use
  → A monograh of Minimum Requirements for Biological Products was registered newly
- **DC based immunotherapy**
  Application for Confirmation, as Cell/Tissue based products, is needed before IND
- **DNA & Viral vaccines**
  are not Gene therapy products, but・・・
  if recombinant, Application for Confirmation, as Gene therapy products, is needed before IND

Environment Changes for Oncology Drug
Regulatory and Clinical Development

- Revised Guideline for Clinical Evaluation on Anti-cancer Dugs (Nov. 2004)
- MHLW study group
  - Cancer Combination Therapy (2005)
  - Unapproved Drug (2006)
- PMDA encourage to planning and conducting Multinational Clinical Trial
  - Point to Consider for MCT (2007)
- Constructive dialogue with industry, academia and regulatory authority

Revision of Guideline for Clinical Evaluation

- New guidelines for clinical evaluation of Anti-cancer drugs (issued Nov. 2004)
- Long time passes from the old version (issued on Feb.1991)
- Required the Phase III data before NDA for cancers with large patients population
- Great flexibility for accepting foreign clinical data and clinical development of the oncology drug

Impact of New Guideline

- Increase utilization foreign clinical data (especially PIII comparative trial)
  - If a new drug has demonstrated efficacy overseas and if its large safety database is available, then it is advantageous in a smooth and efficient development in Japan
- The importance of a development strategy increases
  - From early stage of clinical development, to conduct of a POC study or a multinational study should be considered for scientific and efficient clinical development.
- The opportunity of a dialog between industry and PMDA will increases

Immunotherapies of cancer approved in Japan

- **Whole cell immunotherapies**
  - BCG for intravesical use (bladder cancer)
- **Cytokines**
  - G-CSF
  - interferon
- **Antibodies**
  - trastuzumab
  - rituximab
  - gemtuzumab ozogamicin
  - iburitumomab tiuxetan
  - bevacizumab
  - cetuximab

Review for Efficacy of cancer vaccine

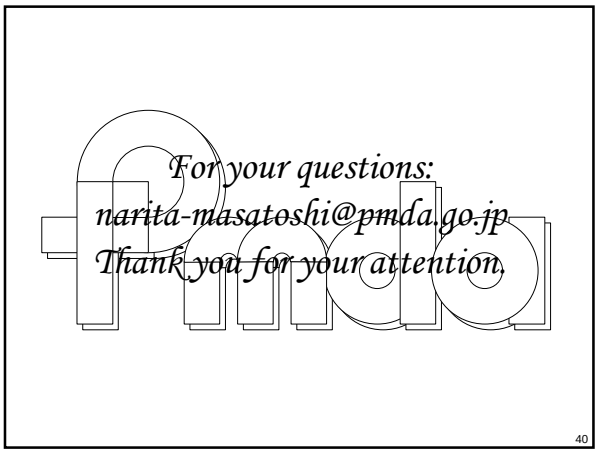
- Unknown dose-response
- Unique toxicity?
- Endpoint is due to its aim
  - adjuvant(secondary prophylaxis / prevention)
  - Therapy with/without traditional chemtherapeutic agents/other biologic agents
  - Primary prophylaxis / prevention

Needed multi-arm, parallel design trials; trial design analysis plan must be pre-specified
Patient selection and endpoint definition require careful consideration.

Our Mission

To Ensure **Faster** Access to
More Effective and **Safer**
Pharmaceuticals & Medical Devices
for the Public

Improving Public Health


For your questions:
narita-masatoshi@pmda.go.jp
Thank you for your attention.
40

Regulatory Considerations in Oncology Biologics Development in Canada

Gina Coleman, MD

Health Canada | Santé Canada — Your health and safety...our priority. | Votre santé et votre sécurité...notre priorité.

Regulatory Considerations for Oncology Biologics Development in Canada

iSBTc Global Regulatory Symposium
San Diego, California
October 29, 2008

MedEffect Canada
Together we can improve health product safety
MedEffet Canada
Ensemble nous pouvons améliorer l'innocuité des produits de santé

Gina Coleman MD
Chief, Clinical Trials Evaluation Division
Health Canada

October 29, 2008

Canada

- **In Canada oncology biologics are regulated under the Food and Drugs Act and Regulations**
- **The Biologics and Genetic Therapies Directorate, part of Health Canada, is responsible for ensuring the safety, efficacy and quality of all biologics for human use marketed in Canada**

2

BGTD Responsibilities

- Part of Health Canada's Health Products & Food Branch
- BGTD is the Canadian federal authority responsible for regulating biological drugs and radiopharmaceuticals for human use
  - Clinical Trial Review and Authorization
  - Product review and assessment
    - Includes laboratory testing and On-Site Evaluation
  - Develops new policies and regulatory framework as needed and keeps existing ones updated
    - Collaborates with clients, stakeholders and the general public
  - Active research laboratories
  - Departmental biotechnology coordination

3

Life Cycle of a New Biological Drug

Research

Create/Isolate Active Ingredient
More Specific animal
(14,000 tested to have one marketable)
testing and in vitro tests
(e.g. carcinogenicity, reproductive studies)

Tissue/Culture
small animals

Human Testing

(Clinical Trial)

4

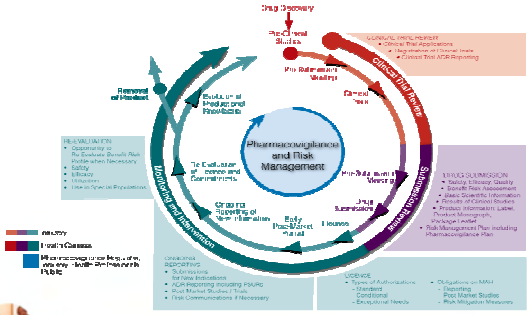
Specifics for regulatory review of biologics in Canada

In addition to paper review, biological drug review includes:

- **On-site evaluations**
  - Assessment of the production process and facility for a specific product which ensures that the manufacturing process conforms to information described in the submission.
- **Additional GMP (Good Manufacturing Practices)**
  - Special considerations and issues pertinent to manufacturing and control of biological drugs, blood and blood components.
- **Lot-release**
  - Laboratory work on samples received from drug companies to confirm potency, purity and safety.
  - Only high risk products are tested (new products and vaccines).

5

Progressive Licensing Model



6


Questions
Thank You
7

Regulatory Considerations in Oncology Biologics Product Development in India

Bindu Dey, PhD

Indian Drugs/Biologics Regulations

Four Essential Elements of Regulations

- There is a **OR** multiple **Regulatory Authority/ies**
- There are **National Laws**
- There are **different entities** to be approved-Drugs, Biologics, Recombinant biologics, Cell-based therapies, Devices etc.
- These entities are at **different levels/stages of development** for approvals-Importation, Pre-clinical, Phase I/II/III or Indigenously developed

Regulatory Authority/ies

Multiple

- The Drugs Controller General of India (DCGI) under the Ministry of Health & Family Welfare
- The Department of Biotechnology under the Ministry of Science and Technology
- The Ministry of Environment and Forests
- The Controller General of Patents, Designs, Trademarks under the Ministry of Commerce and Industry
- Now proposed National Biotechnology Regulatory Authority

Laws on Biologics Regulation in India

Multiple

- The Drugs & Cosmetics Act, 1940
- Schedule Y introduced under Drugs & Cosmetics Act, 1940 in 1988(Amended version, 2005)
- The Environmental Protection Law, 1986
- The Bio-safety Regulations, 1989
- The Patents Law, 1970(The Patents Amendment Act, 2005)

The Drugs & Cosmetics Act, 1940

Schedule Y

Refers to requirements and guidelines to be followed in order to attain permission of:

- Importing

and/or

- Manufacturing New Drugs to market

or

- To undertake clinical trials in India.

Essentials of Schedule Y

- Depends on the status of drug in the country of origin
- Approved Drugs/Biologics-Phase III
- Not Approved Drug-One Phase earlier
- New Discovered Drugs in other countries- Phase I not permitted ; hence Safety data needed
- Trials permitted for drugs of special relevance

Essentials of Bio-safety Laws

- Applicable to all r-DNA products
- Three -tier bio-safety system before clinical trials
    1. IBSC(At the Institute Level)
    2. RCGM(At the D/O Biotechnology level)
    3. GEAC(At the M/O Environment)
- Approval for Human trials given by the DCGI

Drivers of making Laws

- Domestic needs-(Cost-Effective)
- Economic needs- (To capture non-regulated OR semi-regulated markets by making Generics & Bio-similars)
- Political situation-(Adopting Process Patent)
- Providing impetus to technological development (Adopting Process Patent)
- Promoting inventive activities in the country (Adopting Process Patent)
- International obligations on Trade matters (WTO) (Adopting Product Patent)
- Harmonization of International standards for Quality(ICH-GCP)

What is there in Cancer Biologics?

- Cancer Vaccines-Prophylactic (Hep-B, HPV, *H.pylori*)
- Cancer Immuno-modulators(bCG, *M.indicus talwarnii*)
- Cancer Biologics(Predominantly Bio-similars)
- Stem Cell therapy-????
- Other cell-based therapies(DC-based)
- Devices????

Regulatory Considerations on Development of Biological Products for the Treatment of Cancer - China

Luo Jianhui, MD

Regulatory consideration on development of biological products for treatment of cancer

Luo Jianhui

CDE SFDA, China

General introduction

- **Legal compulsion**
  Drug Law of China; September 1984，update February 2001；
- **Regulatory requirement**
  Regulation for the Implementation of Drug Registration; August 2002;
  Management of Drug Registration, 1999，update， July 2007;
- **Guideline documents**
  1999, update and add-on since 2005;

Management of Drug Registration

Section 3 clinical trail of drugs

- **item 31 , clinical trail, phase I to phase IV;**
- **item 36, quality control by NICPBP;**
- **item 44, basic requirements for international multi-center study;**

International clinical trail application or registration application

requirements in detail

- **44.2 SFDA special requirements for international multi- center trail;**
- **44.5 clinical data requirements for submitting or registration;**

Guideline documents

- **57 documents available concerning chemical drug, Chinese herbs drug and biologics;**
- **15 documents concerning biological products;**
- **6 documents concerning quality control of mammalian cell substrate, non-clinical and clinical study of therapeutic or prophylactic biological products, or validation of analytical assay used for quality control of biological products;**

Basic Structure and function of Regulatory Authority

SFDA

CDE	**NICPBP**	**Others**
Biologics division	**Testing laboratory**	
Responsible for evaluation of IND or BLA application	**Responsible for quality control Batch release for clinical trail or on market**	

Advancing procedure of cancer

Disease			Outcome
sensitive	growth	relapse	cachexia, dying
under control	metastasis	resistant	lost control, death

Questions for consideration of clinical trail design

For therapeutic vaccine or cell therapy:

What kind of clinical trail should be considered of for cancer patient at different disease stage ?

Should early cancer patients be involved in explorative clinical trail ?

Key aspects to consider

Cancer cell, malignance and behavior ?

Therapy adopted, radiation, chemical toxin, operation, biotherapy ?

Patient's state, response to therapy, tolerance, quality of life ?

Medical practice, patient's willingness, therapy availability and price, ethical consideration?

Regulation of Oncology Biologics in Switzerland

Andreas Marti, PD, PhD

swissmedic

Regulation of Oncology Biologics in Switzerland

Andreas Marti
Swissmedic
Bern, Switzerland

iSBTc, Global Regulatory Summit
October 29, 2008, San Diego (CA)

swissmedic

Oncology Biologics include

- Monoclonal antibodies, recombinant proteins
- Cancer vaccines
- Gene therapy products
- Transplantation products

swissmedic

Legal Basis

- Swiss Law on Therapeutic Products
- Swiss Law on Transplantation
- European Pharmacopoeia

Guidelines

- Swiss Guidelines
- International Guidelines (e.g. ICH* Guidelines)

*ICH: International Conference on Harmonisation; www.ich.org

swissmedic

Regulation of Oncology Biologics

- Not different from other medicinal products
- Notification/approval of clinical trials
- Marketing authorization of products
- Accelerated approval possible
- Orphan drug status if requirements fulfilled
- Scientific advice

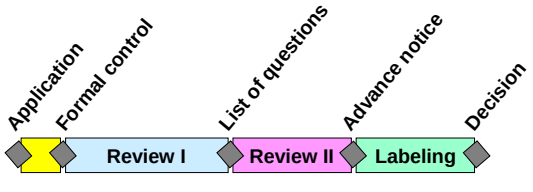
swissmedic

Approval of Clinical Trials (90 days)

(Gene therapy and investigational products containing GMOs)

swissmedic

Marketing Authorization



Time to approval 130 – 300 days
(Swissmedic evaluation time)

Regulatory Considerations in Oncology Biologics Product Development

Samir Khleif, MD

Slides were not available in time for printing

NOTES

NOTES

NOTES

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3. **Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use** *(February 1997)*
   http://www.fda.gov/cber/gdlns/ptc_mab.pdf

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5. **Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)** *(August 2007)*
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6. **Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-Up of Patients in Clinical Trials Using Retroviral Vectors** *(November 2006)*
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   www.fda.gov/cber/gdlns/gtclin.html

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US Reference Materials

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   http://www.fda.gov/cder/guidance/1397fnl.pdf

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   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

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6. **Biological Product – Information on Submitting an Investigational New Drug Application**
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US Reference Materials

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The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater armonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

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Published in: *Journal of Clinical Oncology,* Vol 26, No 4, February 2008, pp 527-34.

16. **A Pooled Analysis of Eastern Cooperative Oncology Group and Intergroup Trials of Adjuvant High-Dose Interferon for Melanoma** by Kirkwood J, Manola J, Ibrahim J, Sondak V, Ernstoff M, Rao U.
Published in: *Clinical Cancer Research*, Vol 10, 2004, pp 1670-77.

17. **Prospect of Targeting the CD40 Pathway for Cancer Therapy** by Vonderheide R
Published in: *Clinical Cancer Research,* Vol 13, No 4, 2007, pp 1083-88.

18. **Interleukin Therapy** by Lotze MT
Published in: DeVita, Hellman, and Rosenberg's *Cancer: Principles and Practice of Oncology* by Vincent T. DeVita, Theodore S. Lawrence, Steven A. Rosenberg, Robert A. Weinberg, and Ronald A. DePinho, Lippincott Williams & Wilkins, Philadelphia, 2008.

19. **Guidelines for Assuring the Quality and Non-Clinical Safety Evaluation of DNA Vaccines** *World Health Organization,* 2005
http://www.who.int/biologicals/publications/ECBS%202005%20Annex%201%20DNA.pdf

Websites to Consider for Bench to Beside Development of New Agents

1. **Clinical and Translational Science Awards** (CTSA) is a national consortium funded through Clinical and Translational Science Awards to transform how clinical and translational research is conducted. www.ctsaweb.org.

2. **Developmental Therapeutics Program at the NCI/NIH** has a number of grants and contracts programs that provide support for various stages of new drug development from preclinical feasibility and toxicology support to the production of clinical grade reagents including IND filing assistance (Rapid Access to Interventional Development (RAID) program. www.dtpnci.nih/gov.

3. **Financial Conflict of Interest** is an increasingly important issue to consider when intellectual property is licensed to biotechnology or pharmaceutical companies for clinical development. The American Association of Medical Colleges (AAMC) provides guidelines for investigators that have been adopted by many Universities for use by University Conflict of Interest Committees that manage these conflicts. These guidelines can be found at: www.AAMC.org/research/COI/.

US Reference Materials

Other Resources

1. **Interagency Oncology Task Force – Joint Fellowship Training Program Information** http://iotftraining.nci.nih.gov/index.html

2. **FDA's Critical Path Initiative**: http://www.fda.gov/oc/initiatives/criticalpath/

3. **FDA, NCI, and CMS Collaboration- Oncology Biomarker Qualification Initiative (OCBI)** – Information on the collaboration/initiative through the press release: http://www.fda.gov/bbs/topics/news/2006/NEW01316.html

4. **The Biomarkers Consortium** – A joint venture of FNIH-NIH-FDA-Academia-Industry. An endeavor to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventative medicine, and medical diagnostics. www.biomarkerconsortium.org

Canada Reference Materials

The Biologics and Genetic Therapies Directorate (BGTD), a part of Health Canada, is the regulatory authority in Canada responsible for working to ensure the safety, efficacy, and quality of all biologics for human use marketed in Canada.
http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index-eng.php

In Canada, biologics are regulated under the *Food and Drugs Act and Regulations (FDA&R)*.
The Food and Drugs Act:
http://laws.justice.gc.ca/en/f-27/text.html

The Food and Drugs Regulations:
http://laws.justice.gc.ca/en/showtdm/cr/C.R.C.-c.870
Part C Division 5: Drugs for Clinical Trials Involving Human Subjects (September 2001)
Part C Division 8: New Drugs

Therapeutic Products Directorate Advisory Committee on Oncology Therapies provides Health Canada (HC) with timely scientific, technical and medical advice related to the regulation of oncology therapies.
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-com/onco/index-eng.php

Clinical Trials Manual:
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_intro-eng.php

Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines: Manufacture of Drugs Used in Clinical Trials:
http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/cln_trials-essais_cln-eng.pdf

Guidelines for Preparation of Drug Submissions
http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/drugs-drogues/index-eng.php

Special Access Programme (January 2008)
http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3-eng.php

ICH Guidances
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/index-eng.php

Forms

1. HC SC 3011: Drug Application for: Human, Veterinary, or Disinfectant Drugs and Clinical Trial Applications/Attestation
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/hc3011_sc3011-eng.php

2. Submission Fee Application Form
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/feef_fraisf-eng.php

Guidance Documents

1. Guidance for Clinical Trial Sponsors: Clinical Trial Applications
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_howto_3011-eng.php

2. Lot Release Program for Schedule D (Biologic) Drugs
   http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/lot/notice-avis_final_lot-eng.php

Canada Reference Materials

Guidance Documents *(continued)*

3. Preparation of Drug Submissions in the CTD Format
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/ctdnds_ctdpdn-eng.php

4. Preparation of Drug Submissions in the eCTD Format
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/ectd/prep_ectd_format-eng.php

5. Preparation of Drug Identification Number Submissions
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/din/index-eng.php

6. Guidance for Industry – Changes in Product Specific Facility Information (2004)
   http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/info/prod_market-comm_change-eng.php

7. Management of Drug Submissions
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.php

8. Notice of Compliance with Conditions (NOC/c)
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/compli-conform/noccg_accd-eng.php

9. Priority Review of Drug Submissions
   http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/priorit/priordr-eng.php

10. Guidance for Industry – Product Monograph
    http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm_mp-eng.php

11. Reconsideration of Final Decisions Issued for Human Drug Submissions
    http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/revision-final/decisions_hum_drug_drogue-eng.php

12. Electronic Templates for the Quality Information of Drug Submissions for Biological Products and Radiopharmaceuticals:
    http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/templates-modeles/notice-avis-bio-eng.php

13. Good Manufacturing Practices for Schedule D Drugs, Part 1: Biological Drugs
    http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/sched_d_part1-annexe_d_part1-eng.php

14. Guidelines for Reporting Adverse Events Associated with Vaccine Products
    http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/00vol26/26s1/index.html

Progressive Licensing:
http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/index-eng.php

Extraordinary Use New Drugs (EUNDs)
http://www.hc-sc.gc.ca/dhp-mps/brgtherap/legislation/notices-avis/eund-dnue_2007-10-31-eng.php

China Reference Materials

China State Food and Drug Administration Reference Documents

1. **Home page**: http://www.sfda.gov.cn

2. **Drug Administration Law of the People's Republic of China** *(English)*
   http://eng.sfda.gov.cn/cmsweb/webportal/W45649037/A48335975.html

3. **Regulations for Implementation of the Drug Administration Law of the People's Republic of China** *(English)*
   http://eng.sfda.gov.cn/cmsweb/webportal/W45649038/A48335997.html

4. **Application and Approval Procedure for Clinical Trails** *(English)*
   http://eng.sfda.gov.cn/cmsweb/webportal/W45649089/A64002920.html

5. **Special Review and Approval Procedure for Drugs** *(text available only in Chinese)*
   http://www.sfda.gov.cn/WS01/CL0053/24520.html

6. **Batch Release Procedure for Biologics** *(text available only in Chinese)*
   http://www.sfda.gov.cn/WS01/CL0053/24488.html

7. **Regulation on Imported Drugs** *(text available only in Chinese)*
   http://www.sfda.gov.cn/WS01/CL0053/31658.html

8. **Notice Guideline on Gold Practice for Non-Clinical Study of Drugs** *(text available only in Chinese)*
   http://www.sfda.gov.cn/WS01/CL0053/24472.html

9. **Notice Guideline on Gold Practice for Clinical Study of Drugs** *(text available only in Chinese)*
   http://www.sfda.gov.cn/WS01/CL0053/24473.html

10. **Drug Registration**
    http://eng.sfda.gov.cn/cmsweb/webportal/W45649089/index.html

11. **Notice of Guideline on Non-Clinical Study of Preventive Vaccine Used in Human 20051014** *(text available only in Chinese) (6 files)*
    http://www.sfda.gov.cn/WS01/CL0058/9350.html

12. **Notice of Guideline on Quality Control of Live Vaccine Derived from Virus Vector 20030320** *(text available only in Chinese) (9 files)*
    http://www.sfda.gov.cn/WS01/CL0058/9339.html

Center for Drug Evaluation Reference Documents

1. **Home page**: http://www.cde.org.cn

2. **General Consideration on Virus Safety in Biologics from Animal Source** *(text available only in Chinese) 2003*
   http://www.cde.org.cn/page/BrowInfo4.cbs?ResName=zdyzxz&no=33&ResultFile

3. **General Consideration on Validation of Analytical Assay Used in Quality Control of Biologics** *(text available only in Chinese) 2003*
   http://www.cde.org.cn/page/BrowInfo4.cbs?ResName=zdyzxz&no=34&ResultFile

China Reference Materials

Center for Drug Evaluation Reference Documents *(continued)*

4. **Quality Control on Mammalian Cell Substrate Used for Production of Therapeutical Products** *(text available only in Chinese) 2006*
   http://www.cde.org.cn/page/BrowInfo4.cbs?ResName=zdyzxz&no=42&ResultFile

5. **Clinical Study of Anti-Cancer Drug** *(text available only in Chinese) 2006*
   http://www.cde.org.cn/page/BrowInfo1_Tmpl6.cbs?ResName=zdyzxz&RC=68&order=52&ResultFile=&SortFld=&sortorder

6. **General Consideration on Clinical Trail of Vaccine with New Adjuvant** *(text available only in Chinese) 2007*
   http://www.cde.org.cn/page/BrowInfo1_Tmpl6.cbs?ResName=dzkw&RC=1132&order=913&ResultFile=&SortFld=&sortorder

Papers *(only available in Chinese)*

1. **Point View of Clinical Evaluation of Biosimilar Products** *2007*
   http://www.cde.org.cn/page/BrowInfo4.cbs?ResName=dzkw&no=1049&ResultFile

2. **Point view of Consideration on Biosimilar Products** *2007*
   http://www.cde.org.cn/page/BrowInfo4.cbs?ResName=dzkw&no=1037&ResultFile

3. *Chinese translation of* **"Clinical Development Paradigm for Cancer Vaccines and Related Biologics"** *2007*
   http://www.cde.org.cn/page/BrowInfo4.cbs?ResName=dzkw&no=906&ResultFile

4. **Special Consideration of Non-Clinical Study on Recombinant Therapeutical Products 2004**
   http://www.cde.org.cn/page/BrowInfo4.cbs?ResName=dzkw&no=309&ResultFile

5. **Notice on Principle for Non-Clinical Study on Recombinant Therapeutical Products 2007**
   http://www.cde.org.cn/page/BrowInfo4.cbs?ResName=dzkw&no=904&ResultFile

EU Reference Materials

European Legislation

1. **EUDRALEX – The Rules Governing Medicinal Products in the European Union**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm

2. **Regulation on Advanced Therapy**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

3. **Updated Regulation on the EMEA and Pharmacovigilance**
   http://ec.europa.eu/enterprise/pharmaceuticals/review/doc/final_publ/reg_2004_726_20040430_en.pdf

4. **Updated Directive on Human Medicinal Products**
   http://ec.europa.eu/enterprise/pharmaceuticals/review/doc/final_publ/dir_2004_27_20040430_en.pdf

5. **Clinical Trials Directive**
   http ://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

6. **Directive on Investigational Medicinal Products and Importation**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf

7. **Directive – GMP Requirement for Human Medicinal Products**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf

8. **Orphan Medicinal Products**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

9. **Criteria for Orphan Medicinal Products**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf

10. **Payment of Fees to, and the Receipt of Administrative Assistance from, the European Medicines Agency by Micro, Small and Medium-Sized Enterprises.**
    http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2005_2049/reg_2005_2049_en.pdf

11. **Regulation on Pediatric Development**
    http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

12. **Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on Medicinal Products for Pediatric Use**
    http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf

13. **Genetically Modified Organisms in the Environment**
    http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_18/dir_2001_18_en.pdf

14. **Volume 10 of Eudralex Devoted to Clinical Trial legislation**
    http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm

EU Reference Materials

Chapter I: Application and Application Form

1. **Guidance on Clinical Trial Application, Notification of Substantial Amendments and Declaration of the End of the Trial**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/11_ca_14-2005.pdf

2. **Ethics Committee Application**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/12_ec_guideline_20060216.pdf

3. **Guidance on the EUDRACT Data Base**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/13_cp_and_guidance_eudract_april_04.pdf

Chapter II: Monitoring and Pharmacovigilance

1. **Guidance on Collection, Presentation and Verification of AE Reports from Clinical Trials**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/21_susar_rev2_2006_04_11.pdf

2. **Guidance on EU Database on SUSARs**
   http ://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/22_cp_and_guidance_database_susars16_april_2004.pdf

Chapter III: Quality of Investigational Medicinal Products

1. **Good Manufacturing Practices**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf

2. **Annex 13 to Good Manufacturing Practices**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf

3. **EU Format for Manufacturing Authorization**
   http://www.emea.europa.eu/Inspections/GMPCompproc.html
   http://www.emea.europa.eu/Inspections/docs/CoCP/CoCP_FormatMA.pdf

4. **GMP Status of Manufacturers in Third Countries**
   http://www.emea.europa.eu/Inspections/docs/CoCP/CoCP_VerificationGMP3rdCountry.pdf

5. **Guideline: Quality Requirements for Investigational Medicinal Products in Clinical Trials**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/18540104en.pdf

Chapter V: Additional Information

1. **Content of Trial Master File and Archiving**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/v10_chap5.pdf

2. **Q & A – Clinical Trial Documents**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/v10_chap5.pdf

3. **Guidance on Investigational Medicinal Products for Clinical Trials**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/guidance-on-imp_nimp_04-2007.pdf

EU Reference Materials

Chapter VI: Legislation

1. **Manufacture and Importation of Investigational Medicinal Products**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf

2. **Marketing Authorization – Notice to Applicants**
   http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm

UK Links – MHRA and others

1. **Electronic Medicines Compendium**
   http://emc.medicines.org.uk

2. **Clinical Trials**
   http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=101

3. **Applying for a Clinical Trial Application**
   http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=723

4. **Maintaining a Clinical Trial Application**
   http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=983

5. **Making Clinical Trial Applications**
   http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1123

6. **Additional Information**
   http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1177

7. **Fees for Clinical Trials**
   http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1124

8. **Forms for Clinical Trials**
   http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1125

9. **Safety Reporting – Annual Safety Reports and SUSARs**
   http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=993

EU Reference Materials

General Information

1. **EudraPharm –** A source for all medicinal products in Europe
   http://eudrapharm.eu/eudrapharm/welcome.do?selectedStaticLocale.languageCode=en

2. **Heads of Agencies**
   http://www.hma.eu/index.html

3. **French Agency – AFSSAPS** *(English Language Link)*
   http://agmed.sante.gouv.fr/ang/indang.htm

4. **List of Ongoing Clinical Studies in France** *(in French)*
   http://agmed.sante.gouv.fr/htm/5/repec/repec0.htm

5. **Medical Products Agency** *(Sweden site in English)*
   http://www.lakemedelsverket.se/Tpl/NormalPage____2159.aspx

6. **Danish Medicines Agency – Legislation** *(English)*
   http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=742

Guidelines

1. **Link to CHMP Efficacy and Safety Guidelines**
   http://www.emea.europa.eu/htms/human/humanguidelines/efficacy.htm

2. **Pharmacokinetics of Therapeutic Proteins**
   http://www.emea.europa.eu/pdfs/human/ewp/8924904enfin.pdf

3. **Evaluation of Anticancer Medicinal Products in Humans**
   http://www.emea.europa.eu/pdfs/human/ewp/020595en.pdf

4. **Annual Safety Report Template** – an example
   www.ucl.ac.uk/biomed-r-d/guides/guide_asrprep_submission.doc

5. **Radiation Protection**
   http ://ec.europa.eu/energy/nuclear/radioprotection/doc/legislation/9629_en.pdf
   http ://ec.europa.eu/energy/nuclear/radioprotection/doc/legislation/9743_en.pdf

6. **Radiation Protection – UK Specific Legislation**
   http ://www.corec.org.uk/applicants/apply/docs/Question-specific_Guidance.doc
   http ://www.corec.org.uk/applicants/docs/NHS_REC_Application_Form_v5_Content_Changes.doc

7. **EMEA – Guideline on Adjuvants in Vaccines for Human Use** *(January 2005)*
   http://www.emea.europa.eu/pdfs/human/vwp/13471604en.pdf

8. **EMEA – Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products** *(July 2007)*
   www.eanm.org/news/doc_infoc/EMEA_Guideline_First_In_Man_Clinical_Trials_07_2007.pdf

India Reference Materials

1. **The Drugs and Cosmetics Act, 1940**
   http://www.wipo.int/tk/en//laws/pdf/india_drugsact.pdf

2. **The Drugs and Cosmetics (Iind Amendment) Rules, 2005**
   http://dbtbiosafety.nic.in/act/Schedule_Y.pdf

3. **Schedule Y**
   http://cdsco.nic.in/html/Schedule-Y%20(Amended%20Version-2005)%20original.htm

4. **The Environment Protection Act, 1986**
   http://envfor.nic.in/legis/env/env1.html

5. **The Environment Protection Act, 1989**
   http://dbtbiosafety.nic.in/introduction.htm
   http://dbtbiosafety.nic.in/default.asp

6. **The Patent Act, 1970**
   http://www.ipindia.nic.in/ipr/patent/patents.htm

7. **The Patent Act, 1970 as amended by the Patents (Amendment) Act, 1999**
   http://www.ircc.iitb.ac.in/Ipcourse/patent.html

8. **The Patent (Amendment) Act, 2005**
   http://ipindia.nic.in/ipr/patent/patent_2005.pdf

9. **Draft Establishment Plan for Setting up of NBRA**
   http://dbtindia.nic.in/Draft%20establishment%20plan%20for%20NBRA_28may2008.pdf

10. **National Biotechnology Regulatory Authority (Draft), 2008**
    http://dbtindia.nic.in/Draft%20NBR%20Act_%2028may2008.pdf

Japan Reference Materials

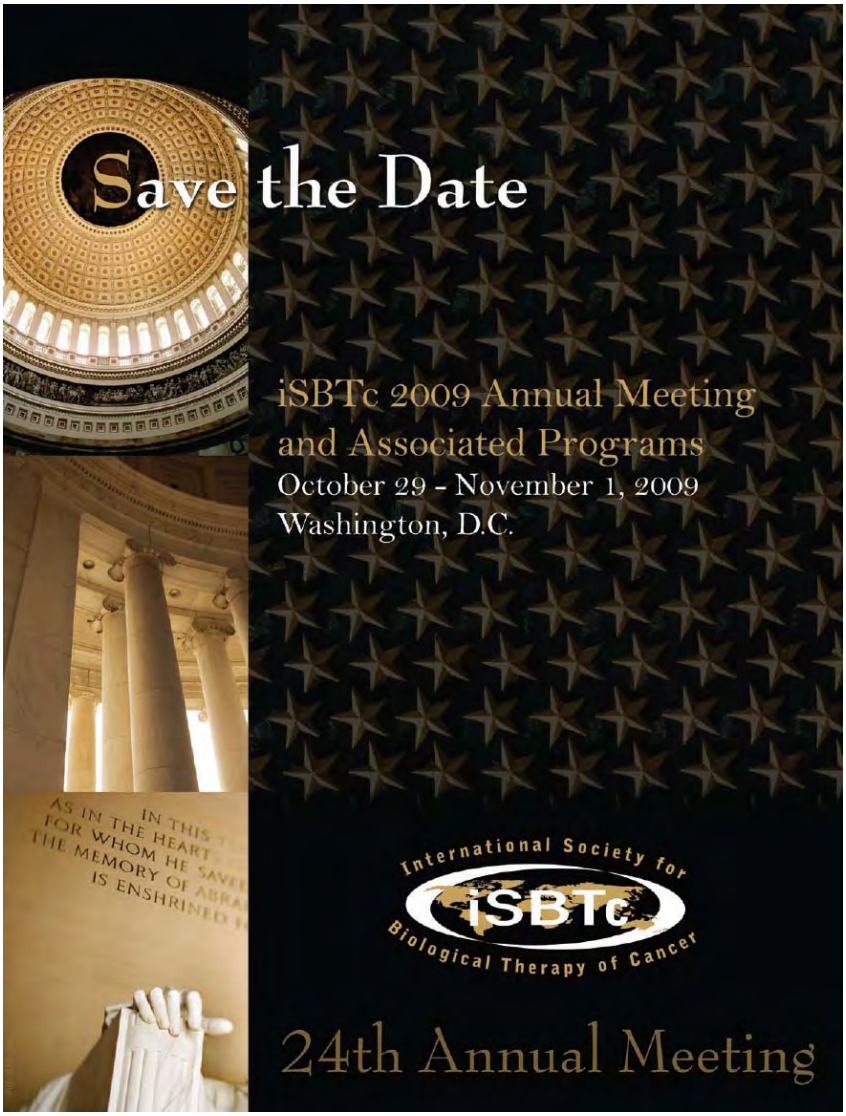
1. "**Drug Approval and Licensing Procedures in Japan 2005**" Published by Jiho Co., Tokyo (ISBN 4-8407-3649-9)
   The most recent official English translation of the industry "Bible" in Japan. The Pharmaceutical Affairs Laws have not changed substantially with respect to biologics since 2005.

2. **Commercialization of Pharmaceutical and Biologics Research: Regulations You Should Know** *(website)* – Contains links to Japanese language documents describing in fairly simple terms the preclinical and clinical regulations on biologics.
   http://www.nibio.go.jp/guide/index.htm

3. **Kitasato University-Harvard School of Public Health Symposium Home Page** *(website)* – Contains useful English and Japanese language slide presentations by various experts in the general field of pharmaceutical industry and drug development.
   http://www.pharm.kitasato-u.ac.jp/biostatis

4. **Biologics Forum** *(Japanese-language website)* – Group that hosts an annual meeting on biologics. Contains links to useful PowerPoint presentations in both English and Japanese.
   http://www.nihs.go.jp/dbcb/Biologics_forum/bioforum-top.html

2009 iSBTc Educational Programs



iSBTc Primer on Tumor Immunology and Biological Therapy of Cancer ~ October 29, 2009

Organizers: Patrick Hwu, MD – *MD Anderson Cancer Center*
Walter J. Urba, MD, PhD – *Earle A. Chiles Research Institute*

iSBTc-FDA Immunotherapy Biomarkers Taskforce Workshop ~ October 29, 2009

Organizers: Lisa H. Butterfield, PhD - *University of Pittsburgh*
Mary L. Disis, MD – *University of Washington*
Francesco Marincola, MD – *National Institutes of Health*
Samir N. Khleif, MD – *National Cancer Institute, CCR*
Magdalena Thurin, PhD – *National Institutes of Health, Diagnostic Research*

iSBTc 24th Annual Meeting ~ October 30 – November 1, 2009

Organizers: Lieping Chen, MD, PhD – *Johns Hopkins University School of Medicine*
Robert L. Ferris, MD, PhD, FACS – *University of Pittsburgh Cancer Institute*
Carl H. June, MD – *University of Pennsylvania*
Giorgio Trinchieri, MD – *National Cancer Institute*
Laurence Zitvogel, MD, PhD – *Institute Gustave Roussy*

For more information about these upcoming iSBTc programs, please visit www.isbtc.org.

About iSBTc

The International Society for Biological Therapy of Cancer (iSBTc) was established in 1984 to facilitate the exchange and promotion of scientific information about the use of biological cancer therapies. The iSBTc defines biological cancer therapies as those based on host response mechanisms used to control or prevent tumor growth. The iSBTc is a 501 (c)(3) not for profit organization of medical professionals with a constituency of academic, government, industry, clinical, and basic scientists from around the world. The Society was founded on the belief that new systemic therapeutic treatments would continue to complement chemotherapies and move into the mainstream in the fight against cancer. To aid in this effort, iSBTc provides channels for the constructive discussion of current clinical trial results and methodologies, as well as a means to collaborate on new initiatives in tumor immunology and biological therapy. It is these key interactions and innovations that help advance the progress of cancer research and therapies and ultimately lead to better patient outcomes.

iSBTc Core Purpose

To improve cancer patient outcomes by advancing the development and application of biological therapy.

iSBTc Core Values

- **Interaction** – exchange of information and education among basic researchers and clinicians
- **Innovation** – development and application of biological therapy; seeking the best research and thinking related to the Society's purpose and vision
- **Leadership** – defining what is new and important

Disease States

iSBTc programming and membership covers the full spectrum of both solid tumors and hematologic malignancies including:

- Breast
- Colorectal
- Head & Neck
- Hepatocellular
- Kidney
- Leukemia
- Lung
- Lymphoma
- Melanoma
- Neuroblastoma
- Ovarian
- Prostate
- Renal Cell

Medical Specialties

iSBTc members and delegates represent many areas of biological science including:

- Cell Biology
- Dermatology
- Genetics
- Gynecologic Oncology
- Hematology
- Immunotherapy
- Internal Medicine
- Medical Oncology
- Microbiology
- Molecular Biology
- Pediatric Oncology
- Pharmacology / Toxicology
- Radiation Oncology
- Radiology
- Stem Cell Biology
- Surgical Oncology
- Transplantation

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ADDENDUM

Global Regulatory Considerations in the Development of Oncology Biologics Products for the Treatment of Cancer

October 29, 2008
Westin Gaslamp Quarter Hotel
San Diego, CA

iSBTc Global Regulatory Summit – Additional Related Guidelines of Biological Products for Cancer in Japan

Biological Source Materials (Written in Japanese)

1. **The Requirements for Biological Source Materials**
   MHLW Notification No.210 (20 May 2003)
   http://wwwhourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=hourei&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD=&EFSNO=584

Gene Therapy (Written in Japanese)

1. **Assuring the Quality and Safety of Gene Therapy Products** (Guideline for Assuring the Quality and Safety of Gene Therapy Products)
   Notification No.1062 (15 Nov. 1995) (Rev1. 29 Mar. 2002)(Rev2. 28 Dec. 2004)
   http://wwwhourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=tsuchi&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD=&EFSNO=3137

Cell/Tissue Based Products (Written in Japanese)

1. **Assuring the Quality and Safety of Cell/Tissue Based Products**
   Notification No.906 (30 Jul. 1999) (Rev. 30 Mar. 2007)
   http://wwwhourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=tsuchi&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD=&EFSNO=3421

2. **Guideline on Ensuring Quality and Safety of Products Derived from Processed Human Cell and Tissues** (Guideline for Assuring the Quality and Safety of Cell/Tissue Based Products)
   Notification No.1314 (26 Dec. 2000)
   http://wwwhourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=tsuchi&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD=&EFSNO=3540

Clinical Evaluation (Written in Japanese)

1. **Revised Guideline for Clinical Evaluation on Anti-cancer Drugs** (1 Nov. 2004)
   http://wwwhourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=tsuchi&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD=&EFSNO=4099

2. **ICH Guidelines** (Written in Japanese and English)
   (Quality) http://www.pmda.go.jp/ich/quality.htm
   (Safety) http://www.pmda.go.jp/ich/safety.htm
   (Efficacy) http://www.pmda.go.jp/ich/efficacy.htm
   (Multidisciplinary) http://www.pmda.go.jp/ich/m4.htm

FDA Perspective on the Preclinical Evaluation of Biological Therapies for Cancer

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iSBTc "Global Regulatory Summit"
October 29, 2008 ~ San Diego, CA

Presentation Outline

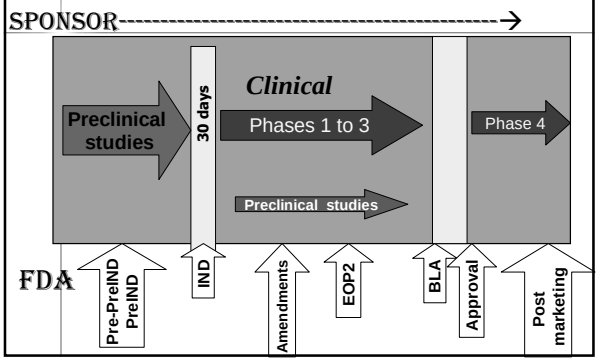
- Introduction
- Biological therapies for cancer regulated by FDA
- Rationale for conducting preclinical studies
- Pharmacology studies
- Toxicology studies
- Translating preclinical data to the clinical trial

Safety is Always Primary

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.

IND Regulations [21 CFR 312.22 (a)]

Product Development Timeline



Expectations for Preclinical Studies

Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or *in vitro*, on the basis of which the sponsor has concluded that it is reasonable safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.

IND Regulations [21 CFR 312.23 (a)(8)]

Biological Therapies for Cancer Regulated by FDA

Center for Drug Evaluation and Research (CDER)

- Cytokines
- Enzymes
- Growth Factors
- Monoclonal antibodies
- Other biological immunomodulators
- Radio-labeled biologics for therapeutic use
- Recombinant proteins

Biological Therapies for Cancer Regulated by FDA

Center for Biologics Evaluation and Research (CBER)

Conventional antigen-based:
Polypeptides; fusion/conjugated proteins; anti-idiotype antibodies

Cell therapy-based:
Autologous/allogeneic somatic cells/stem cells with or without activation/expansion; tumor cells or lysates; or tumor cells fused with normal somatic cells (e.g., dendritic cells)

Gene therapy-based:
Attenuated bacteria; plasmid DNA; DNA/RNA/viral vectors; *ex vivo* genetically modified cells; yeast vectors with/without gene modification

Biological Therapies for Cancer Regulated by CBER:

Challenges:

- **Products:** Can be complex, diverse, and contain novel features in order to achieve anti-tumor effect
- Administered in combination with adjuvants (e.g., TLR agonists, cytokines), immunomodulators, monoclonal antibodies, growth factors, chemotherapy or radiation therapy

Rationale for Conducting Preclinical Studies

- Mechanism of action
- Pharmacological or biological activities
- Target or off-target toxicities
- Preliminary risk/benefit assessment
- Guide clinical trial(s) design

Pharmacology Studies Proof-of-Concept (POC)

Goal:

Provide the scientific basis to support the rationale and feasibility for conducting the clinical trial

Pharmacology Studies

In vitro or *in vivo* studies conducted to determine:

- Functional response (i.e., anti-tumor activity)
- The nature of immunological responses
- Permissive cell populations or cell lines for further testing
- Biologically responsive animal species for further testing
- Pharmacologically effective dose(s) and dose response
- Optimization of the route of administration (ROA)
- Optimization of the dosing regimen

Toxicology Studies

Goal:

Selection of a safe starting dose and dose escalation scheme for the clinical trial

Toxicology Studies

Conducted to identify:

- Potential toxicities to organs/tissues, cells/proteins/genetic elements
- Delayed toxicities/reversibility of toxicities
- Dose/exposure (NOAEL)
- Subject Selection
- Parameters for clinical monitoring

FDA Approach to Preclinical Study Designs for Biologics

- Data-driven
- Question-based
- Based on the best available science, technology to date
- Follow FDA guidances, ICH guidelines and the CFR

Animal Species

- Biological relevance
  - •Anatomy and pathophysiology
  - •Biological activity & toxicity
- Animal numbers/sex/age
- Healthy animals vs. disease models
  - Healthy: toxicology endpoints
  - Disease:
    - Pharmacology endpoints
    - Pharmacology-toxicology endpoints

Control and Test Articles

- **Control article**:
  - Clinical vehicle/diluent/buffer
  - Provides background/baseline information
- **Test article:**
  - Intended clinical product or product comparable to clinical product

Route of Administration

Mimic the intended clinical route of administration as closely as possible

Dose Levels and Dosing Schedule

- Do the dose levels used in the toxicology study support a safe clinical starting dose and the planned clinical dose escalation scheme?
- Does the dosing schedule used in the toxicology study support the safety of the proposed clinical dosing schedule?

Study Duration

- Is the study duration sufficient to characterize the pharmacological/ biological activity profile?
- Is the study duration sufficient to characterize the toxicology profile?

Toxicology Study Endpoints

- Mortality
- Clinical signs/physical exams
- Body weights, food consumption
- Clinical pathology (hematology, chemistry, coagulation, urinalysis)
- Gross pathology
- Histopathology
- Immunological responses
- Other* (local tolerance, ophthalmology, neurological, developmental/reproductive, etc…)

* Some endpoints may be evaluated during later phase clinical trials

'Pharmacokinetic' Assessment

- Sensitive, specific and reproducible assays
- *In vitro* and *in vivo* studies
  - **Biodistribution**: vector-based products
  - **Cell trafficking/migration**: cellular-based products
  - **Tissue distribution**: antigen-based products
  - Binding specificity, binding affinity, cellular location or genetic integration, if applicable

Good Laboratory Practice

The toxicology studies should be conducted in compliance with Good Laboratory Practice (GLP) as per 21 CFR Part 58.

Sources of Preclinical Data to Support Clinical Trials

- Pharmacology/toxicology assessment in animals or *in vitro* conducted by the IND sponsor
- Cross reference to identical/similar products in previously submitted MFs/INDs
- Published data in peer-reviewed journals

Translating Preclinical Data to the Clinical Trial

- To what extent will data obtained from preclinical studies in the current animal models 'predict' the biological activity (immunological, anti-tumor, etc..) and/or the potential toxicities in human subjects?
- What *in vitro* studies and other new technologies can provide information that will bridge the *in vivo* preclinical data?

[Some] FDA Guidance Documents

Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events -11/28/06

Nonclinical Safety Evaluation of Drug or Biologic Combinations - 3/14/06

Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use - 2/28/97

Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications - 10/29/07

Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients - 5/18/05

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Thank you

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