



## ***Clinical Development of Biotech-Therapeutics in Japan***

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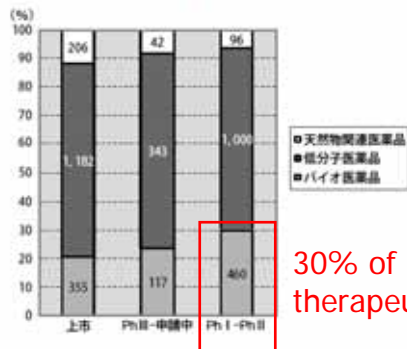


## **Biotechnology Therapeutics (Biologics)**

- Gene therapy
- Somatic Cell Therapy
- Xenotransplantation
- Tumor Vaccines
- Allergen patch tests
- Allergens
- Antitoxins, antivenins, and venoms
- In vitro diagnostics
- Vaccines, prophylactic
- Toxoids and toxins intended for immunization
- Blood, blood components and related products

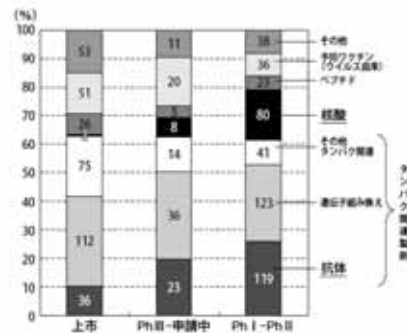
## Development of Biotherapeutics in the World

図1. 新薬の開発・上市状況<sup>2)</sup>



30% of all therapeutics

図2. バイオ医薬品の種類別の開発・上市状況<sup>2)</sup>



## Vaccine Market

### **Worldwide market**

15 Bil US\$ (estimated)

25% increase from last year

Vaccine stands for 2.3% of total medicines

Big pharmaceutical companies cover the market:

GSK, Merck, Aventis, Wyeth, Novartis

...In the future, Pfizer and AstraZeneca will be coming

### **Japan market**

67 Bil JPY (FY2006)

1 Bil decreased from last year

Vaccine stands for 10% of total medicines

Currently, 98% of vaccines are domestic products

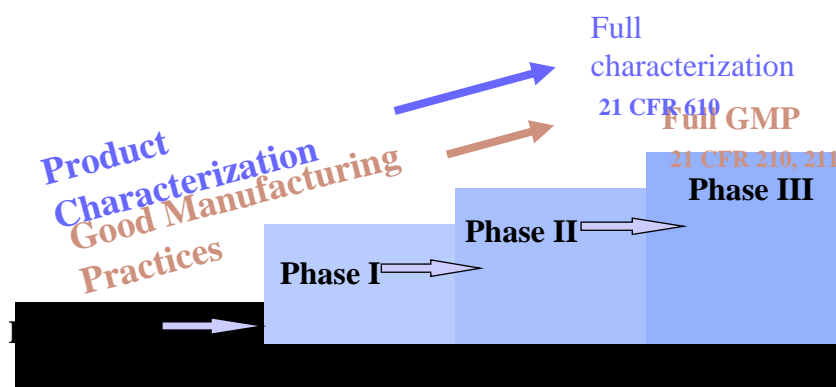
: Kaketsuken, Handai biken, Kitasatoken, Denka seiken etc

...In the future, global companies including Wyeth and GSK will be coming

## Regulatory Concerns Common to All Biologicals

- Product Biosafety
  - sterility, endotoxin, mycoplasma, adventitious agents
- Product Characterization
  - identity, potency, purity, other assessments
- Control of the Manufacturing Process
  - quality of materials and in-process tests, facility, SOPs, record keeping, QA/QC
- Reproducibility/Consistency of Product Lots
  - Lot release testing of final product, specifications

## Clinical Development



Prior to Phase I : need product safety testing and basic characterization info

## ***Project Bioshield* and Emergency Use Authorization (EUA)**

Secretary of HHS can declare an emergency after Secretary of Defense, Homeland Security, or HHS determines an emergency (or potential for) exists.

- Secretary of HHS can authorize use of an unapproved product or unapproved use of an approved product if:
  - Agent can cause serious or life-threatening disease or condition;
  - No adequate and sufficiently available approved alternative;
  - Product's known and potential benefits must outweigh known and potential risks; and
  - The product may be effective.
- EUA is granted for up to 1 year, or until termination of declaration or revocation; can be renewed.

## **HPV Vaccines**

- DNA vaccine for HPV16, 18, and 28
- Shot to 16-18 female to prevent cervical cancer

**paradigm shift**

**prophylactic vaccine**

**therapeutic vaccine**



# Biologics Development in Japan (1)

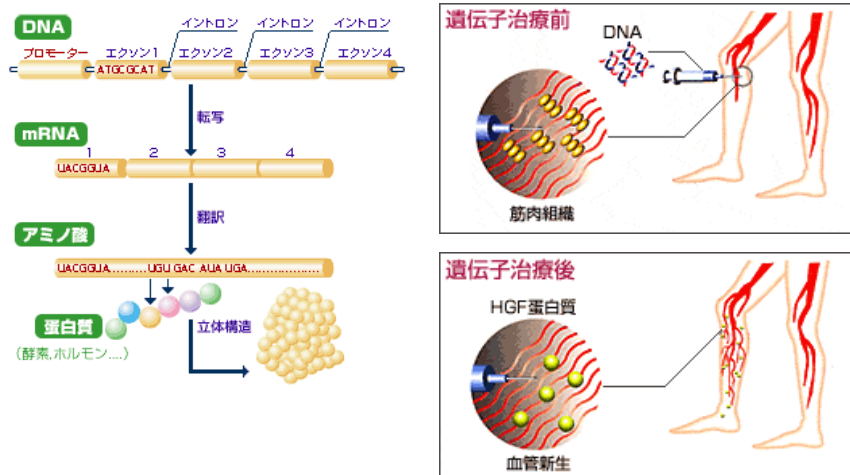
## <Gene Therapy>

- Angen MG (Phase 2 in US; NDA in Japan)  
HGF vascular disease – angiogenesis
- Oncolys Biopharma (Phase 1 in US)  
Adenovirus-telomerase inhibitor

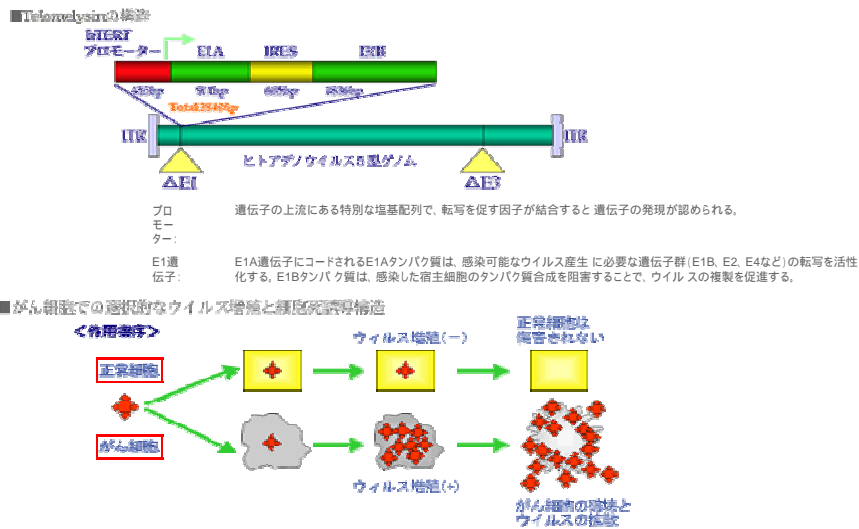
## <RNAi>

- Alfagen (Preclinical)

## HGF gene therapy for obstructive vascular diseases



# Adenovirus encoding hTERT

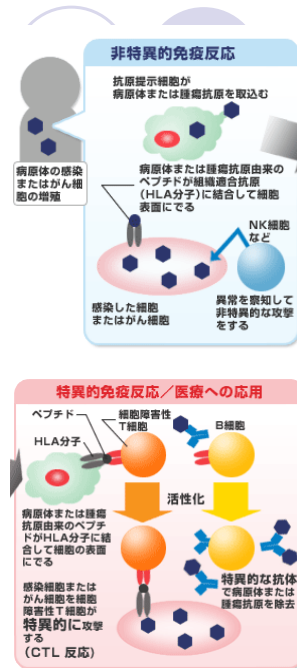
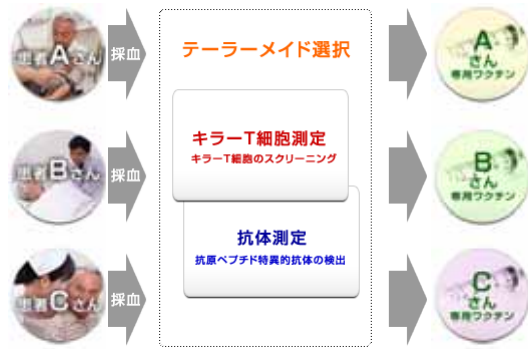


## Biologics Development in Japan (2)

### <Cancer Vaccines>

- Greenpeptide, Co. (Phase 2 in Japan)
- Peptide vaccine – “tailormade” or “ordermade”
- Onco-Therapy Systems

# "Tailormade" cancer vaccine



# Pharmaceutical Manufacturing magazine, June, 2006 issue

Pharmaceutical  
MANUFACTURING

Japanese pharma enters a brave new world.

Upfront



JAPAN'S PHARMA OPENS UP

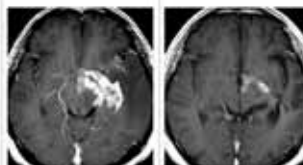
## Personalized Medicine: Immunotherapy Vaccines

Japanese pharma is entering the brave new world of personalized medicine, and the first show its change in April through with a new line of immunotherapy vaccines for individualized cancer treatment. Forthcoming this year, Genepharma Co., Ltd. (Tokyo, Japan) is developing targeted immunotherapies for malignant brain cancer and prostate cancer. Last August and this year, the company submitted IND applications for Phase I studies in Japan.

Based on the fact that we design with naturally with the body's own proteins, Genepharma's brain cancer vaccine aims to control metastasis, and preventing patients with a better "quality of life" alternative to chemotherapy or radiation therapy, explains Kazuo Okamoto, Dr. Peter Yoshida. They conducted at the National University

to their design, the company would conduct studies in patients to determine those who would be most likely to respond to treatment, offering patients an alternative to

evaluating the safety and efficacy of these vaccines for use in patients. Dr. Yoshida says, Genepharma's immunotherapy vaccines had with the



Shown here are the brain scans from the right side of each image. (Brain tumor before and after treatment with Genepharma's immunotherapy, image courtesy of Genepharma Co., Ltd.)

## Biologics Development in Japan (3)

### <Cell & Tissue Therapy>

- BCS, Inc. (discontinued)

Autologous skin regeneration

- Cell Seed, Co. (Clinical trial in France)
- AIBlast, Co. (Clinical trial in Japan)

### <Blood Substitutes>

- Oxygenix, Co. (discontinued)

・PEG表面修飾による物理的安定度向上(長期保存可)  
・血液成分との相互作用回避(血中滞留性の延長)

・ヒトHbと同等の高いHb濃度  
・ウイルスを除去した高純度精製Hbの内包  
・赤血球と類似構造による副作用の回避  
・脱酸素保存による化学的安定度向上(長期保存)

・混合リン脂質型合成脂質の使用により血小板活性化回避

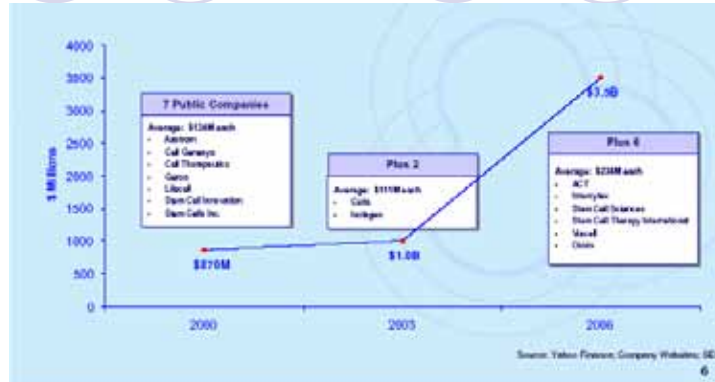
・構造/形状  
脂質2分子膜が精製ヘモグロビンを内包  
高分子鎖が粒子表面に結合  
直径約250nm  
・規格  
製剤としての暫定規格を決定

・特徴  
高いヘモグロビン濃度(ヒト赤血球と同等)  
高い安全性  
(加熱&ナノフィルターの2段階ウイルス不活化・除去)  
保存安定性が優れる(常温2年間)  
血小板などとの相互作用が無く、血中滞留性が高い

粒径約250nm

Oxygen Carriers Development  
As a pioneer in the world, we aim to supply Oxygen therapeutics / Oxygen Carriers to the market and gain the top share of the market.  
In 2004, Oxygenix's facility for the development in Kyoto has started the production of hemoglobin vesicle samples for GLP studies.  
It is planned to start GLP studies in animals under FDA guide line in 2005 and clinical trials in 2006.  
And Nipro Corporation is our partner for GMP based manufacturing, therefore we can focus on the development of Oxygen Carriers without the large-scale plant expense.

## Development of the regenerative medicine products in the US

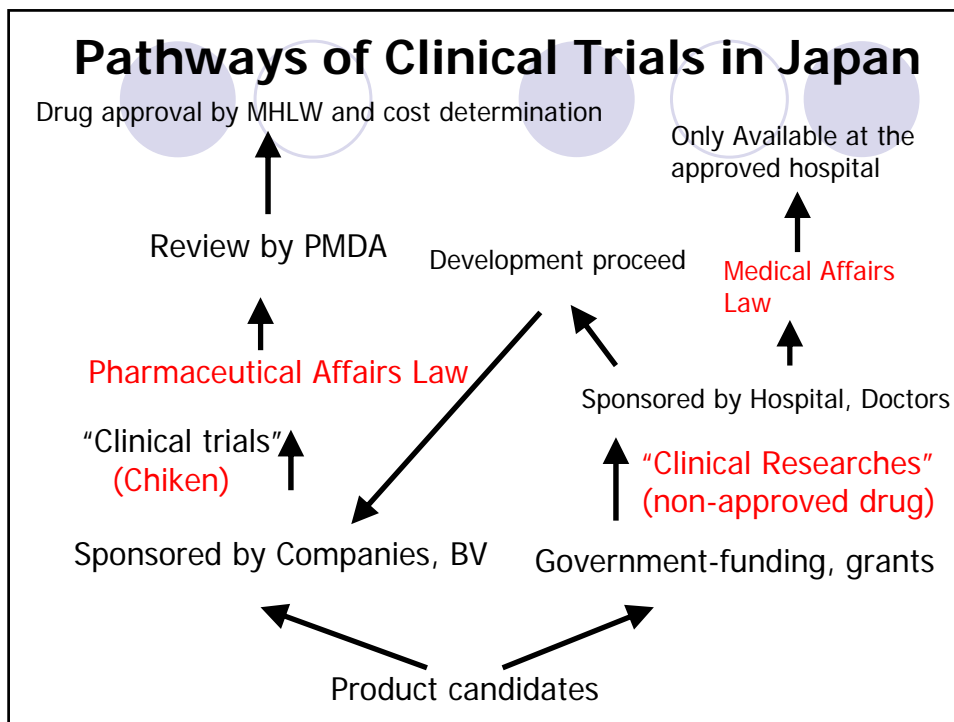


The outlook for companies who make these products has improved, as stock markets have shown increasing interest in regenerative medicine companies. There have been 15 new IPOs (Initial Public Offerings) in the last few years with a total market capitalization of \$3.5B.

## Regulations and Regenerative medicine

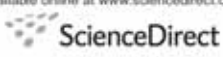
Table 1  
Comparison of topics covered in regulatory guidelines concerning the CMC of cellular and tissue-based products in Japan, the US, and the EU.

Topic	Japan Notification no. 1114	Japan Notification no. 906	Guidelines for clinical research <sup>1</sup>	US Guidance for CMC review <sup>2</sup>	EU Regulation advanced therapy <sup>3</sup>
Scope	○	○	○	○	○
Material and cell collection	○	○	○	○	○
Description of cells and/or tissues (source, characterization, and stability)	○	○	○	○	○
Cell and/or tissue collection (source, method, safety)	○	○	○	○	○
Storage, release, and shipping of cells and/or tissues	○	○	○	○	○
donor screening	○	○	○	○	○
Informed consent for donors	○	○	○	○	○
Donation	○	○	○	○	○
Documents linking donors and materials	○	○	○	○	○
Product manufacturing and preparation	○	○	○	○	○
Process used for manufacturing and preparation (manufacture of lots, stability, documentation)	○	○	○	○	○
Cell culture culture conditions, stability, source component	○	○	○	○	○
Cell bank system	○	○	○	○	○
Processing procedure	○	○	○	○	○
Evaluation of identity and consistency	○	○	○	○	○
Modifications by genetic engineering	○	○	○	○	○
Description of regents used in manufacturing (characteristics, type of testing)	○	○	○	○	○
Standard operating procedure	○	○	○	○	○
Safety and quality control of product	○	○	○	○	○
Procedure for safety and quality control	○	○	○	○	○
Type of testing (microbiological testing, identity, purity, stability, viral testing, potency)	○	○	○	○	○
Product stability testing, shipping methods	○	○	○	○	○
Final product release criteria testing	○	○	○	○	○
Acceptance criteria (materials and regents)	○	○	○	○	○
Requirements for testing, release, and shipping of product	○	○	○	○	○
Testing and application of final products	○	○	○	○	○
Efficacy testing	○	○	○	○	○
Pharmacovigilance	○	○	○	○	○
Combination products	○	○	○	○	○






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Health Policy 88 (2008) 62–72



**Overview of the clinical application of regenerative medicine products in Japan**

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RESEARCH ARTICLE

**Critical issues for effective collaboration between academia and industry in the field of regenerative medicine in Japan**

**Abstract:** To identify which factors are important barriers to effective collaboration between Japanese academia and industry in the field of regenerative medicine. **Methods:** In November–December 2006, in-depth semi-structured interviews were conducted with representatives from nine Japanese companies that are engaged in developing regenerative medicine products in collaboration with academic and non-academic scientists with the successful collaborative experiences with companies. **Results & conclusions:** The major barriers to collaboration relate to the inhomogeneity of particular systems in academic institutions (particularly technology licensing organizations) and mobility between industry and academia, the knowledge deficit of academic personnel with respect to industry, the incoherence of particular governmental support systems and the Japanese policy view of these collaborations, which has resulted in overly strict conflict of interest guidelines. We suggest some approaches to overcome these barriers.

In the field of life sciences, collaborations between academia and industry for the development of commercial products have become a topic of considerable interest [1–6]. Since 2004, Japanese national universities have become “incubators”, meaning that each university now controls the intellectual property rights of inventions of the limited numbers of research grants are open to competition, such that only a limited number of institutions receive grants. Consequently, academic researchers have striven to obtain more funds from other sources, including VCs. In many cases, start-up companies develop the R&D in Japan and investment of VCs in the international market, and finally the start-up



## Industry views of biosimilar development in Japan

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Interview survey  
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### ABSTRACT

**Objective:** To understand the issues around biosimilar development by pharmaceutical companies in Japan, which has emerged as an urgent issue in guaranteeing the availability of affordable biopharmaceuticals and a reduction in drug costs.

**Method:** Various regulatory guidelines related to biosimilar development are carefully reviewed. We then interviewed representatives of 11 Japanese companies to explore issues related to the manufacturing, immunogenicity, development costs and regulation of biosimilars.

**Results:** Our investigations show that Japan is unlikely to produce more than a handful of biosimilars domestically in the near future. We also found that regulatory guidelines for biosimilars will be needed for Japanese developers to plan and initiate production, in order to provide affordable biopharmaceuticals to Japanese patients.

**Conclusion:** These results represent that regulatory guidelines for biosimilars, encouraging competition with maintaining incentive for innovation, will be needed for Japanese developers to plan and initiate biosimilar development.

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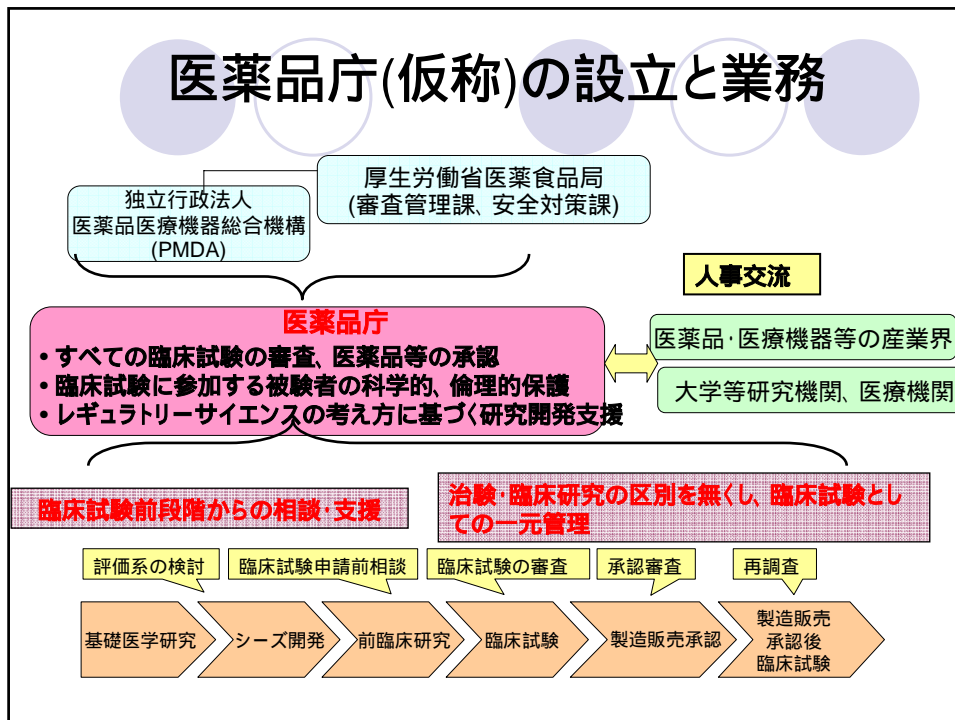
**Table 2**  
Biosimilars approved in the EU<sup>a</sup>.

Product (INN <sup>b</sup> )	Company	Date approved
Omnitrope (somatotropin)	Sandoz	April 2006
Valtropin (somatotropin)	BioPartners	April 2006
Biosccept (epoetin alfa)	Sandoz	August 2007
Erythropoietin alfa hexel (epoetin alfa)	Hexal Biotech	August 2007
Absomed (epoetin alfa)	Medice Arzneimittel	August 2007
Silapo (epoetin zeta)	Stata Arzneimittel	December 2007
Bio-grastin (filgrastim)	CT Arzneimittel	Recommended for approval by the EMEA in February 2008
Filgrastim Ratiopharm (filgrastim)	Ratiopharm	
Tevagrasties (filgrastim)	Teva Generics	
Ratiograsties (filgrastim)	Ratiopharm	

**Table 3**  
Sales of erythropoietin and G-CSF in Japan.

Brand name (INN)	Company	2007 Sales (Billion yen)	
Epogen (epoetin beta)	Chugai <sup>c</sup>	54.8	
Espo/Nesp (epoetin alpha)	Kirin <sup>b</sup>	41.7	
Neutrogen (filgrastim)	Chugai		12.6(39.4 <sup>d</sup> )
GRAN (filgrastim)	Kirin		15.2
Neu-up (filgrastim)	Kyowa <sup>e</sup>		4.5
Total (erythropoietin)		96.5	
Total (filgrastim)			32.3(59.1 <sup>d</sup> )

# 医薬品庁(仮称)の設立と業務



## International Cooperation: GLP Studies

Participation situation to the MAD system

Status	Countries
Full member of the MAD system	South Africa, Slovenia, Israel
Provisional Adherent to the MAD system	India, Singapore, Brazil, Argentina, Malaysia
Approach to OECD	China, Taiwan, Hong Kong, Russia, others