

# **Protection of Intellectual Property for Biotechnology-Based Pharmaceuticals in Japan**

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# **Agenda to Be Discussed Today**

- Current State of Biotechnology-based Pharmaceuticals**
- Protection of Intellectual Property for Biotechnology-based Pharmaceuticals**
- Patent Infringement Cases for Biotechnology-based Pharmaceuticals**
- Matters to be Addressed for Patent Protection**

# Current State of Biotechnology-Based Pharmaceuticals

- **21% of new drugs in Japan 2007 was occupied by biotechnology-based pharmaceuticals (13 cases among 62 cases)**
- **Increased double as much as ten years ago**
- **Expansion of therapeutic antibody market**
- **30% of new drugs worldwide is occupied by biotechnology-based pharmaceuticals**

**(Source: Nikkei Biotechnology Almanac 2008)**

# Antibody Drugs Commercially on Sale

Drug name	Distributor company	Originator company	Launch year	Indication
Herceptin	Chugai Pharmaceutical Co., Ltd.	Genentech, Inc.	2001	Metastatic breast cancer
Rituxan	Chugai Pharmaceutical Co., Ltd.	Genentech, Inc.	2001	Malignant lymphoma
Simulect	Novartis Pharma K.K.	Novartis International AG	2002	Acute rejection in renal transplantation
Synergis	ABBOTT JAPAN CO., LTD.	MedImmune, Inc.	2002	Suppression of lower respiratory tract disease initiation caused by RS virus
Remicade	Mitsubishi Tanabe Co.	Centocor, Inc.	2002	Rheumatoid arthritis
Actemra	Chugai Pharmaceutical Co., Ltd.	Chugai Pharmaceutical Co., Ltd.	2005	Castleman's disease and RA
Myelotarg	Wyeth K.K.	Wyeth	2005	Acute myeloid leukemia
Avastin	Chugai Pharmaceutical Co., Ltd.	F. Hoffmann-La Roche Limited	2007	Incurable or unresectable progressive or recurrent colorectal cancer

The sales amount for 2005 increased 25% to ¥55 billion yen year-on-year (The increase of the overall ethical drug sales is about 7%). However, the Japanese original product is only product by Chugai Pharmaceutical Co., Ltd.

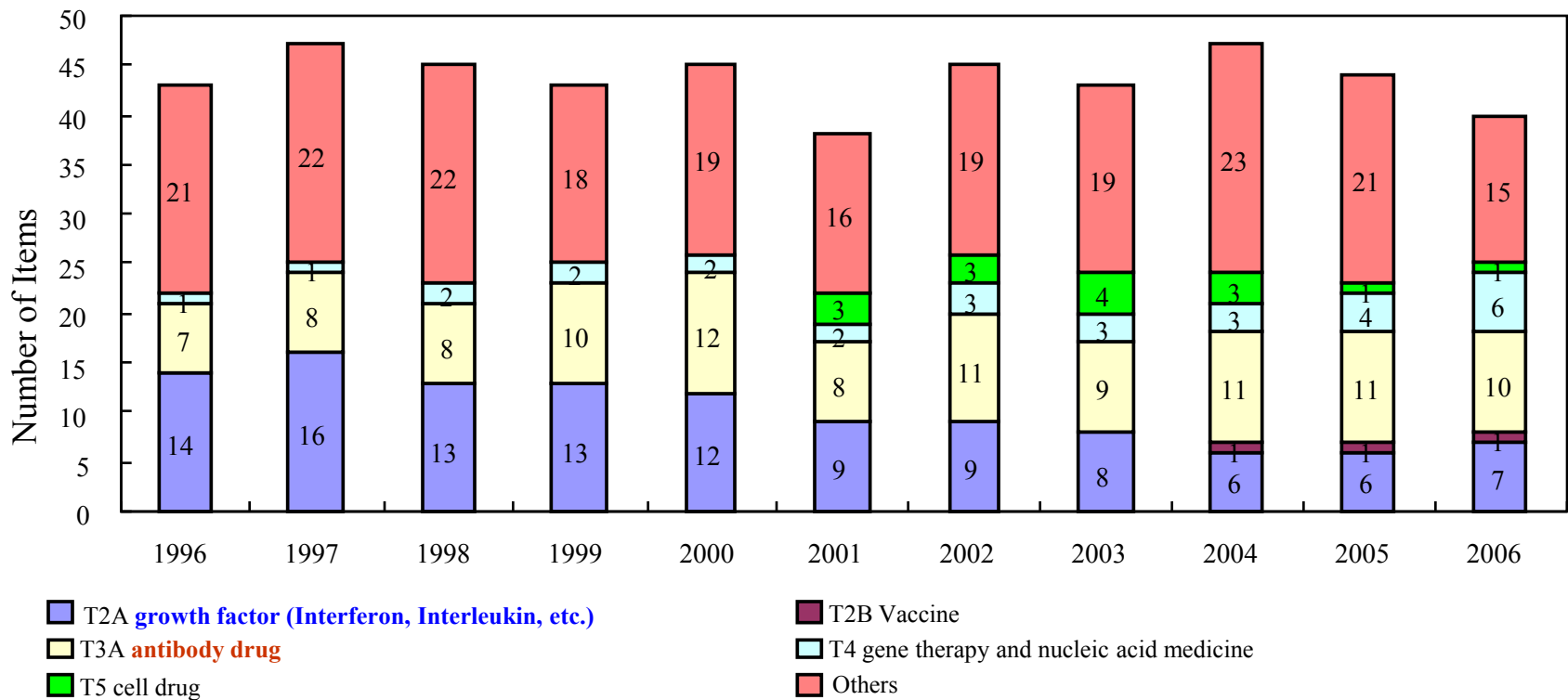
# Development Status of Biotechnology-Based Pharmaceuticals

	<b>Japan</b>	United States	Britain	France	Germany
Number of all developed items (A)	<b>349</b>	1884	678	454	441
Number of biotech-based items (B)	<b>40</b>	400	135	78	92
B/A (%)	<b>11.5</b>	21.2	19.9	17.2	20.9

Source: Pharmaprojects (as of February 14, 2007)

Source: "Future of Pharmaceutical Industry (May, 2007)" by Office of Pharmaceutical Industry Research

# Change in Number of Biotech-Based Pharmaceuticals under development in Japan



Note: The developed items are items from Phase 1 to application stage. The data for 2001 lacks continuity because part of data prepared to be applied was missed.

Source: Pharmaprojects (as of February 14, 2007)

# **Protection of Intellectual Property for Biotechnology-Based Pharmaceuticals in Japan**

- Patent protection basically same as that of low-molecular pharmaceuticals**
- A lot of patents for fundamental technology related to products**
- System for recovering the erosion of patent term**
- Patent linkage**
- Data protection: Reexamination Period**

# System for Recovering the Erosion of Patent term

	<b>Extended duration</b>	<b>Effect</b>
<b>Japan</b>	<p><b>Max. 5 years</b></p> <p>Duration from the later date for patent registration or the first clinical trial notification to the approval date</p>	<p><b>Only for approved indications</b></p> <p><b>Multiple patents and numbers of times at each approval are acceptable.</b></p>
<b>United States</b>	<p><b>Max. 5 years</b></p> <p>Combination of half of duration from IND submission date to NDA application date and NDA examination duration</p> <p>However, the patent expiration date after extending the duration shall not exceed 14 years.</p>	<p>All the indications</p> <p>Once</p>
<b>Europe</b>	<p><b>Max. 5 years</b></p> <p>Duration for which 5 years are subtracted from the duration from the patent application date to the approval date.</p> <p>Addition of pediatric indication: 0.5 years</p>	<p>All the indications</p> <p>Once</p>

# Patent Linkage

	Existence and Content of the System	Tool
<b>Japan</b>	<p><b>Exists</b></p> <p><b>Only substance patent is considered in principal.</b></p> <p><b>When approving the additional indications, only the relevant indications are considered (only when the reexamination duration is required).</b></p>	<p><b>Patent status report</b></p> <p><b>Advanced negotiation (During approval of genetic products to NHI price listing)</b></p>
<b>United States</b>	<p><b>Exists (Biotechnology-based pharmaceuticals are excluded)</b></p> <p><b>Para I: No patent information</b></p> <p><b>Para II: Patent expiration or already expired</b></p> <p><b>Para III: Generic products go on sale after the patent has expired.</b></p> <p><b>Para IV: Patent invalidity or non-infringement</b></p>	<p><b>Orange book</b></p> <p><b>Hatch-Waxman Act</b></p>
<b>Europe</b>	<p><b>Does not exist</b></p>	<p><b>Generic product approval information is disclosed in some countries.</b></p>

# Data Protection

	Data protection duration	Biotech products
<b>Japan</b>	<p><b>Generic product application is not accepted during the reexamination duration (due to safety consciousness)</b></p> <p><b>New active ingredient: 8 years</b></p> <p><b>Addition of new indication and formulation: 4 years</b></p> <p><b>Orphan Drug: 10 years</b></p>	<b>Same as for low molecular pharmaceuticals</b>
<b>United States</b>	<p><b>Duration of rejecting the ANDA approval</b></p> <p><b>New active ingredient: 5 years (ANDA application is acceptable after 4 years)</b></p> <p><b>Addition of new indication: 3 years</b></p> <p><b>Addition of pediatric indication: 0.5 years</b></p>	<p><b>Not targeted</b></p> <p><b>A bill aiming for 12 – 14 years is under discussion</b></p>
<b>Europe</b>	<p><b>Duration for which generic product application is not accepted: 8 years</b></p> <p><b>Duration for which generic product sale is suspended: 2 years</b></p> <p><b>Addition of epoch-making indication: 1 year</b></p>	<b>Same as for low molecular pharmaceuticals</b>

# Lawsuit for Biotechnology-Based Pharmaceuticals in Japan (1)

## **Article (ne) in 1991 No. 2485, Genentech vs. Toyobo Co., Ltd.**

Lawsuit for infringement of recombinant t-PA

- By reason that priority-claimed amino acid sequence was thought to be error in writing, the claim for priority is judged to be legal.
- Seeking the injunction was approved.

## **Article (ne) in 1994 No. 2857, Otsuka Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Hayashibara Group vs F. Hoffmann-La Roche Limited**

Lawsuit for infringement of interferon  $\alpha$

- It is judged that human leukocyte interferon is not limited to one obtained from human leukocyte and if it is the same as object, the ones obtained from other cells are also included in the human leukocyte interferon.
- By reason that the aminosugar content is not included in the claims in terms of wording and is not equivalent due to lack of possibility of substitution, this is judged not to be infringement.

# Lawsuit for Biotechnology-Based Pharmaceuticals in Japan (2)

**Article (ne) in 1999 No. 5303, Snow Brand Milk Products Co., Ltd. vs. Kirin Brewery Company, Limited**

Lawsuit for infringement of EPO

- The judgment by District Court that the technical scope of “Product by Process” meets the constitutional requirements as long as it is the same as that specified by the production method, was upheld.
- By reason that this product is not included in the technical scope, this is judged not to be infringement.

**Article (wa) in 1996 No. 8627, Amgen, Inc. vs F. Hoffmann-La Roche Limited**

Lawsuit for infringement of consensus interferon

- It is judged that the test for gaining the approval of producing medical drugs based on the Pharmaceutical Law as drug with new active ingredients falls under “Implementation of Patented Invention for Test or Study” set forth in Section 1, Paragraph 69 of the Patent Law.
- “Threat of infringement” which is a requirement of infringement prevention claim based on Section 1, Paragraph 100 of the Patent Law is required to exist at conclusion of oral procedure. Therefore, such threat of infringement cannot be found in this case where even application for production approval is not conducted.

# Lawsuit for Tissue Plasminogen Activator (1)

**Plaintiff:** Genentech

**Defendant:** Sumitomo Pharmaceuticals Co., Ltd.

**October, 1989:** Filed a complaint to Osaka District Court

**July, 1993:** Defendant: Manufacturing was approved.

Defendant: Advertisement was carried out.

**October, 1994:** **The claim was rejected** by Osaka District Court.

**May, 1995:** The sale started.

**March, 1996:** Original decision was canceled by Osaka High Court.

**Decision of injunction**



# Lawsuit for Tissue Plasminogen Activator (2)

## Patent claims:

**1. Recombinant human tissue plasminogen activator produced by host cells other than human cell, having below items 1) to 5), containing no other human-derived proteins, and containing the following partial amino-acid sequence :**

- 1) Containing the catalytic ability of converting plasminogen to plasmin**
- 2) Containing fibrin binding ability**
- 3) Immunoreactive against human tissue plasminogen activator derived from Bowes melanoma cell**
- 4) Containing amino-acid sequence constituting kringle domain and serine protease domain**
- 5) Existing as single-strand or double-strand protein**

**(Amino-acid sequence: Number 69 through 527 of t-PA)**

# Lawsuit for Tissue Plasminogen Activator (3)

## Subject matter in dispute:

245th amino-acid residue from N-terminal is methionine residue (245th amino-acid residue in the claimed sequence is valine residue.)

## Main issues in dispute:

Whether the subject matter in dispute is included in the technical scope of this invention.

More specifically, although the subject matter in dispute does not have such amino-acid sequence as literally described in the patent claims, whether or not it should be evaluated that this subject matter is substantially the same as or equivalent to this invention?



# Lawsuit for Tissue Plasminogen Activator (4)

Judgment by Osaka District Court: **Not included in the technical scope** of this invention

## ■ Identity:

Although there cannot be seen significant difference in the clinical effect, different or same points of immunogenicity of both t-PAs and the details of relationship of specific activity and structure were not clarified at the priority date. **Therefore, it is impossible to conclude that they are the same enzyme** at the priority declaration date.

## ■ Possibility of substitution:

**It is difficult to recognize** that substitution of 245th valine residue into methionine residue **could be easily conducted** by those skilled in the art under the technological level **at the time of priority declaration date.**

## ■ Predictability:

Even if those skilled in the art made judgments according to the technical instruction disclosed in this invention using common technological knowledge and well-known means at the priority declaration date, and 245th valine residue was substituted into methionine residue, **it is difficult to conclude that it was possible to predict promptly** that the subject matter in dispute substantially same as or equivalent to t-PA of this invention could be obtained.

# Lawsuit for Tissue Plasminogen Activator (5)

Judgment by Osaka High Court:

Equivalent. **Falls under the technical scope** of the present invention.

## ■ Affirmative requirements for equivalents

### – Possibility of substitution:

Due to the same property, the action effect is the same and the requirements for possibility of substitution are satisfied.

### – Possibility to easily hit upon the idea

Admitted the possibility to easily hit upon the idea based on the priority declaration date.

## ■ Negative requirements for equivalents

### – Reason for obstacles such as problem at the patent application.

None



## (For Reference)

# Requirements for Equivalents by Supreme Court

### Ball spline case

- The different point is **not essential point** of the patented invention.
- Even if the different point is substituted, the purpose of this invention can be accomplished to exert the same action effect (**Possibility of substitution**).
- The different point could be easily substituted by those skilled in the art at the time of manufacturing the subject matter in dispute (**Possibility of easy substitution at the infringement**).
- The subject matter in dispute is not the same as well-known technology at the time of applying the patent of this invention or **cannot be easily assumed** by those skilled in the art **at the time of patent application** using such well-known technology.
- There is **no special reason** such as that the subject matter in dispute is **intentionally excluded** from the patent claims through the application procedure of this invention.

# Difference in Patent Examination among Japan, United States, and Europe (1)

**Novelty of structurally-similar gene congenic and protein having one or several different amino acids**

<b>Country</b>	<b>With novelty</b>	<b>With no novelty</b>
<b>Japan</b>	<b>36%</b>	<b>64%</b>
<b>United States</b>	<b>88%</b>	<b>12%</b>
<b>Europe</b>	<b>81%</b>	<b>19%</b>

# Difference in Patent Examination among Japan, United States, and Europe (2)

## Inventive step of Humanized Antibody

[Title of the Invention] Human-mouse chimeric antibody that protects respiratory syncytial virus

Country	Japan Patent 3896160	United States US5824307	Europe EP783525B
Judgment by Patent Office	Asked for remarkable effect of Humanized 1129 (this invention) compared with known mouse monoclonal antibody 1129.	Although anti-RSV monoclonal antibody of a third party did not show the infection prevention effect in clinical trial, humanized 1129 could show the RSV infection prevention effect, so the humanized 1129 was granted.	By reason that humanized 1129 is superior to humanized 1308F known as anti-RSV monoclonal antibody in neutralization activity, the humanized 1129 was granted.

# Difference in Patent Examination among Japan, United States, and Europe (3)

**Inventive step of application whose medicinal data is not disclosed in the specification**

[Title of the Invention] Recombinant IL-5 antagonist useful for treating the disease transmitted by IL-5

Country	Japan Patent Application Publication 2001-523083	United States US5693323	Europe EP800536B
Judgment by Patent Office	<p><b>Although the clinical trial result was shown and the progressivity was claimed in terms of high-dose administration and persistence, the examiner judged that the claim based on new matter could not be considered, so this claim was rejected.</b></p>	<p>It was claimed that this invention was not disclosed or suggested in the reference and the standard claiming that it is obvious to try is not obvious standard. This claim was granted.</p>	<p>Showing after-application document where the clinical trial results were described, the remarkable effect was claimed. This claim was granted.</p>

# Issues to Be Addressed for Enforcing the Patent Right

## Patent examination of gene and protein in Japan

- Previous examination: **In the granted claim, the sequence is very limited.**
- Present examination: If there is no problem in the prior art,
  - amino acid sequences with several substitutions, deletions, and additions, or
  - amino acid sequences having 90% or more identity, an **extended claim** is accepted when having identical activity.

(For United States: The above claim does not meet the written description requirement.)

- A wider scope of claims is accepted in Japan (wider than the scope where they are judged equivalent). Does the scope described in the claim coincide with the technical scope?