Better Health, Brighter Future

Regional Workshop on IP management around WIPO Re: Search and WIPO GREEN

Practices of IP applied to economic and social development: Experience from Japan Industry

March 3, 2016, Manila

Takeda Pharmaceutical Company Limited
Head of Operations (IP), Intellectual Property
Seiji Mori

Menu

1. Introduction of Takeda
2. Pharma Industry and Patent
   - Unmet Medical Needs
   - High Risk and Huge R&D cost on Drug Discovery
   - Unique Nature of Pharma Patent
3. Japan's capability to generate New Drug Generation
4. Patent Drives Innovation
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   - Facilitate Flow of New Technology
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   - Unmet Medical Needs
   - Open Innovation in Japan for Drug Discovery
   - Open Innovation to Improve Global Health
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     - GHIT
     - WIPO Re:Search

1. Introduction of Takeda

History of Innovation

Christophe Weber
CEO

For more than 230 years, Takeda has developed its business with integrity while undergoing a process of continuous transformation.

1700 1900 2000

1781
Foundation
Takeda began operations in 1781 when Chobei Takeda I started a business selling traditional Japanese and Chinese medicines in Doshomachi, Osaka. Following Japan's Meiji Restoration in the late 1860s, Takeda was one of the first companies in Japan to begin importing western medicines.

Founder: Chobei Takeda I

1895
Pharmaceutical Manufacturing Business Launched
In 1895, the Company established its own factory in Osaka, thereby achieving its transformation into a pharmaceutical manufacturer.

1914
Research Activities Begin with Establishment of the Takeda Research Division

A researcher performing an experiment in the laboratory (1939)

1950
First multivitamin in Japan
***Panvitan* Launched**

1954
Vitamin B1 derivative
***Alinamin* Launched**

1962
Entered Overseas Markets
Takeda greatly expanded its overseas activities by entering Asia, Europe, and the U.S.

1989
For Prostate Cancer, Breast Cancer, and Endometriosis
***Leuprorelin Acetate* Launched** (U.S. and Europe)

1991
For Peptic Ulcer
***Lansoprazole* Launched** (Europe)

1997
For Hypertension
***Candesartan Cilexetil* Launched** (Europe)

1999
For Type 2 Diabetes
***Pioglitazone Hydrochloride* Launched** (U.S. and Japan)

2005
For Insomnia
***Ramelteon* Launched** (U.S.)

2008
Millennium Pharmaceuticals, Inc. Integrated

2009
For Acid Reflux Disease
***DEXILANT* Launched** (U.S.)

For Gout and Hyperuricemia
***ULORIC* Launched** (U.S.)

2010
For Type 2 Diabetes
***NESINA* Launched** (Japan)

For Cancer
***Vectibix* Launched** (Japan)

2011
For Hypertension
***EDARBI* Launched** (U.S.)

Shonan Research Center Established

Shonan Research Center

Nycomed Integrated
The integration of legacy Nycomed expanded the Group's sales channels in fast-growing emerging markets, while strengthening its business base across Europe.

Zurich Office

2012
Vaccine Business Division Established
Takeda strengthened its global vaccine operations.

For Hypertension
***AZILVA* Launched** (Japan)

URL Pharma, Inc. Integrated
The integration included *Colcrys*, a treatment for hyperuricemia and gout.

Multilab Indústria e Comércio de Produtos Farmacêuticos Ltda. Integrated
Through this integration, Takeda has increased its presence in the Brazilian market.

LigoCyte Pharmaceuticals, Inc. Integrated
Takeda gained first-in-class norovirus vaccine candidate and virus-like particle platform.

Envoy Therapeutics, Inc. Integrated
Takeda gained Innovative Research Platform-bacTRAP technology and added novel CNS programs.

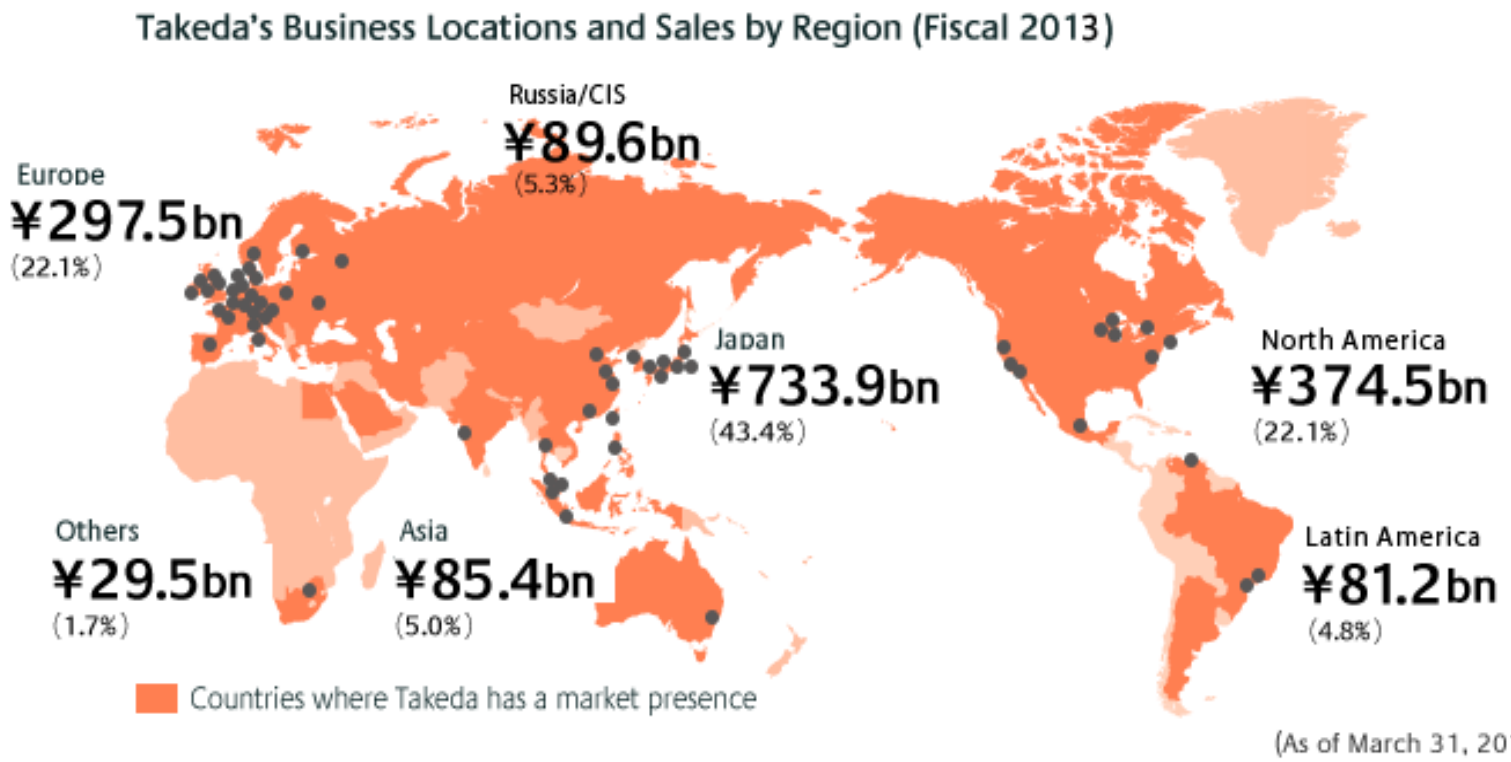
2013
For Hyperlipidemia
***LOTRIGA* Launched (Japan)**

Inviragen, Inc. Integrated
Takeda obtained promising vaccine candidates against dengue and hand, foot and mouth disease.

For Type 2 Diabetes
***NESINA, KAZANO and OSENI* Launched** (U.S.)

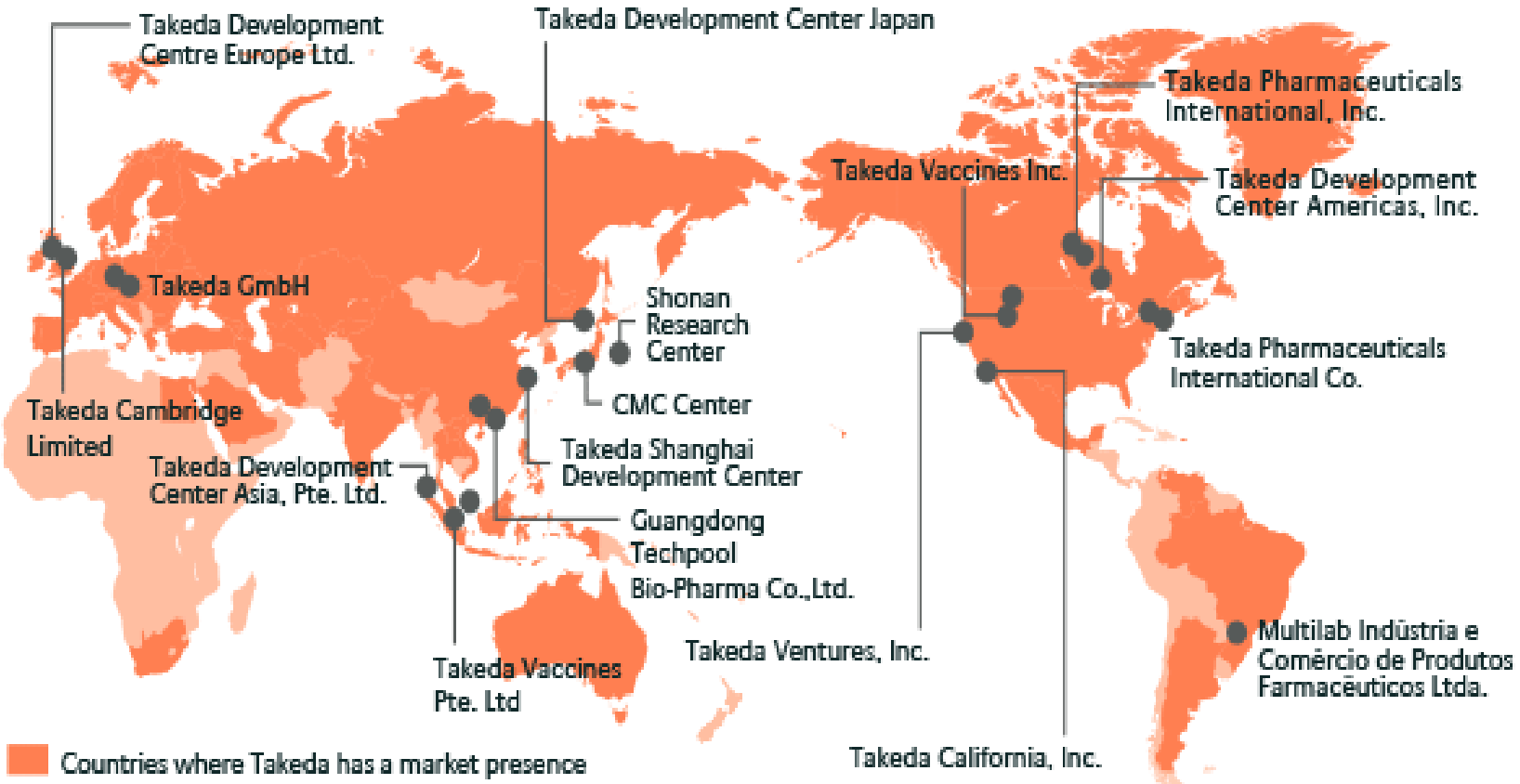
Business Overview

- Sales (2014) : **¥1,777.8 bn**
- R&D (2014) : **¥382. 1 bn** (21.5% of Sales)
- Presence in over **70** countries
- Employee: **31,328** (as of 2015 March)



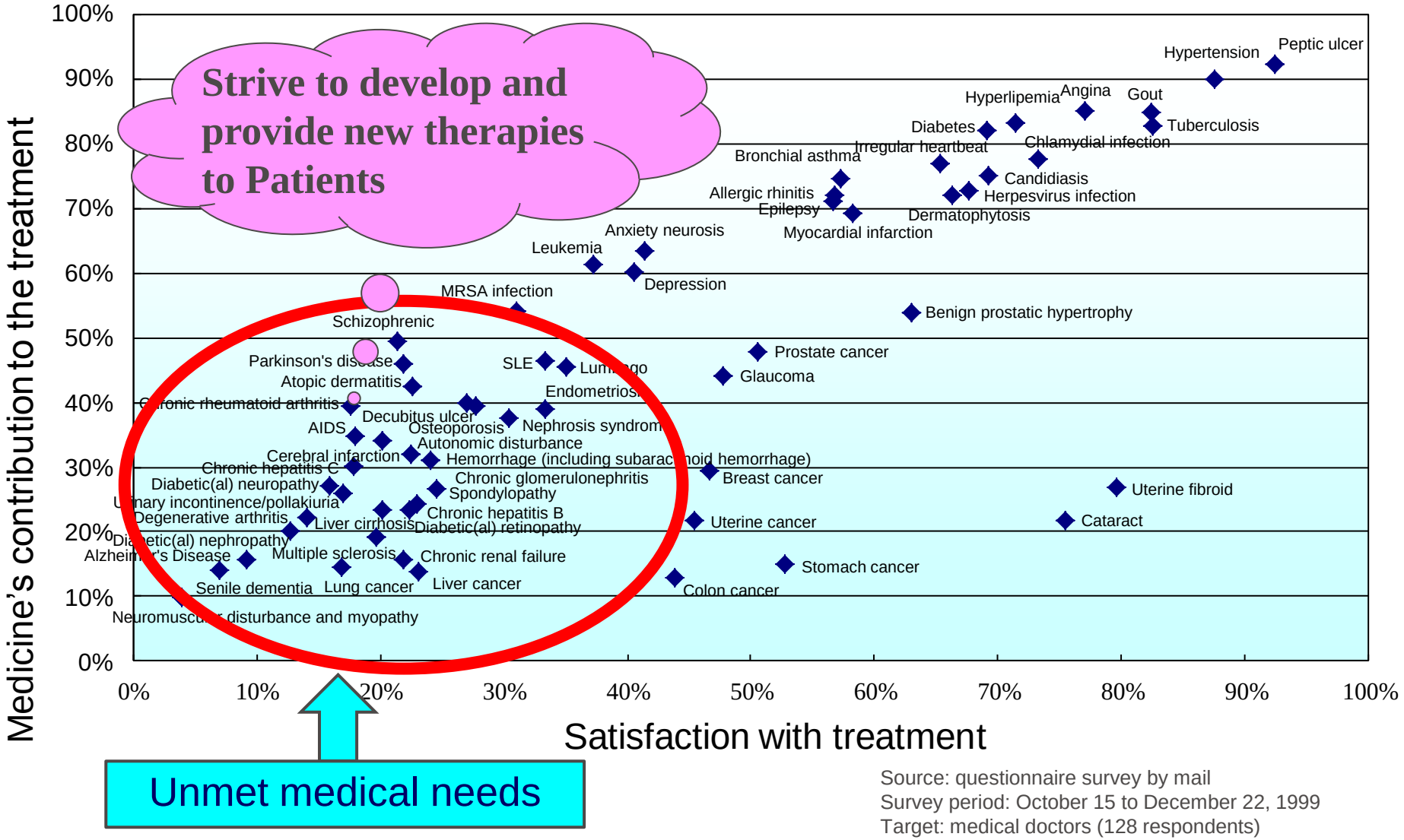
R&D Presence

Global Research & Development Network



2. Pharma Industry and Patent

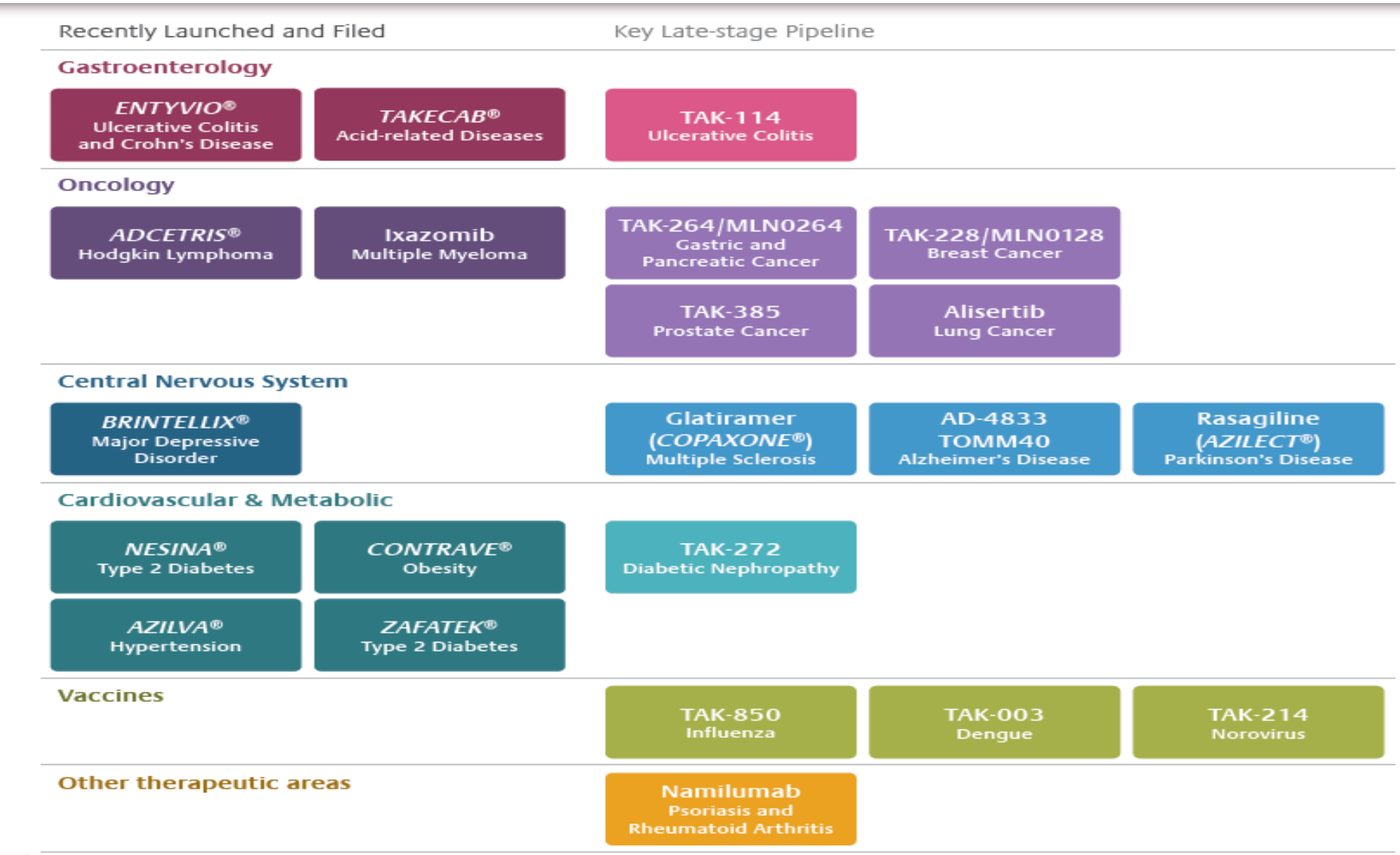
■Unmet Medical Needs



Source: questionnaire survey by mail
Survey period: October 15 to December 22, 1999
Target: medical doctors (128 respondents)

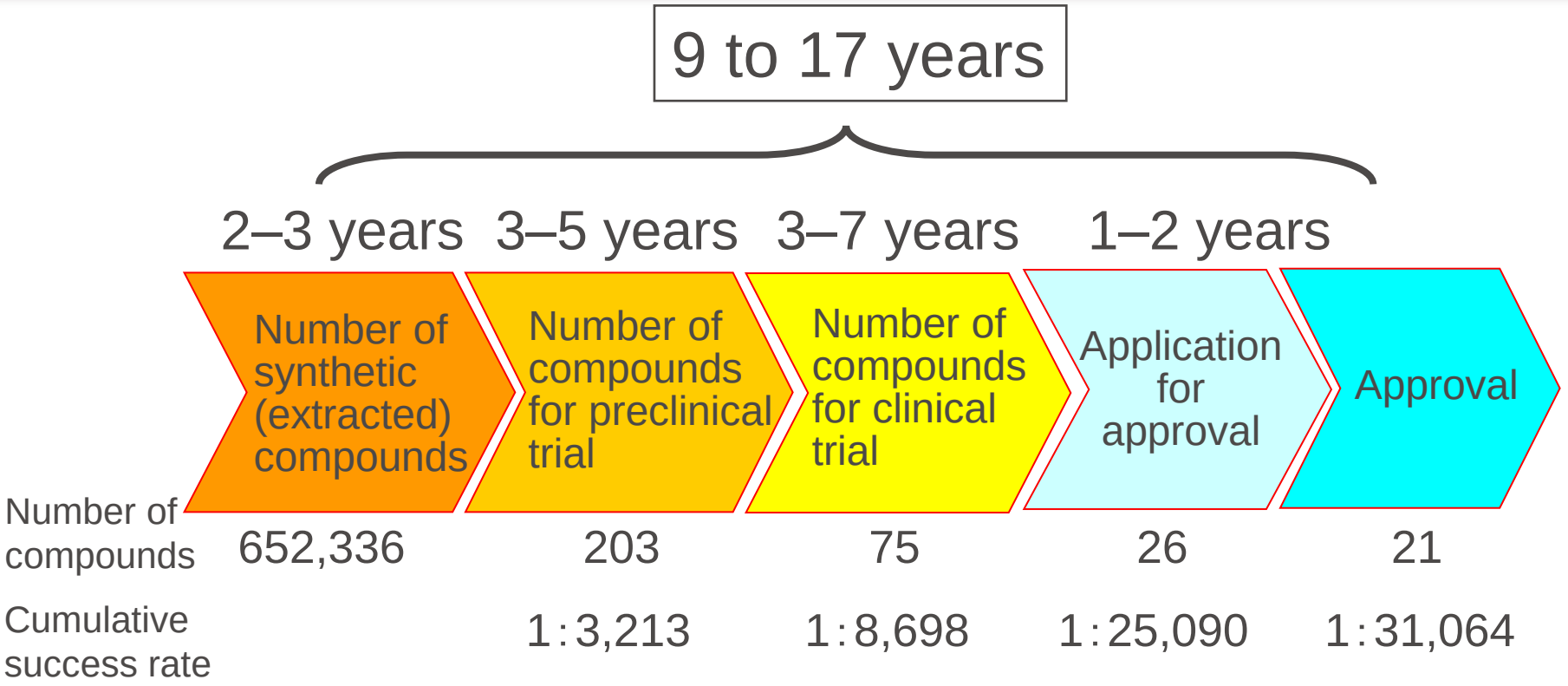
Source : The Japan Health Sciences Foundation: "Report on Key Domestic Technologies 2000 – Outlook of medical needs in 2010 –"

Takeda Key Products and Pipeline (as of Aug, 2015)



August 2015

■High Risk and Huge R&D cost on Drug Discovery



- Extremely low success rate
- R & D costs : several 10 billions~ over100 billions yen（JPMA）
  1,300 millions $（PhRMA）

2005 to 2009 Survey by JPMA

Lowering of PTS for Drug Development

2005-2009 : 1/31,064

2004-2008 : 1/25,482

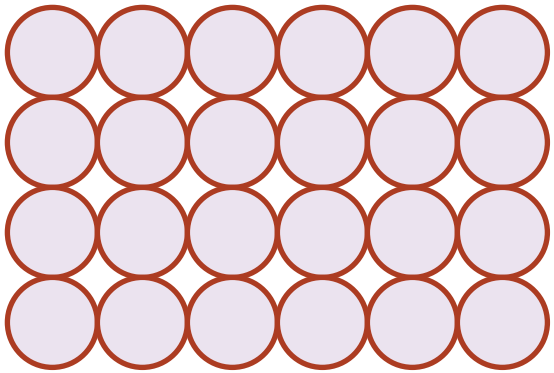
2003-2007 : 1/21,677

1999-2003 : 1/12,324

1989-1993 : 1/ 3,700

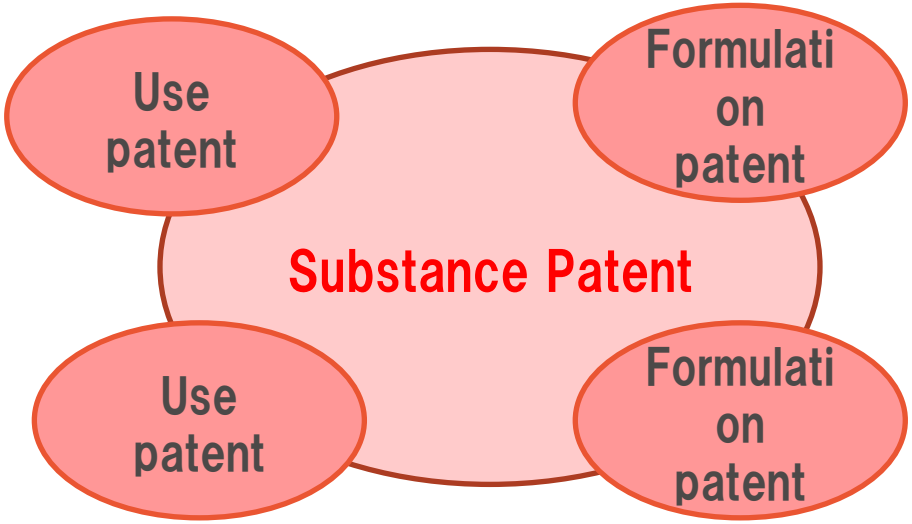
■Unique nature of pharma patent

Patent for Automobiles, IT



a) Hundreds, thousands patents for one product
b) Value of individual patent is not so high
c) Unlikely that a third party patent constitutes an absolute bar for product development and launch
d) International Standardization

Patent for Pharma Products



a) One basic patent for one product
b) Value of individual patent is high
c) Not rare to give up product development due to a third party patent

3. Japan's Capability to Generate New Drug

<Japan-originated new medicines marketed in more than 20 countries by 1999>

Before introduction of product patent system	1960s ; 2 products
	1970s ; 4 products
Introduction of product patent system ;	January 1, 1976
After introduction of product patent system	1980s ; 18 products
	1990s ; 14 products

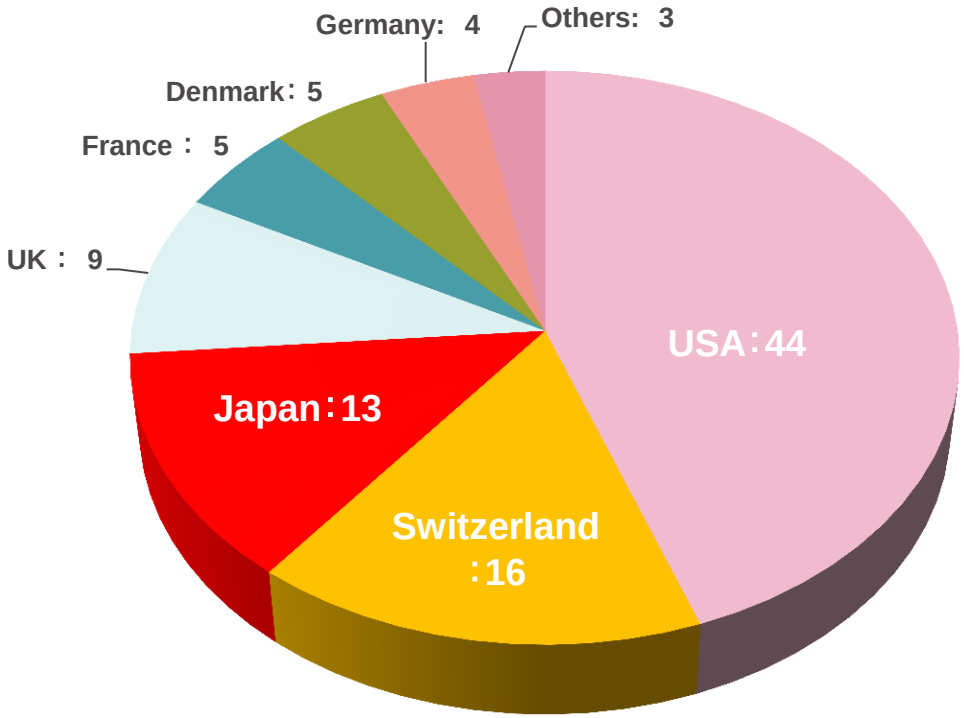
<World top 50; 10 Japan-originated new medicines in 2008>

16th	Crestor (Shionogi, antilipidemic agent)	4.1 billion dollars
17th	Actos (Takeda, Type II diabetes)	4.1 billion dollars
21st	Blopress (Takeda, hypotensive agent)	3.8 billion dollars
26th	Aricept (Eisai, anti-Alzheimer agent)	3.4 billion dollars
30th	Abilify (Otsuka, antipsychotic agent)	3.3 billion dollars
31st	Takepron (Takeda, antiulcer agent)	3.2 billion dollars
35th	Cravit (Daiichi-Sankyo, antibiotic agent)	2.9 billion dollars
39th	Pariet (Eisai, antiulcer agent)	2.7 billion dollars
41st	Harnal (Astellas, prostatic hypertrophy)	2.7 billion dollars
49th	Olmetec (Daiichi-Sankyo, hypotensive agent)	2.3 billion dollars

Source: Uto Brain

New Drug Generation in World

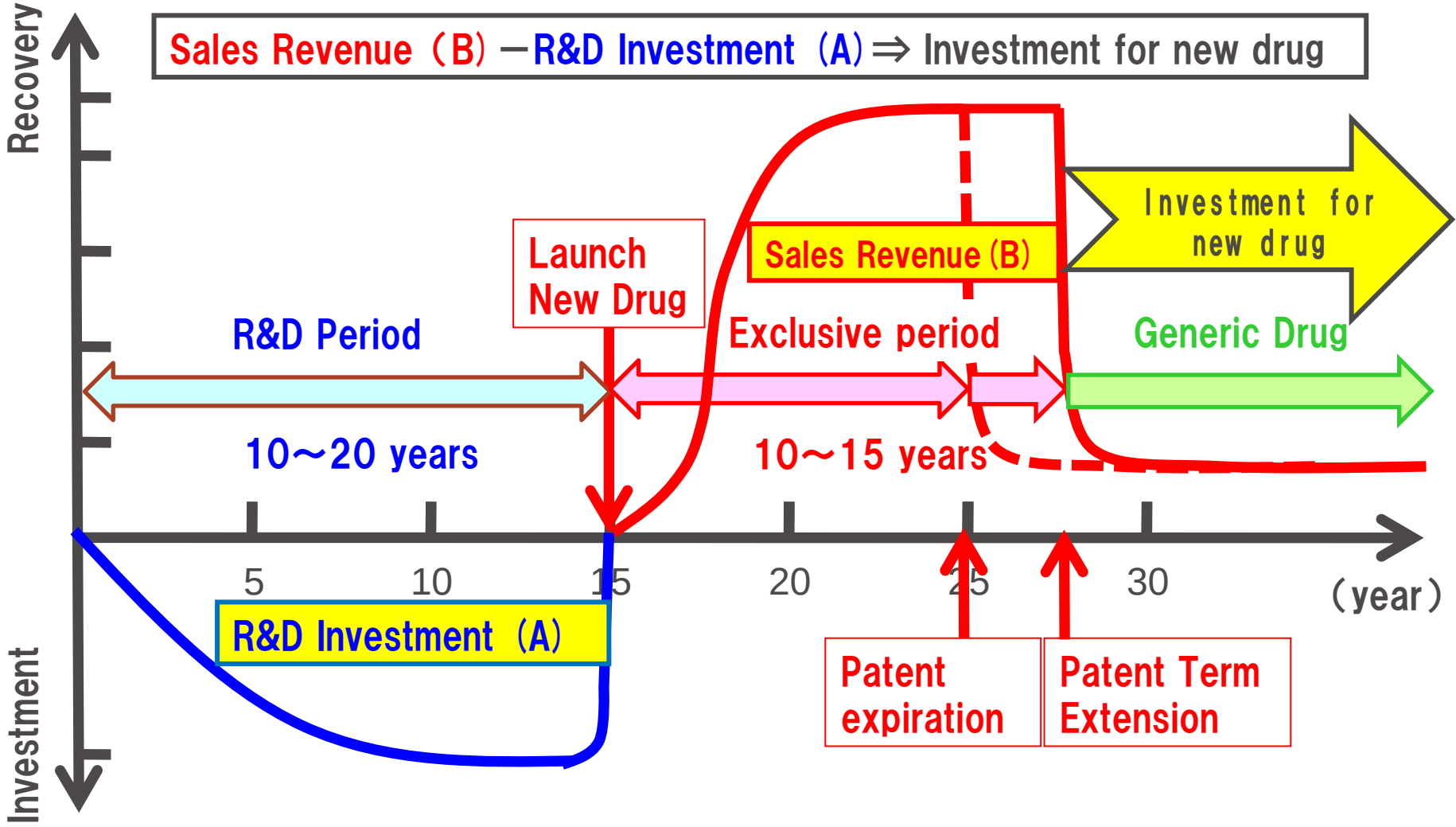
Japan is rated as the third capable country to generate new drugs in the world



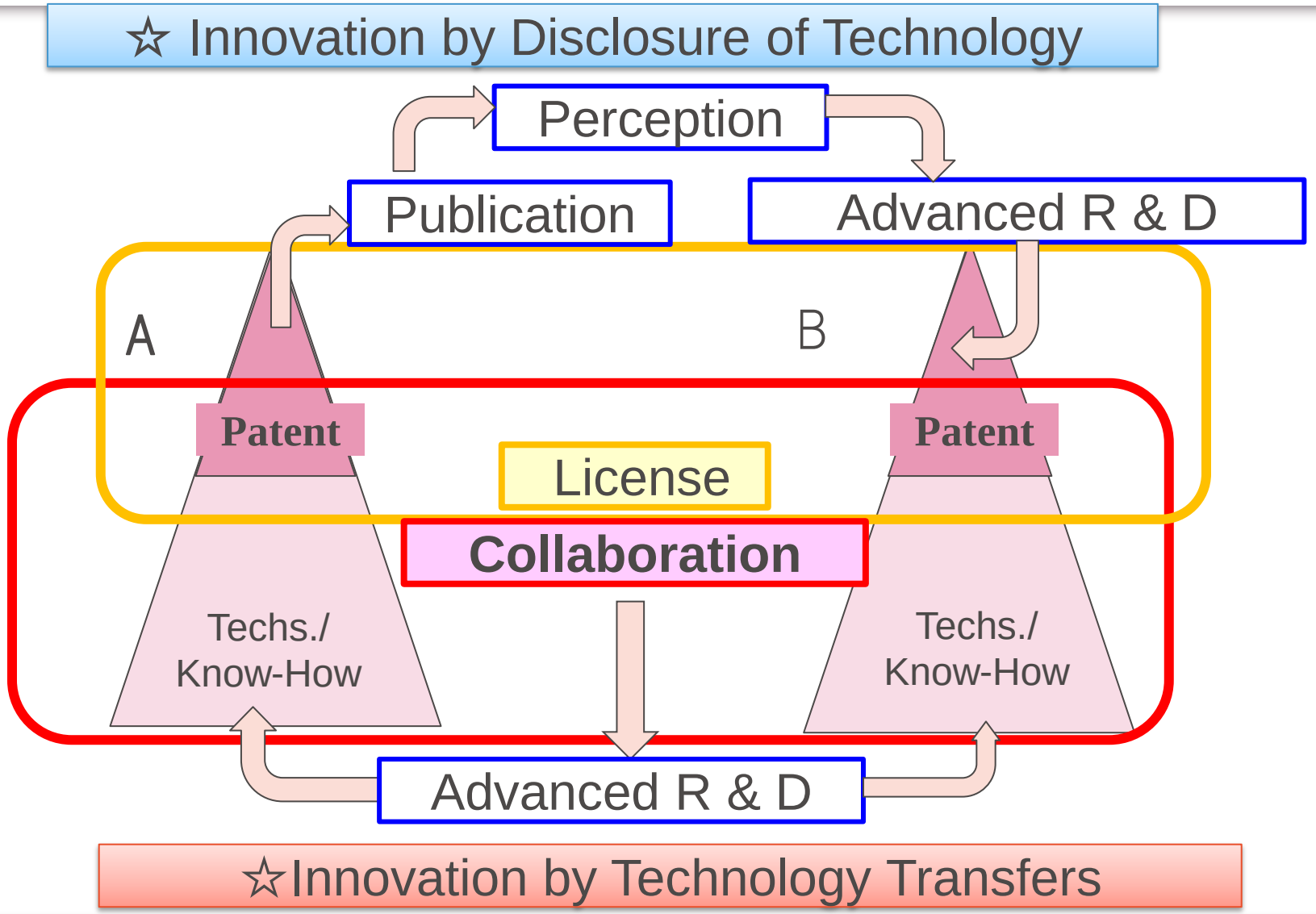
Origin: The JPMA's Office of Pharmaceutical Industry Research Pharmaprojects, @2013 IMS Health. IMS World Review

4. Patent Drives Innovation

■Secure investment to develop new drug



■Patent facilitates flow of new technology



Takeda's cases

1. Leuprorelin Product Case

2. Lansoprazole Product Case

3. Collaboration Research Cases

Overview of Leuprorelin Product Case

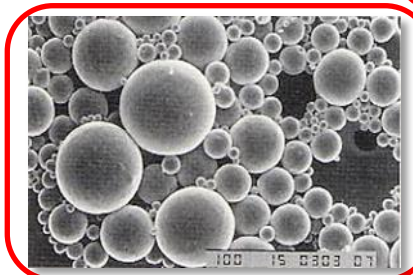
Item	Content
General Name	Leuprorelin Acetate
Indication	Prostate Cancer
Product Options	Daily injection 1-month Depot(Administration: daily to 1 month) 1-month Depot(improved)(Elimination of BSE risk) 3-month Depot(Administration: 1 month to 3 months) 6-month Depot(Administration: 3 months to 6 months) 6-month Depot(improved)(Decrease of administration volume by higher drug content)
Sales Country	70-80 countries including Asian countries such as Philippines, Malaysia, Singapore, Indonesia, Taiwan, Thai, China, Korea, etc.
Characteristic	1M, 3M, 6M Depot is sustained-release microsphere production consisting of Leuprorelin Acetate and Biodegradable Polymer such as PLGA, PLA. Those Depots can suppress the initial excess release and achieve a stable release speed over a long period of time.

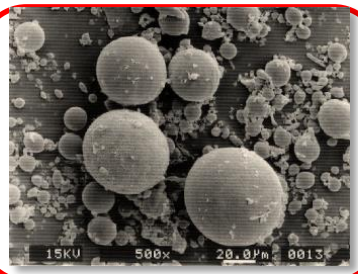
Characteristic of Leuprorelin Products

All Leuprorellin substance patent expired before 1996.

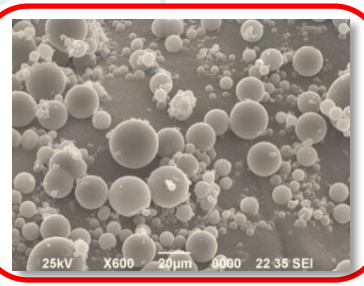
The products need to be injected.

Japanese Patent 01761586





1-month Depot (improved)

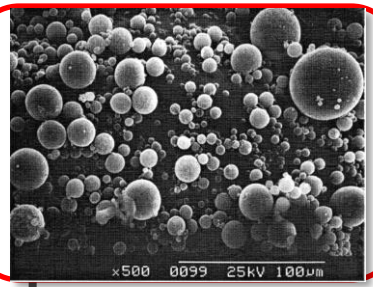


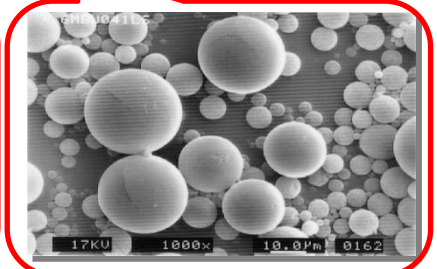
6-month Depot (improved)

1-month Depot

6-month Depot

Daily injection





3-month Depot

Japanese Patent 02653255

Philippines Patent 28683

Japanese Patent 4819172

Philippines Patent 1-2003-501343

Patient Friendliness

1980 1990 2000 2010 2020

Time

Contributions to Health Care Professionals sing Leuprorelin

DPS (dual-chamber prefilled syringe) was applied for workload reduction of health care professionals.

User Friendliness

Time

1st

Vial & Ampule

Complex procedures and some potential risk

Japanese Patent 02911086
Philippines Patent 1-1993-47573-A

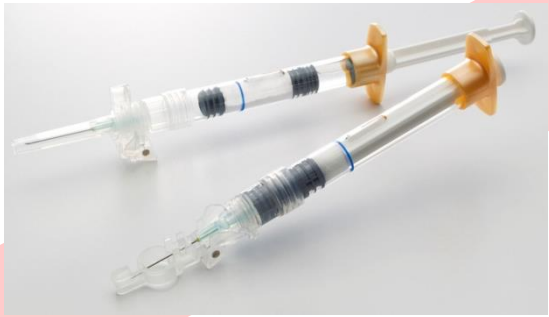
2nd

DPS (all-in-one)

Simple, convenient, efficient and safe!!!

3rd

PCT application filed in 2015



DPS with safe device (needle stick protection)

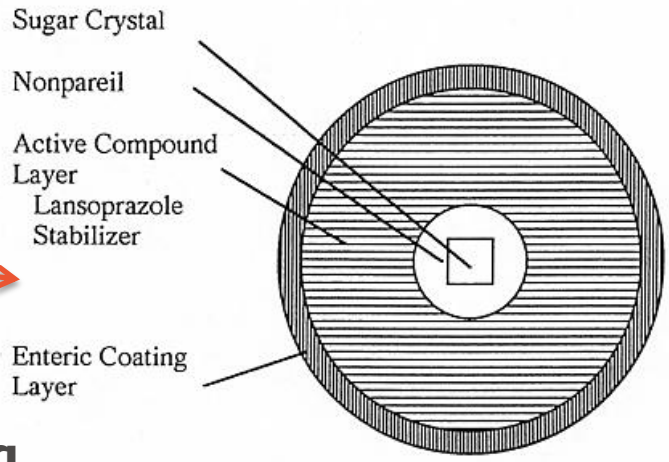
Overview of Lansoprazole Product Case

Item	Content
General Name	Lansoprazole
Indication	Stomach and intestinal ulcers Erosive esophagitis(damage to the esophagus from stomach acid) Other conditions involving excessive stomach acid such as Zollinger-Ellison syndrome
Product Options	Capsules 15mg and 30 mg 1992 Oral disintegrating (OD) tablets, 2002 Pack products for a helicobacter pylori-eradicating, 2002 Downsizing 30mg capsules, 2004 Intravenous 30mg 2006 Pack products for a helicobacter pylori-eradicating, 2010 Combination tablets 2014
Sales Country	about 890 countries including Asian countries such as Philippines, Malaysia, Singapore, Taiwan, Thailamd, China, Korea, etc.
Characteristic	Stabilized gastro-resistant capsules can protect against degradation in the stomach, improve bioavailability and acquire better absorption properties. OD tablets can improve adherence.

Lansoprazole capsules and granules

15mg (#3) 30mg (#1)

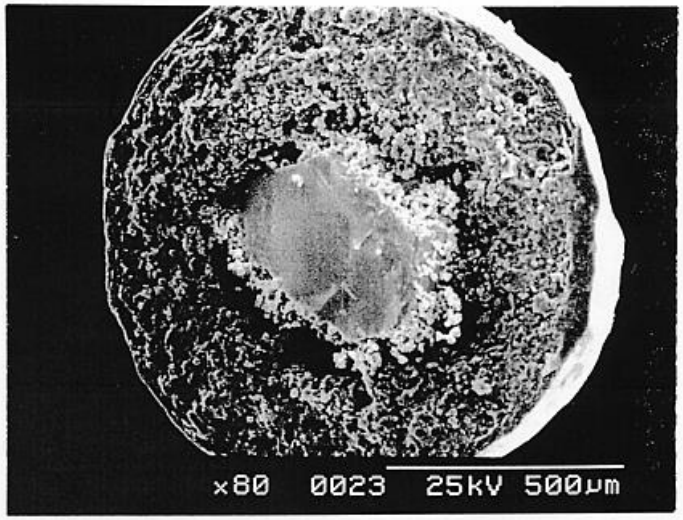
Cross-Section



downsized 30mg capsules

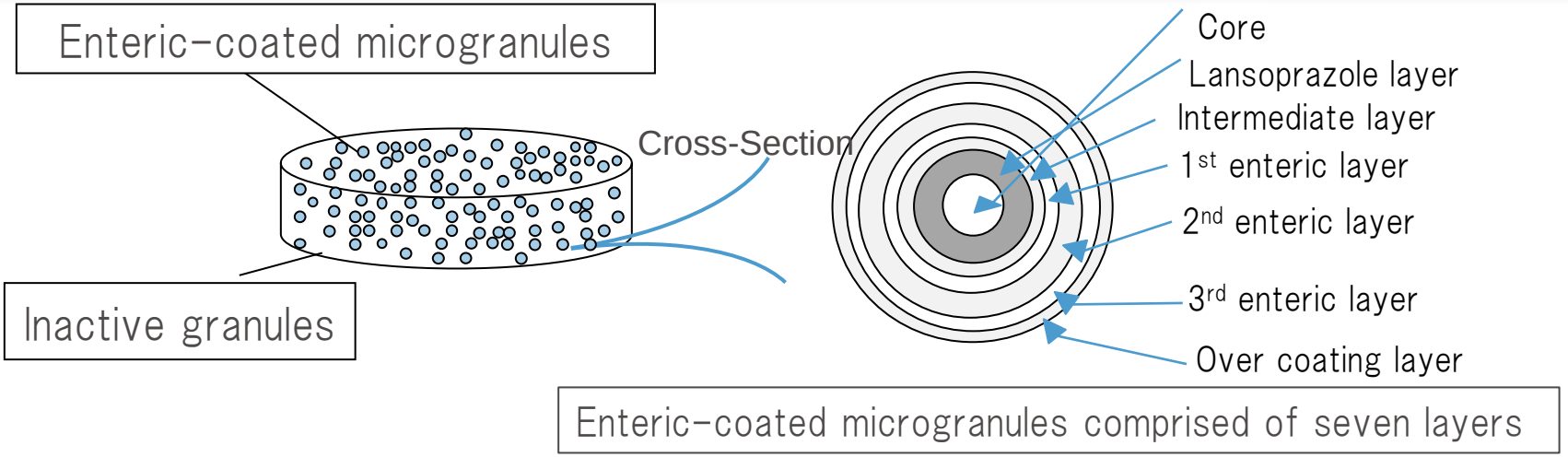
30mg (#3) 30mg (#1)

Easy for patients to take because of adherence improvement!



Japanese Patent 04331930 Philippines Patent 1-2004-500385

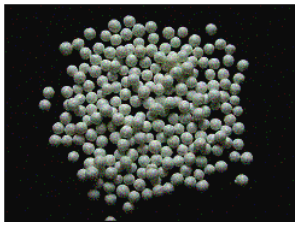
Lansoprazole oral disintegrating (OD) tablets and microgranules



Enteric-coated microgranules comprised of seven layers

Comparison of granules of between capsules and OD tablets

Formulation	Capsules	OD tablets
particle	granules	microgranules
particle size	ca. 1,000μm	ca. 300μm
number of particles (30mg products)	ca. 200	ca. 10,000



Japanese Patent 03746167

Philippines Patent 1-1999-01163

Easy for patients to take without water because of adherence improvement!

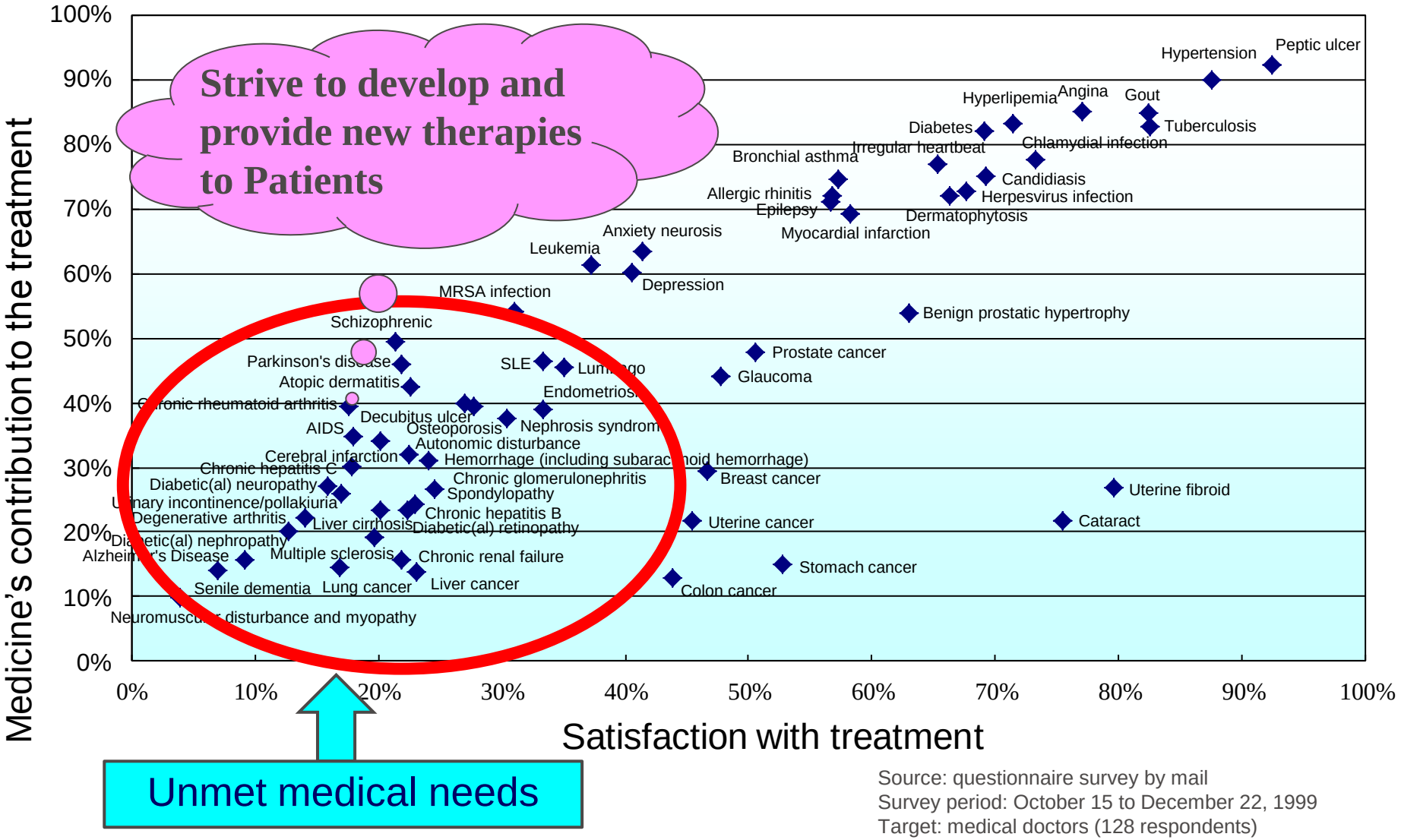
Collaboration Research Cases

The following technologies produced with the third party are being used for Leuprorelin Product.

Formulation Technology	Collaboration Research Partner
Biodegradable polymers	Japanese Company A
Dual chamber pre-filled syringe	Japanese Company B

5. New Paradigm in Drug Development

■Unmet Medical Needs



Source: questionnaire survey by mail
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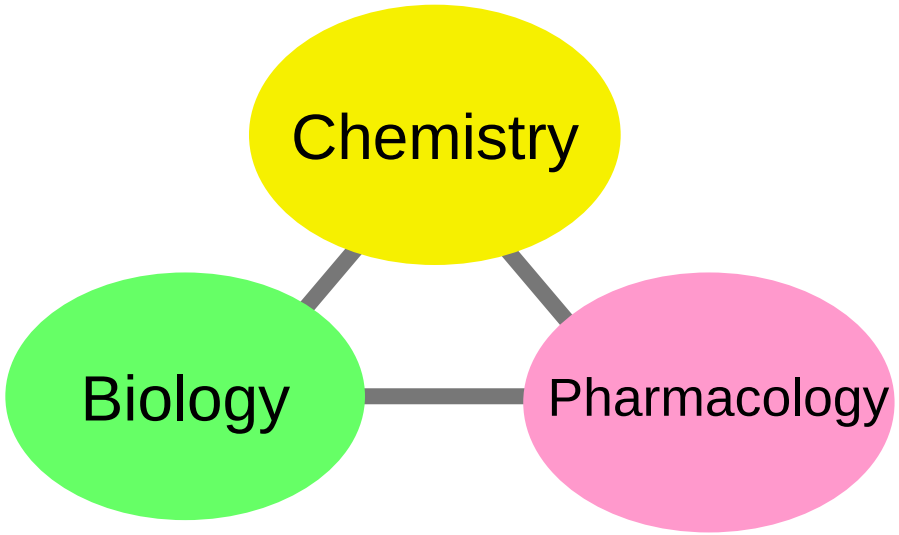
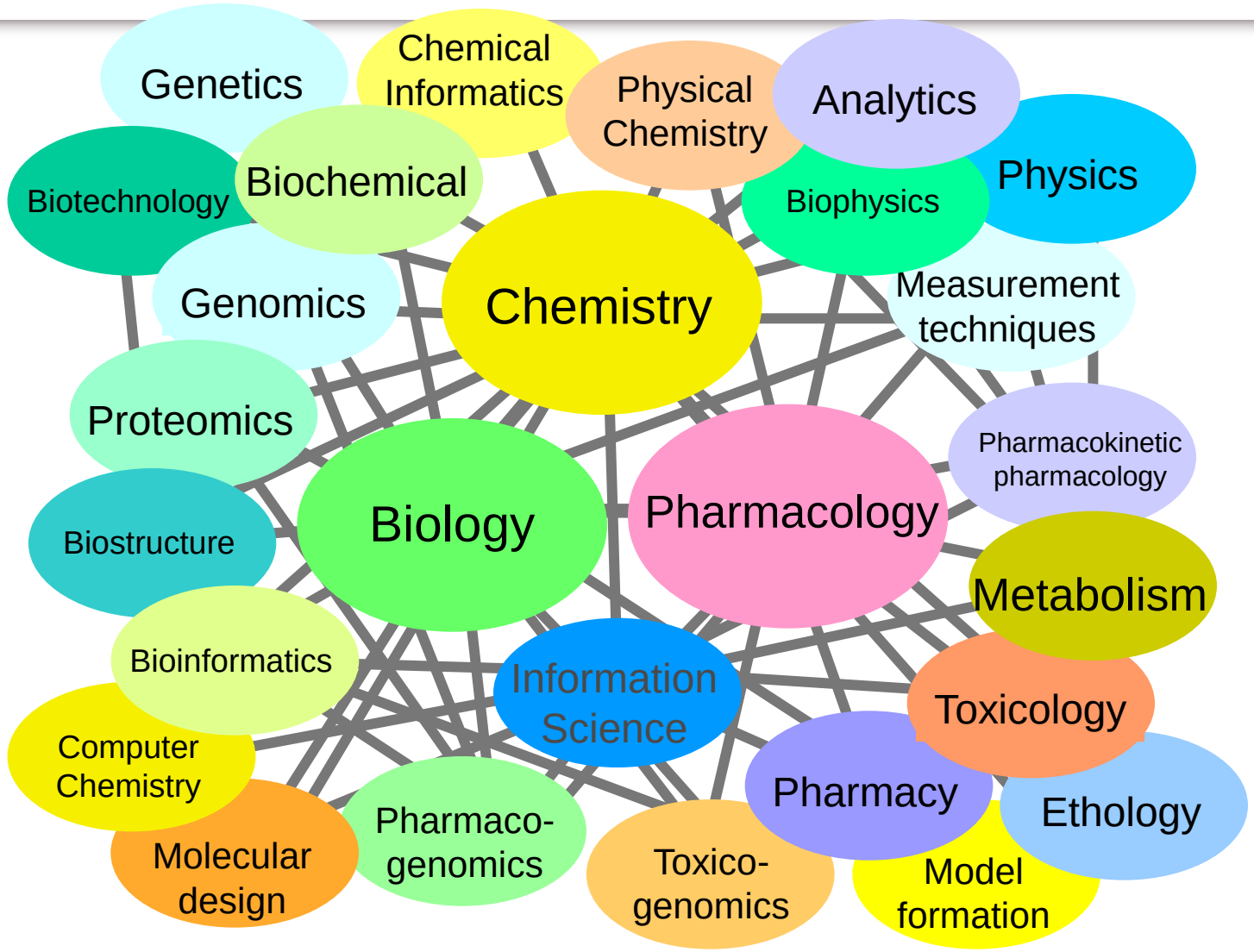
Target: medical doctors (128 respondents)

Source : The Japan Health Sciences Foundation: "Report on Key Domestic Technologies 2000 – Outlook of medical needs in 2010 –"

Authentic Drug Discovery Model

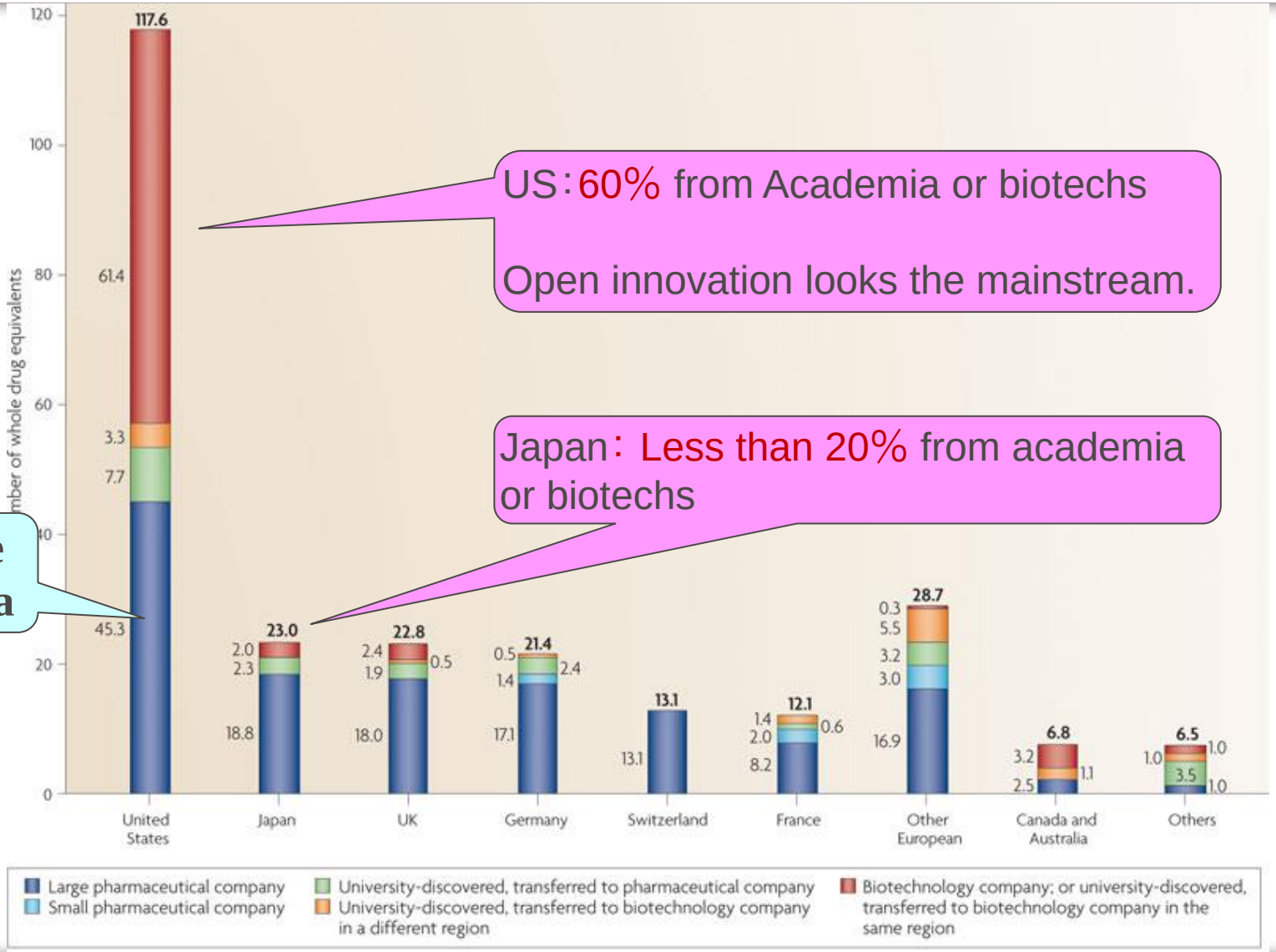


Up-to-date model（diversified / Complicated ）



⇨Many areas are connected by advanced networks

New drug seeds from academia or bio-venture （1998－2007）



Robert Kneller , Nature Reviews Drug Discovery 9, 867-882, 2010

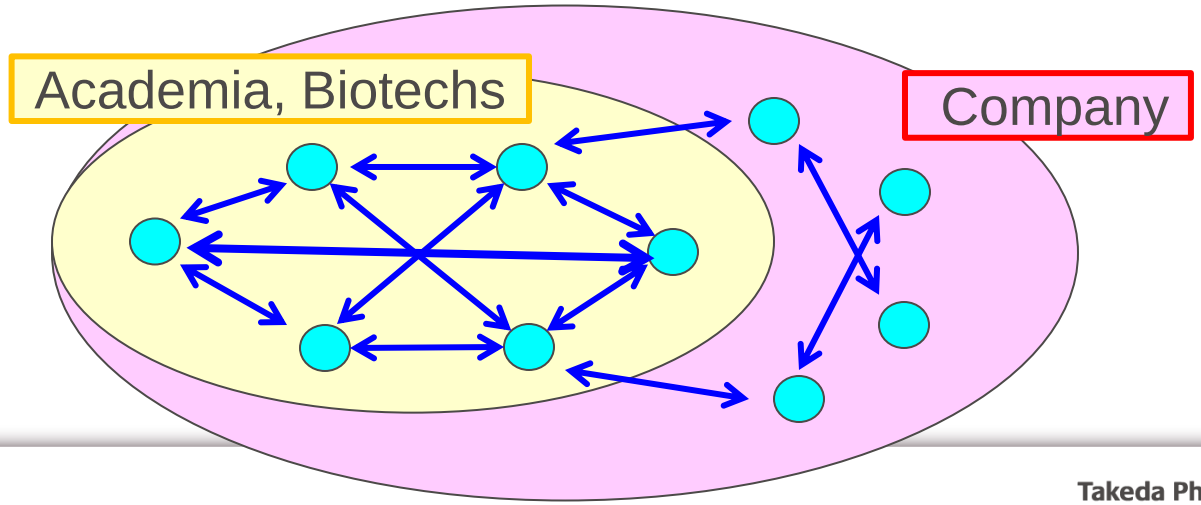
More drugs from academia / biotech company

Facilitate networking

・Pursue originality by conjugating various and creative research activities

・Needs to create new mechanism where academia and pharma companies get together more easily and spontaneously

More Openness and Accessibility
(data, information, strategy, etc.)



Shift into More "Open Innovation"

- **Traditional Model**
  - Small Molecule
  - Lifestyle Disease
  - Blockbuster
- **Closed - all things done in house –**
- **Patent Strategy to protect in-house R&D fruits**

More exposure to cutting - edge technologies.

- **Diversified, Complicated**
  - Large molecule, Molecularly targeted drug, biologics, regenerative medicine
- **Open Innovation for innovative therapy / medicine**
- **Open Innovation for Global Health by Innovative R&D model**

  Unmet medical needs in Neglected tropical diseases and communicable diseases

Open Innovation in Japan

- Academia - Pharma
  - Kyoto Univ. - Takeda :T-CIRA

- Pharma – Pharma
  - Daiichi-Sankyo – Astellas: Co-use of Compound Library

- Public offer by Pharma
  - Shionogi : FINDS
  - Daiichi-Sankyo: TaNeDS
  - Astellas: a-cube
  - Takeda: Cockpi-T, RINGO-T
- Academia – Academia
  - Tokyo Univ.: Drug Discovery Open Innovation Center
  - Kyoto Univ. Center for Innovation in Immunoregulative Technologies and Therapeutics
- Government Driven
  - Drug Discovery Supporting Network


京都大学
KYOTO UNIVERSITY
Takeda
CiRA

Highlights of the Research Collaboration

1. Center for iPS Cell Research and Application (CiRA) at Kyoto University and Takeda Pharmaceutical Company Ltd. (Takeda) start a ten-year-long research collaboration (T-CiRA Joint Program).
2. iPS cell and its related technologies to pharmaceutical R&D activities, such as drug discovery, cell therapy and drug safety.
3. Professor Shinya Yamanaka, the head of CiRA, directs the Program.
4. Takeda will provide:
    i. Total research budget: Approximately 20 billion-yen per over ten years
    ii. Research facility: Dedicated space in Shonan Research Center (Fujisawa, Japan) of Takeda
    iii. In-kind research support: 50 Takeda researchers, drug discovery technologies and other R&D know-hows.

Unique T-CiRA academic/industry collaboration

1. Long term (10 years) commitment by both CiRA and Takeda to a nationally important project.
2. The program is solely directed by Professor Yamanaka, the discoverer of iPS cell.
3. "Open Innovation": Housed in the center of a drug company's research headquarter.
4. A large scale collaboration: Over 100 researchers at one site.
5. Public Contribution: After filing patents, CiRA and Takeda encourage publication of outcomes that will accelerate public research.
6. Internationality: The Program will recruit scientists from all over the world.

Recruit Innovative Ideas to Generate Original Targets Takeda（RINGO-T）

- Invite academia to present new assay systems.
- Takeda will put its compound libraries into screenings, using the assay system.
- Takeda reports back to the presenter the findings gained by the screenings.
- The presenter can freely disclose and utilize the outcome.
- The outcome may lead to breakthrough to new drug discovery by academia, industries or Takeda.

COCKPI-T

Co-Create Knowledge for Pharma Innovation with Takeda (COCKPI-T)

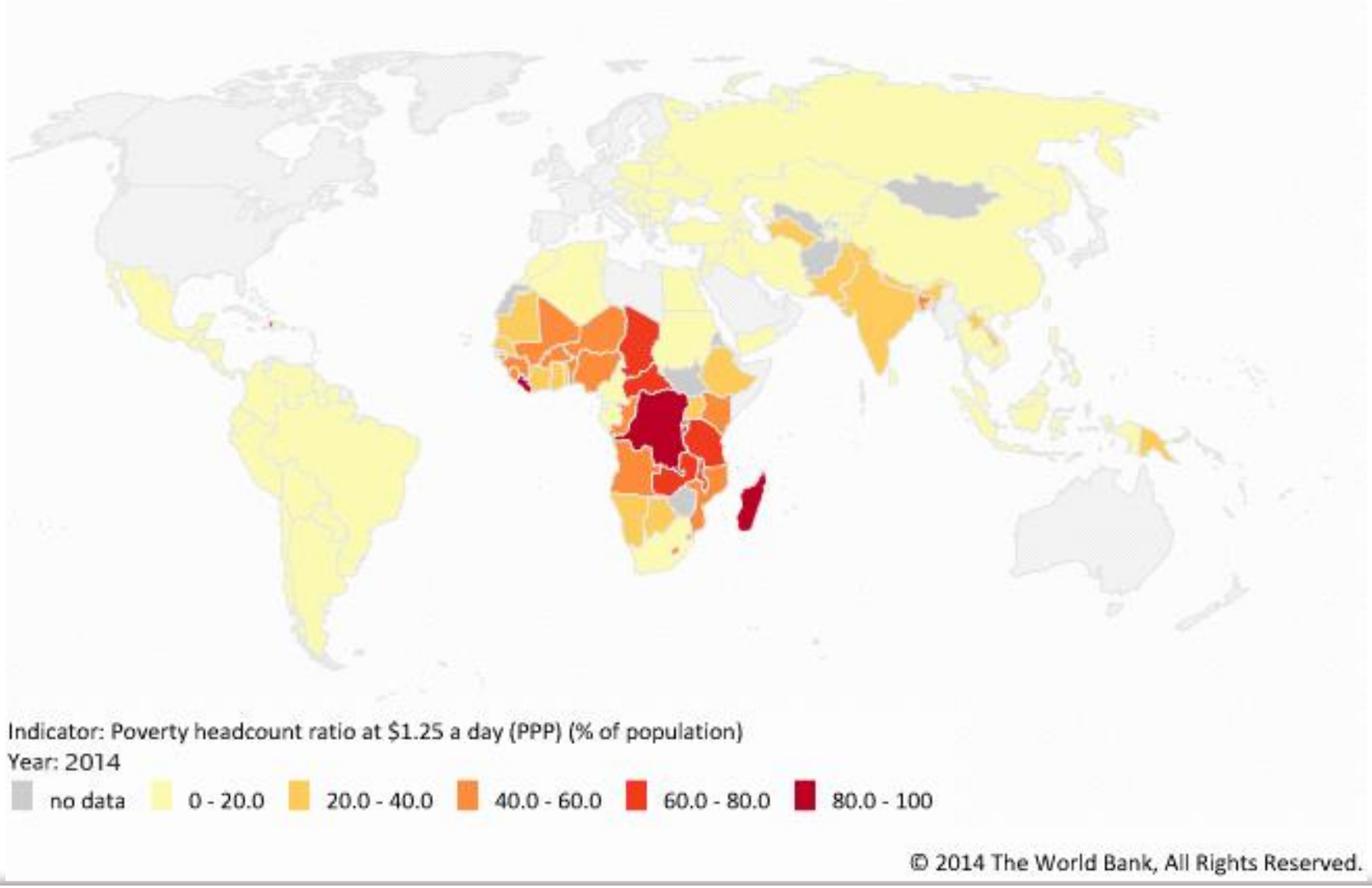
- Encourage and invite junior researchers at universities, research institutes and private industries to apply for sponsorship by Takeda.

- Innovative idea on drug target or research technology relating to specific therapeutic areas and themes designated by Takeda
  - Central Nervous System, Gastro Intestinal, Oncology, Immunology, inflammatory, Microbiome

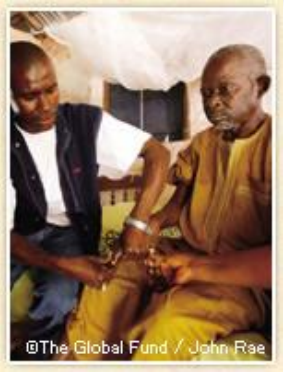
- Support
  - 100,000 USD (at max.) funding
  - Relevant Takeda's technology and assets

- Resulting invention and patents
  - Vested in Partner
  - Not enforced against Takeda's research activities
  - Takeda has first right to negotiate for exclusive license

Open Innovation to Improve Global Health



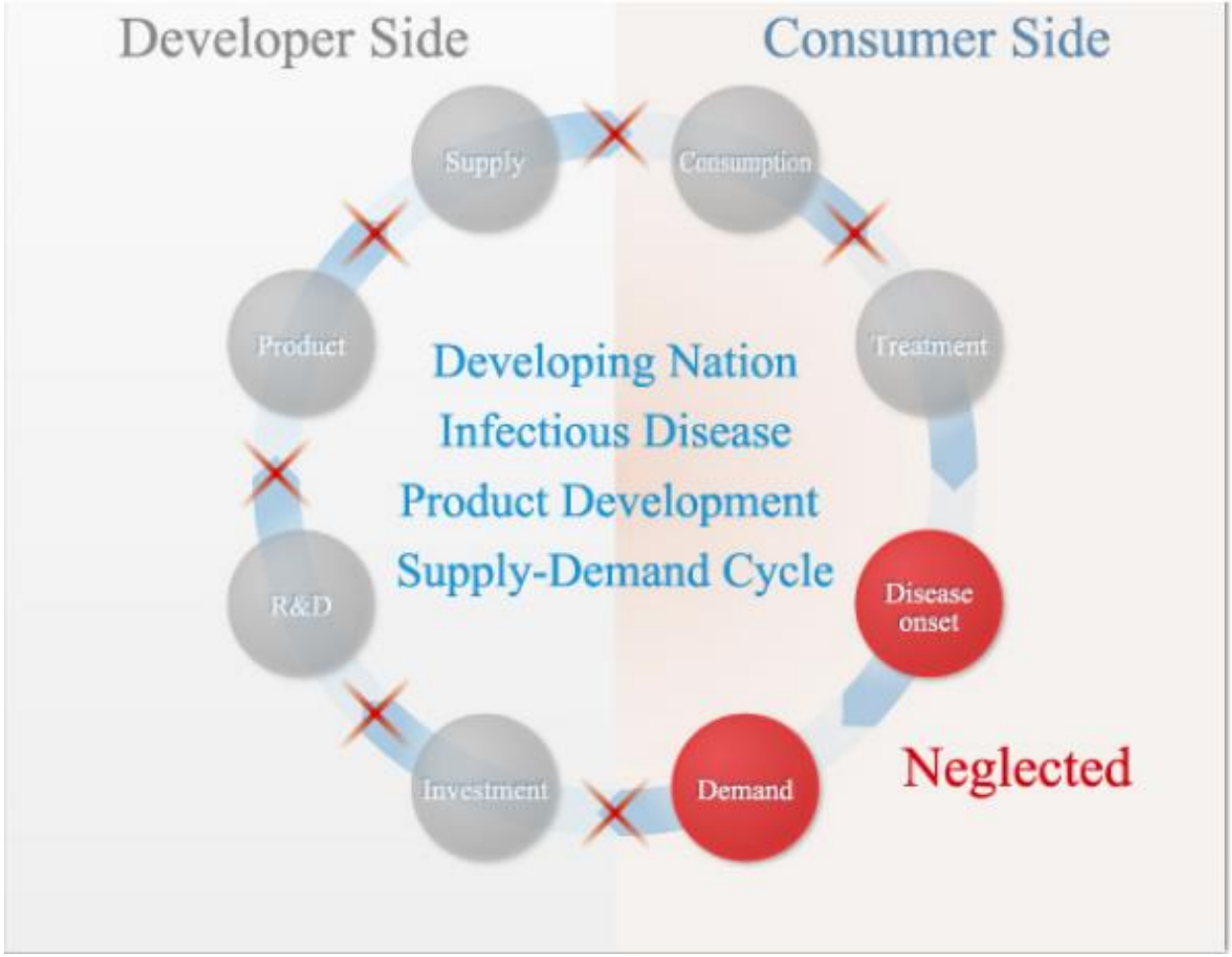
Global Health and Open Innovation



- HIV/ AIDs, Tuberculosis, Malaria, NTDs (Neglected Tropical Diseases) in developing countries ---> "Unmet Medical Needs"
- Public health care system, health insurance system, distribution system, pricing system, healthcare professional, public education and new drug development.....
- It is essential to realize Flexible Partnerships between public sector and private sector as well as other forms of cooperation within the various stakeholders. >>> Product Partnership.
- Patent drives technology flow and open innovation, and brings the life to the Technology
- Cases involving Japan
  - GHIT
  - WIPO Re:Search

GHIT - The **G**lobal **h**ealth **I**nnovation **T**echnology Fund

Why products not being provided?



GHIT

Promote R&D and supply of products targeting infectious diseases in developing nations

Pharmaceutical Companies
- Contributions to global health
- Expanded portfolios for developing countries
- Global branding

Bioventure business
- Business opportunities
- System for fixed volume purchases by public agencies targeting developing nations

Universities
- Expanded research opportunities
- Participation in product commercialization

Research institutions
- Expanded research opportunities
- Reduced public hygiene risks

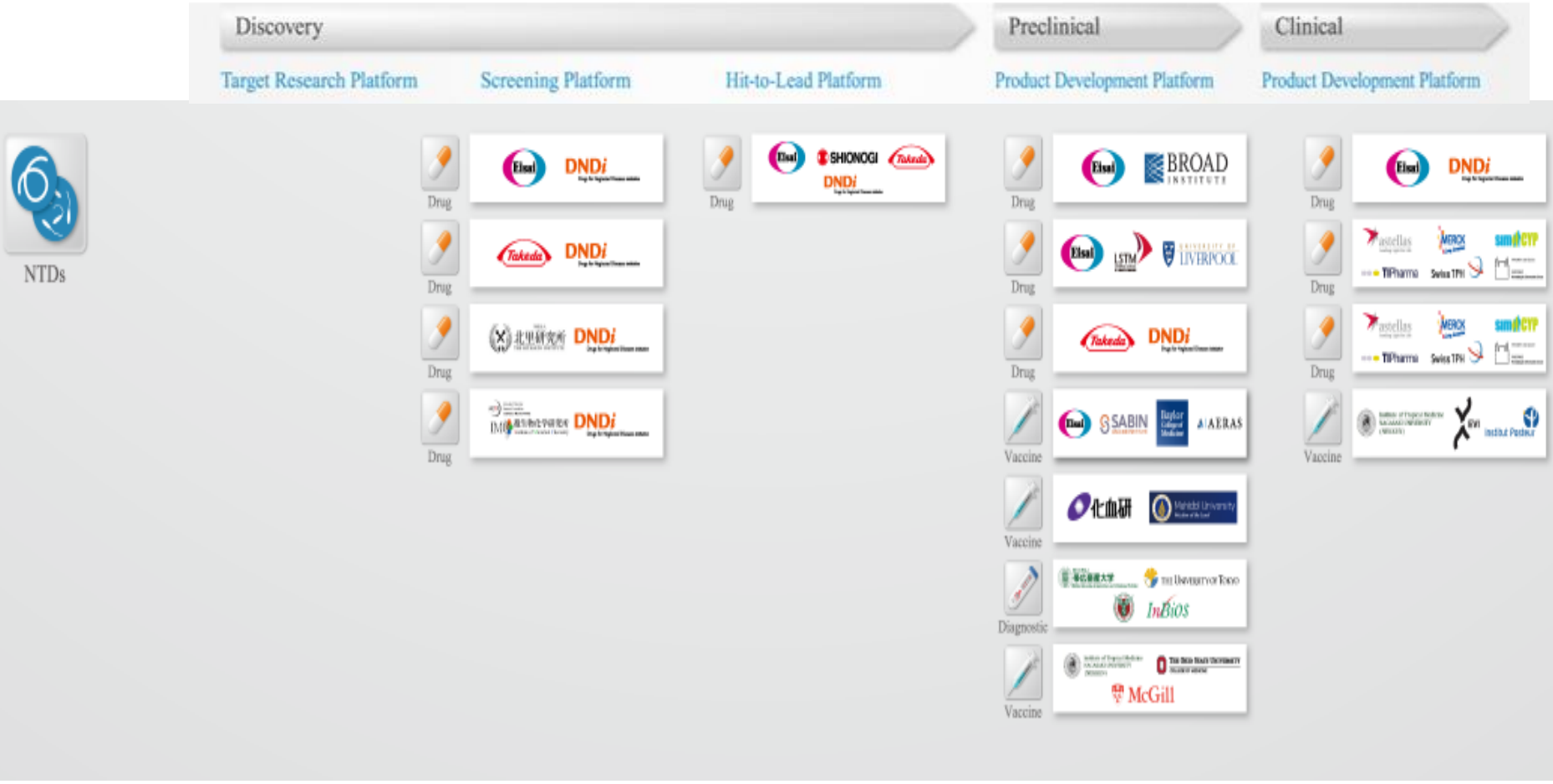
GHIT


Discovery
Preclinical
Clinical
Target Research Platform
Screening Platform
Hit-to-Lead Platform
Product Development Platform
Product Development Platform
Malaria
Drug
Diagnostic
CellFree Sciences
BROAD INSTITUTE
Vaccine

GHIT


Discovery
Preclinical
Clinical
Target Research Platform
Screening Platform
Hit-to-Lead Platform
Product Development Platform
Product Development Platform
Tuberculosis
Drug
Drug
Drug
Drug
Drug
Drug
Drug
Drug
Drug
Drug
Vaccine
Vaccine
Vaccine
NIBIO
AERAS
NIBIO
AERAS

GHIT

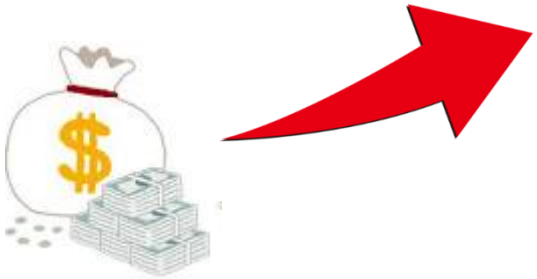

Discovery
Preclinical
Clinical
Target Research Platform
Screening Platform
Hit-to-Lead Platform
Product Development Platform
Product Development Platform
NTDs
Drug
Drug
Drug
Drug
Drug
Drug
Drug
Drug
Drug
Vaccine
Vaccine
Vaccine
Diagnostic
DNDi
SHIONOGI
BROAD INSTITUTE
LSTM
LIVERPOOL
SABIN
AERAS
Baylor College of Medicine
McGill
InBios
astellas
MERCK
sumitomo dainippon pharma
TB Pharma
Swiss TPH

GHIT
Takeda's case: Lead Optimization for Aminopyrazole

- **DNDi and Takeda Collaborate**
- **for the Lead Optimization for Aminopyrazole Series for Visceral Leishmaniasis drugs**

Takeda and DNDi collaboration

for Developing a Drug for Treating Visceral Leishmaniasis



Efforts Funded by GHIT Fund

GHIT
Collaboration by Multiple Pharmas

NTD Drug Discovery Booster

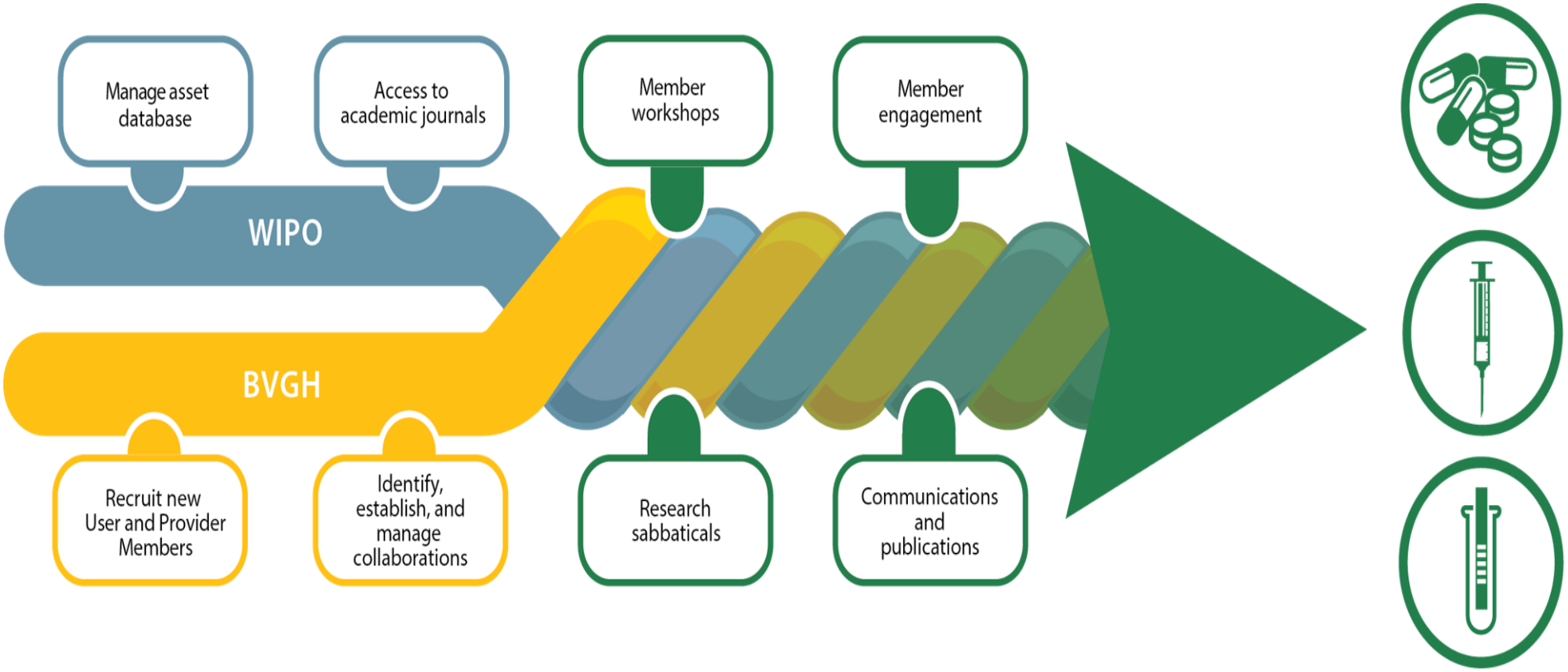
- Launched May 2015
- Participants: DND*i*, Eisai, Shionogi, Takeda, AstraZeneca
- Target disease: Chagas Disease and Leishmaniasis, 450 million people are at risk of contracting worldwide
- Time frame: From 2015-2017 with the possibility of extension & expansion
- Speed up the process and cut the cost of finding new treatments for the target diseases
- DNDi will access millions of unique compounds, generated over many decades of research, to screen for potential treatments or cures for the target diseases.
- Companies will continually examine their libraries for better matches as the search is refined.
- The GHIT Fund supports EUR 640,000 (79.5 million JPY), and the involvement of the three Japanese companies.

WIPO Re:Search - background

- Founded in 2011 by the World Intellectual Property Organization (WIPO), BIO Ventures for Global Health (BVGH), and several leading pharmaceutical companies
- Global initiative established to encourage and facilitate the sharing of intellectual property assets to advance **drug**, **vaccine**, and **diagnostic** development for **malaria**, **tuberculosis**, and **neglected tropical diseases** (NTDs)
- Consortium membership includes academic and non-profit research institutions, governmental and non-governmental organizations, and biopharmaceutical companies
- Any resulting product would be made available royalty free in the least developed countries and at a reasonable cost in other developing countries.

⇒ Takeda joined WIPO Re:Search in Sept. 2015

WIPO Re:Search - Structure



WIPO Re:Search – Advancing NTD Product R&D

Jim

- **Dr. Jim McKerrow** (University of California, San Diego [UCSD], USA) & **Eisai Co., Ltd.** (Japan)
- Jim is assessing inhibitors of ergosterol synthesis as potential leishmaniasis and Chagas disease drugs
- Eisai shared a novel squalene synthase inhibitor with Jim

- **Dr. Alister Craig** (Liverpool School of Tropical Medicine) & **Eisai Co., Ltd.** (Japan)
  - Alister is searching for adjunct treatments for cerebral malaria by targeting PAR1
- Eisai shared its PAR1 inhibitors with Alister to assess in his *in vitro* cerebral malaria model

Alister

APPENDIX

Marketed Drugs in Japan

( ) : still under development or examination

In 2003 - Marketed drug among 99 (out of TOP103)

USA	UK	FR	DE	KR	CN	Japan
98	97(2)	97(2)	97(2)	94	70	63(23)

Improved Data Protection period in Japan
8 year period instead of 6 year one

In 2013 - Marketed drug among Top100

USA	UK	FR	DE	KR	CN	Japan
100	100	99(1)	100	95(2)	73(12)	93(3)

Origin : ©2015 IMS Health. World Review, LifeCycle、Pharmaprojects、Evaluatepharma

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- **Existing Data**
  Any and all existing data and findings owned by a product development partner at the initiation of a project, including but not limited to information, know-how or intellectual property, will remain that of the original holder. The original holder may share, assign, or license their rights to a third party.

  New Data
  Ownership of any and all data and findings that is obtained or created through activities invested by the GHIT will be discussed and negotiated between participants and/or product development.

  Patent Applications
  Any existing data owned by a product development partner and/or any new data obtained through activities invested by the GHIT Fund may be disclosed by the GHIT Fund to a third party if such data is used in a patent application for a product which was derived from the activities invested by the GHIT Fund; provided, however: (1) that the disclosure of such data shall be limited to the proposed title of the invention, a draft of the abstract, the international non-proprietary name (INN) where applicable, and an outline of the specifications of such patent application; and (2) such third party shall take reasonable measures to keep confidential any such data received from the GHIT Fund.

- **Principle of Product Access Policy**
- **Licenses**
  When product development partners and/or participants are successfully granted a patent deriving from projects invested by the GHIT Fund, product development partners and/or participants will grant royalty-free licenses to users operating in Least Developed Countries (LDCs) as categorized by the United Nations classification and Low-Income Countries (LICs) categorized by the World Bank classification. License-related matters concerning middle income countries will be reviewed on an individual basis with the goal of ensuring reasonable royalty licenses.

  Pricing
  In LDCs, LICs and middle income countries, product development partners and/or participants will set prices for products on the basis of a no gains/no loss policy that can improve access to the product for patients and citizens of LDCs, LICs and middle income countries

WIPO Re:Search – Sharing IP Assets

- Compounds & compound libraries
  - HMG-CoA reductase inhibitors
- Technologies
  - High-throughput screening platform
- Reagents
  - Anti-dengue virus antibody
- Know-how and therapeutic area expertise
  - Drug structure-activity relationship (SAR) advice
- Clinical/field samples
  - Severe and asymptomatic malaria patient samples
- Data
  - Investigator's brochure, clinical trials data summary
- Other support
  - Vaccine thermostability formulation