Overview of the antibacterial R&D landscape in Japan

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  - Private, Academia, and Government
- Progress
  - Regulatory, Pipeline, and Incentives
- Barriers

History of the Development of Antimicrobial Agents in Japan

Table 1. Development of antibacterial agents in Japan

Period	1911–1955	1956–1975	1976–1995	1996–2015	Total
Penicillins	11	16	10	1	38
Cephems	0	6	40	2	48
Carbapenems and other β-lactams*1	0	0	8	5	13
Aminoglycosides	7	8	8	0	23
Macrolides and lincosamides	5	15	8	2	30
Tetracyclines	5	9	0	1	15
Peptides*2 and other antibiotics*3	9	8	4	4	25
Sulfonamides	19	11	2	0	32
Pyridone carboxylates	0	2	12	6	20
Miscellaneous antibacterials*4	10	4	0	2	16
Anti-TB*5 and anti-HD*6 drugs	11	14	0	3	28
Total	77	93	92	26	288

*1 monobactams, β-lactamase inhibitors

*2 including glycopeptides and lipopeptides

*3 chloramphenicol, fosfomycin, novobiocin, fusidic acid, mupirocin, streptogramins

*4 arzenobenzoles, nitrofurans, thiamphenicol, linezolid

*5 anti-TB: anti-tuberculous

*6 anti-HD: anti-Hansen's disease

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Movements in Japan

- 2013: The Committee of Promotion of Drug Discovery was launched in the Japanese Society of Chemotherapy for facilitation of development of new antimicrobial agents.
- 2014: Statement from the Committee of six academic societies, requiring facilitation in the development of new antimicrobial agents was submitted to the Minister of Health, Labour and Welfare, the Minister of Education, Culture, Sports, Science and Technology, and the Minister of Economy, Trade and Industry.
- 2016: The Committee of eight academic societies issued document: "Measures Against Antibiotic-Resistant Bacteria Through Global Cooperation"

Movements in Japan

- April 2016: The Japanese government announced the “National Action Plan on Antimicrobial Resistance (AMR)”

  Major Items regarding R/D:

  1. Research to facilitate R/D
  2. Promotion of industry-government-academia collaboration
  3. Formulation of international clinical evaluation guidelines, etc.
  4. Priority review system for antimicrobials
  5. Collaboration with global funding agencies

Movements in Japan

- April 2017: The Japan Pharmaceutical Manufacturers Association (JPMA) submitted the Suggestion of Measures to R/D to Ministry of Health, Labour and Welfare

  Suggestions:

  1. Stockpile/purchase system of new drugs
  2. Establishing funds, and R/D organization (consortium) through PPP
  3. Formulation of international common clinical evaluation guidelines for facilitation of the clinical development of new drugs
  4. Market Entry Rewards
  5. Preliminary drug price review system based on drug profiles

Movements in Japan

- June 2019: The JPMA submitted "Suggestion from the pharmaceutical industry on the introduction of Pull incentive towards facilitation of the research and development of drugs, etc. for AMR" to the Minister of Health, Labour and Welfare
  a. Market Entry Rewards
  b. Transferable Exclusivity Extensions

Progress

Regulatory

International Harmonization

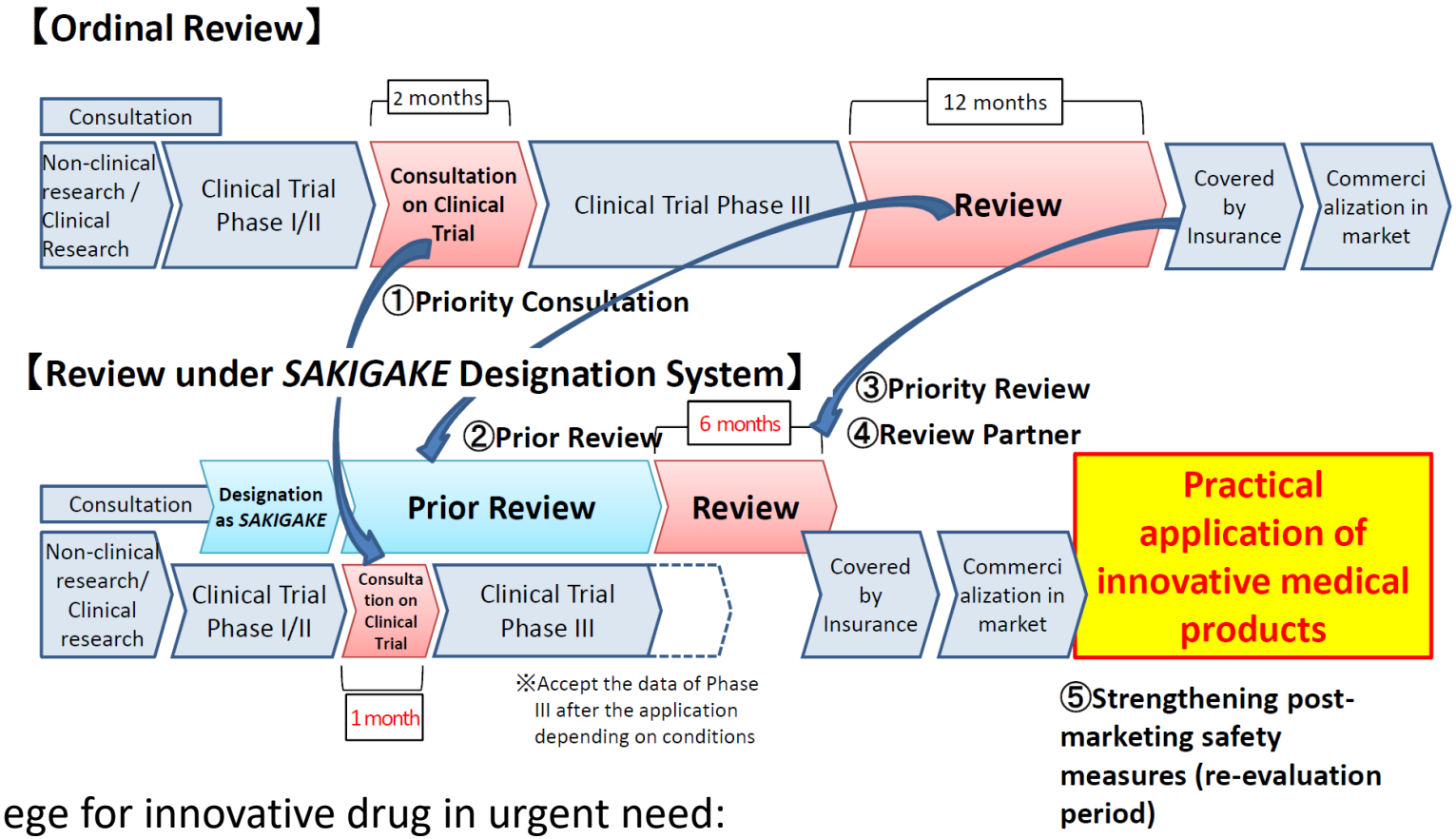
- The Pharmaceuticals and Medical Devices Agency (PMDA) participates in the tripartite meeting of the FDA/EMA/PMDA: A review is being conducted to formulate common clinical study guidelines through meetings between Japanese, US and European regulatory authorities
- Revision of the guideline for the method of clinical evaluation of antimicrobial agents

SAKIGAKE Designation System

- Scheme for rapid approval
- Scheme for rapid authorization of unapproved drug via the council on unapproved drug/ Off label use to meet unmet needs

Scheme for rapid approval

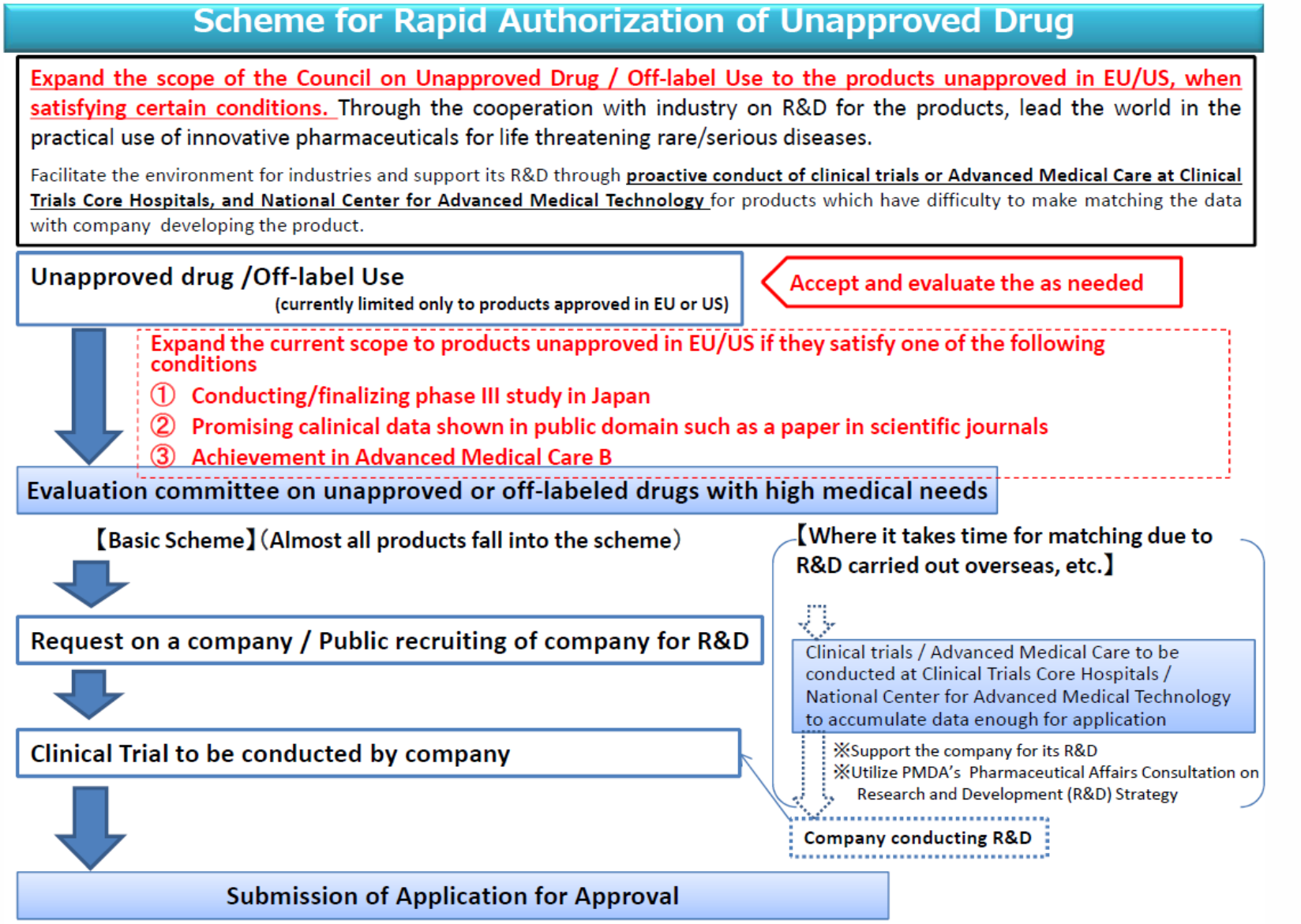
General Timeframe of *SAKIGAKE*



Privilege for innovative drug in urgent need:

1) Prioritized Consultation [Waiting time: 2 months→1 month]
2) Pre-application Consultation
3) Prioritized Review [12 months → 6 months]

Scheme for rapid authorization via the council on unapproved drug/ Off label use to meet unmet needs -



Pipeline

Company/Institution	Product name or descriptor (ID if available)	Pre-clinical development stage	Product type	Product type more information (please choose from the list in the methodology)	Spectrum	Mode of action
Bacterial						
Shionogi	anti-GN bacteria program 1	Lead optimization	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Gram-negative (WHO critical priority pathogens – at least one)	Beta-lactam antibiotic
Shionogi	anti-GN bacteria program 2	Lead optimization	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Gram-negative (WHO critical priority pathogens – at least one)	Beta-lactam antibiotic
Hisamitsu	besifloxacin hydrochloride	Unknown	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Gram-positive (WHO priority pathogens – at least one)	DNA topoisomerase II inhibitor; DNA topoisomerase IV inhibitor
Wakunaga	WFQ228	Pre-clinical candidate	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Gram-negative (WHO critical priority pathogens – at least one)	DNA topoisomerase II inhibitor; DNA topoisomerase IV inhibitor
Daiichi Sankyo	DS86760016	Pre-clinical candidate	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Gram-negative (WHO critical priority pathogens – at least one)	Leucyl-tRNA synthetase inhibitor
Sumitomo Dainippon Pharma	anti-bacterial therapies	Lead optimization	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Unknown	Unknown

Company/Institution	Product name or descriptor (ID if available)	Pre-clinical development stage	Product type	Product type more information (please choose from the list in the methodology)	Spectrum	Mode of action
Tuberculosis						
TB						
Shionogi	S-004992	IND enabling studies	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Targeted pathogen-specific (WHO priority pathogens, TB or C. difficile)	Cell wall synthesis inhibition
Shionogi	anti-mycobacterial therapies	Lead optimization	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Targeted pathogen-specific (WHO priority pathogens, TB or C. difficile)	Unknown
Takeda	anti-mycobacterial therapies	Lead optimization	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Targeted pathogen-specific (WHO priority pathogens, TB or C. difficile)	Unknown
Biochemical						
Shionogi	COT143	Pre-clinical candidate	Curative treatment: directly acting large molecule antibacterial agents	Biologic	Gram-negative (WHO critical priority pathogens – at least one)	TypeIII secretion system inhibition
Chiome Bioscience	anti-infectious diseases	Lead optimization	Curative treatment: directly acting large molecule antibacterial agents	Biologic	Unknown	Monoclonal antibody
Thyas	anti-infectious diseases	Lead optimization	Curative treatment: directly acting large molecule antibacterial agents	Biologic	Unknown	Cellular therapy

Company/Institution	Product name or descriptor (ID if available)	Pre-clinical development stage	Product type	Product type more information (please choose from the list in the methodology)	Spectrum	Spectrum (more detailed information) (if available)	Indication	Mode of action
Shionogi	antifungal program 1	Lead optimization	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Unspecified	Aspergillus, Candida	Fungal infection	-
Shionogi	antifungal program 2	Lead optimization	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Unspecified	Aspergillus, Candida	Fungal infection	-
Eisai	E-1210	IND enabling studies (commencement of human testing)	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Unspecified		Fungal infection	Unidentified pharmacological activity
Toyama Chemical	T-2307	IND enabling studies (commencement of human testing)	Curative treatment: directly acting small molecule antibacterial agents	Single agent	Unspecified		Fungal infection	Unidentified pharmacological activity

Incentives

第2回 薬剤耐性(AMR)シンポジウム

日時 令和元年5月27日(月)
13:00～18:00(12:00受付開始)

会場 日本橋ライフサイエンスハブ 会議室
東京都中央区日本橋室町1-5-5室町ちばぎん三井ビル8F
▶アクセス 東京メトロ銀座線・半蔵門線「三越前」駅より直結
JR総武線「新日本橋」駅より直結

定員 200名
※参加対象者:研究者、製薬関係者、行政関係者、医療関係者

参加費 無料

参加申し込み方法 下記のwebサイトからお申し込みください。
https://krs.bz/amed/m?f=68

お問い合わせ 第２回薬剤耐性(AMR)シンポジウム運営事務局 (受付
TEL: 03-6459-3210 FAX:03-6740-8311 E-mail: amr2

プログラム

13:00－13:20 開会
倉根 一郎 プログラム・ディレクター、新興再興感染症制御プロジェクト
宇都宮 啓 厚生労働省健康局長

13:20－14:20 セッションI AMRサーベイランス及び耐性菌バンク
(1)舘田 一博 日本感染症学会理事長 (2)菅井 基行 国立

14:20－14:40 休憩

14:40－16:50 セッションII Push/Pullインセンティブ及びその他の取り組み
(1) Dr. Mark Albrecht, BARDA, 米国保健福祉省(HHS) (2) Dr. Louise
(3) 俵木 保典 日本製薬工業協会国際部長 (4) 大曲 貴
(5) 山岸 義晃 医薬品医療機器総合機構新薬審査第四部

16:50－17:10 休憩

17:10－17:50 セッションIII 新規抗菌剤研究開発の取り組み
(1) 供田 洋 北里大学薬学部教授 研究課題代表者・創薬ブースタ
(2) 花木 秀明 分担担当者(統括責任者)・CiCLE事業支援課題

17:50－18:00 閉会
末松 誠 日本医療研究開発機構(AMED)理事長

18:00－ 意見交換会及びポスターセッション

主催: AMED 国立研究開発法人 日本医療
Japan Agency for Medical R

AMR consortium: Not yet

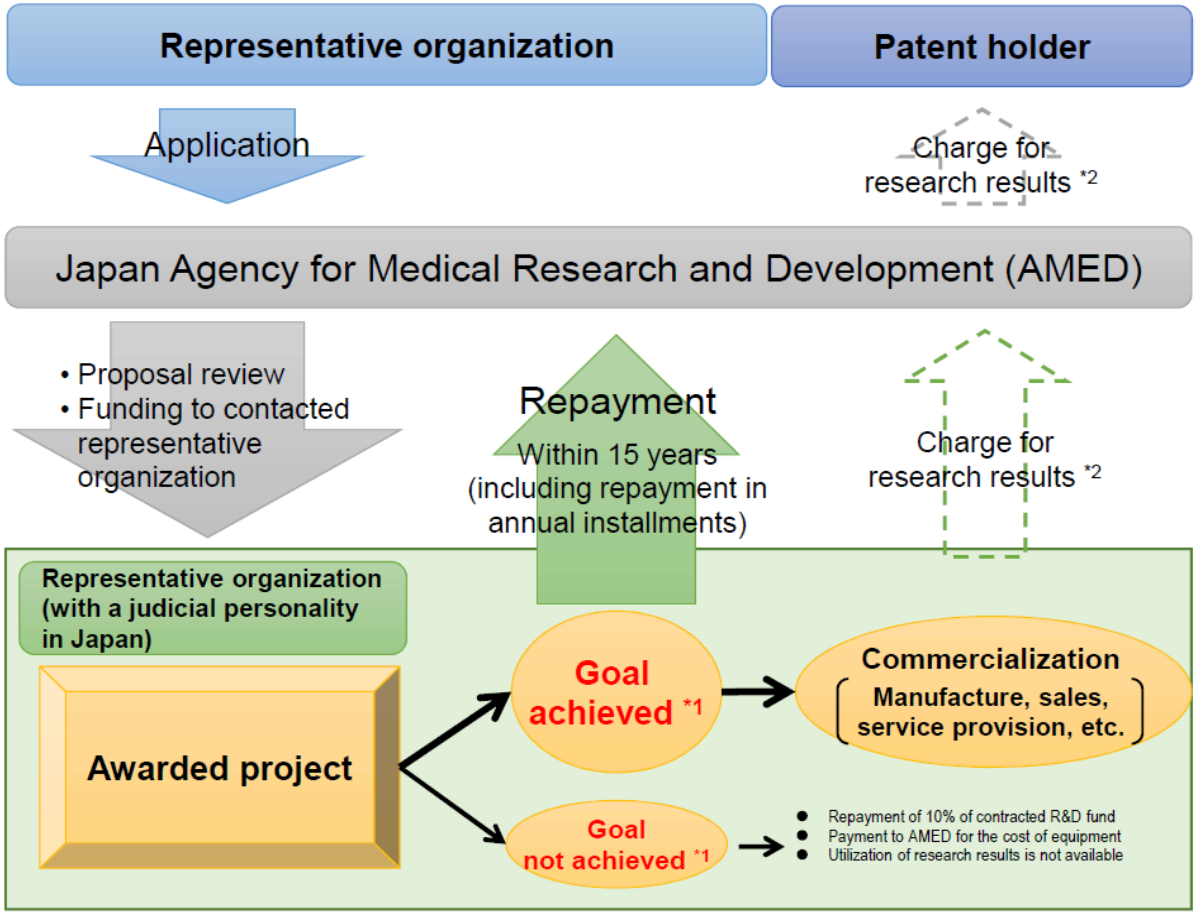
Japan Agency for Medical Research and Development

Cyclic Innovation for Clinical Empowerment
(C*i*CLE)

Japan Agency for Medical Research and Development (AMED),
National Research and Development Agency

国立研究開発法人 日本医療研究開発機構
Japan Agency for Medical Research and Development

Schemes Implemented



This program is classified into three types:

(A) Improving the environment for medical R&D type

Improving the environment for development of collaborative foundation that contributes to R&D for the practical application of drugs, medical devices, regenerative medicine products, medical technologies and human resource training.

(B) R&D type

R&D geared towards practical application of drugs, medical devices, regenerative medicine products, medical technologies with a mixed team of companies, universities and institutes based on industry-academia collaboration or industry-industry collaboration.

(C) Practical realization development type

Practical realization development of drugs, medical devices, regenerative medicine products, medical technologies, implemented in industry-academia collaboration based on seeds (patents, etc.)

***1 Whether the goal has been achieved or not is determined by the attainment degree of the minimum technical level/improvement level at the time of proposal submission.**

***2 The charge for research results is to be paid to AMED in accordance with sales (with some exceptions). If seed patents exist, AMED pay the charge for research results to patent holder.**

2

Pull incentives

Although proposed…

- Market Entry Rewards
- Transferable Exclusivity Extensions

Barrier

- Lack of incentives, especially Pull incentive
- Access to essential antimicrobials; shortage of cefazolin

Japanese Initiative for Progress of Research on Infectious Disease for Global Epidemic (J-PRIDE)

Outline

Japanese Initiative for Progress of Research on Infectious Disease for global Epidemic

- Issues such as the spread of Ebola hemorrhagic fever in East Africa, Zika virus infectious disease, which is related with microcephaly in children mainly in Latin America, and increasing drug resistance have shocked and concerned the international community and has forced to take prompt measures.
- "the Basic Plans for Strengthening Measures on Emerging Infectious Diseases (2016.2)", "the National Action Plan on Antimicrobial Resistance (AMR) (2016.4)" and "the involvement of the nation regarding the consolidation of the BSL4 facility of Nagasaki University (2016.11)" determined at The Ministerial Meeting on Measures on Emerging Infectious Diseases pointed out the necessity of reinforcement of the research function by consolidating infectious disease research centers and development of researchers in the field of infectious diseases.
- Based on these highlighted issues, J-PRIDE supports research directed to search for potential drug targets against highly pathogenic infectious diseases and also research and human resource development involved in BSL4 facility for creation of innovative drugs against infectious diseases.

Establishment of network constituted by researchers in diverse fields

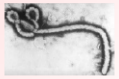
Researchers in medicine, pharmacy, veterinary medicine and agriculture, as well as those in other fields (structural biology, imaging, bioinformatics, etc.) collaborate to promote cross-disciplinary research to deliver breakthrough findings.

Research area

Research on highly pathogenic infectious diseases such as Ebola hemorrhagic fever

To promote studies on the structure and function of viral proteins, structure and function of the viral genome, viral life cycle, and productive infection for highly pathogenic infectious diseases such as Ebola hemorrhagic fever that could lead to creation of novel drugs:

- The program supports studies that focus on basic research in infectious diseases in Japan at the infectious disease research center centering on BSL4 facility.
- The program promotes studies that expand the range of research regarding highly pathogenic infectious diseases.



•(Provided by National Institute of Infectious Diseases)

Research on interaction between viral-host factors and infection control mechanism

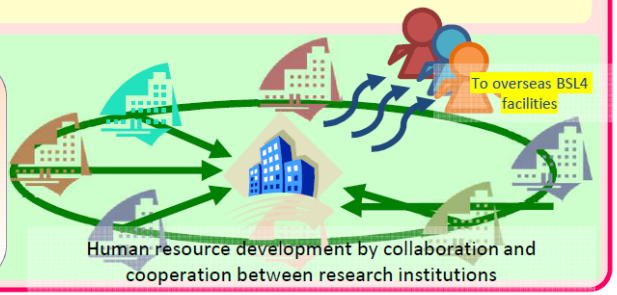
Promotion of studies focused on process involved in an establishment of infection such as viral replication within the cells or on elucidation of host infection control.

Research to elucidate the pathology of infectious diseases that cause congenital abnormalities in fetuses or serious symptoms in children

Promotion of studies that elucidate the molecular mechanism of how various infection defense mechanism is evaded for establishment of infection.

Human resources development

Development of researchers who study highly pathogenic pathogens
Development of researchers with the knowledge and experience necessary to conduct research in BSL4 facilities through training at overseas BSL4 facilities.
Promotion of the development of researchers through collaboration and cooperation with research institutions in Japan and overseas BSL4 facilities.



Alliance

- Research Program on Emerging/ Re-emerging Infectious Diseases
- Japan Initiative for Global Research Network on Infectious Diseases (J-GRID)
- Other projects of AMED (e.g., Drug Discovery Support Network)
- National Institute of Infectious Diseases
- Infectious disease-related societies
- International research institutes
- Pharmaceutical companies

- Overall enhancement on basic research against infectious diseases in Japan
- Develop innovative drugs of Japanese origin
- Strengthen infection crisis-management system
- Continuous contribution to international community

https://www.amed.go.jp/en/program/list/01/06/005.html