SARS CoV-2 Infection: Development of therapeutic agents in Japan

Senior Managing Director
Japan Pharmaceutical and Manufacturers Association (JPMA)

Kazuhiko Mori

Disclaimer

The views expressed herein are those of the presenter; they do not necessarily reflect the views of JPMA or any entity with which I have been affiliated.

Background:
Challenges from the beginning of the 21st century

- Rising costs of new drugs developed worldwide the productivity decreases markedly, it was beginning sustainability impaired
- Cost improvement and speed improvement of new drug development are necessary
  - ➡ Cost: 90%down, Time: 50% reduction
  - ➡ Conditional approval system, post marketing-surveillance
  - ➡ High-quality and transparent patient registries, Utilization of electronic medical information

Tufts Center for the Study
of Drug Development

Briefing

Cost of Developing a New Drug

November 18, 2014

The estimated average pre-tax industry cost per new prescription drug approval (inclusive of failures and capital costs) is:

http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf

News
March 10, 2016
Tufts CSDD Assessment of Cost to Develop and Win Marketing Approval for a New Drug Now Published
BOSTON – March 10, 2016 – The most recent analysis by the Tufts Center for the Study of Drug Development of the average cost to develop and gain marketing approval for a new drug—pegged at $2.558 billion—has been published in the *Journal of Health Economics*, it was announced today.

"Drug developers are taking action to rein in rising development costs, including increasing efforts to **discover, validate, and use biomarkers**, adopting new approaches to **patient recruitment and retention**, and implementing **leading-edge project management practices**, but they face strong headwinds, given the complexity of the problems they're addressing,"

The NEW ENGLAND JOURNAL of MEDICINE

The most expensive step in creating a new drug is conducting clinical trials. Conducting a trial costs $25,000 or more per patient studied, and phase 3 trial programs consume more than 40% of a sponsoring company's expenditures.

Unfortunately, every patient is not equally valuable when it comes to clinical trials, and many clinical development programs are economically inefficient in that they are excessively large relative to the amount of information they yield, especially in light of the information-technology breakthroughs that have lowered the cost of data acquisition and analysis over the past 20 years.

The Calculus of Cures

Robert Kocher, M.D., and Bryan Roberts, Ph.D.

In 2013, the Food and Drug Administration (FDA) approved 27 new drugs for marketing. Eight of these drugs are for orphan diseases, including six rare cancers. In fact, more than half of the 139 drugs

least two of these dimensions. Many drugs designed for orphan diseases and cancers are good investments of scarce capital, since they tend to have relatively low development costs and selling

published on February 26, 2014, at NEJM.org.

From Venrock, Palo Alto (R.K., B.R.), and the Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, Los Angeles (R.K.) — both in California.

① 開発コスト90%を削減し、開発期間を50%に短縮可能！

② 「条件付き承認」と「市販後調査」を前提とした開発合理化

③ 高い質の患者レジストリー、電子診療情報の活用が有望

We estimate that development costs for drugs could be reduced by as much as 90%, and the time required by 50%, if the threshold for initial approval were defined in terms of efficacy and fundamental safety. ①

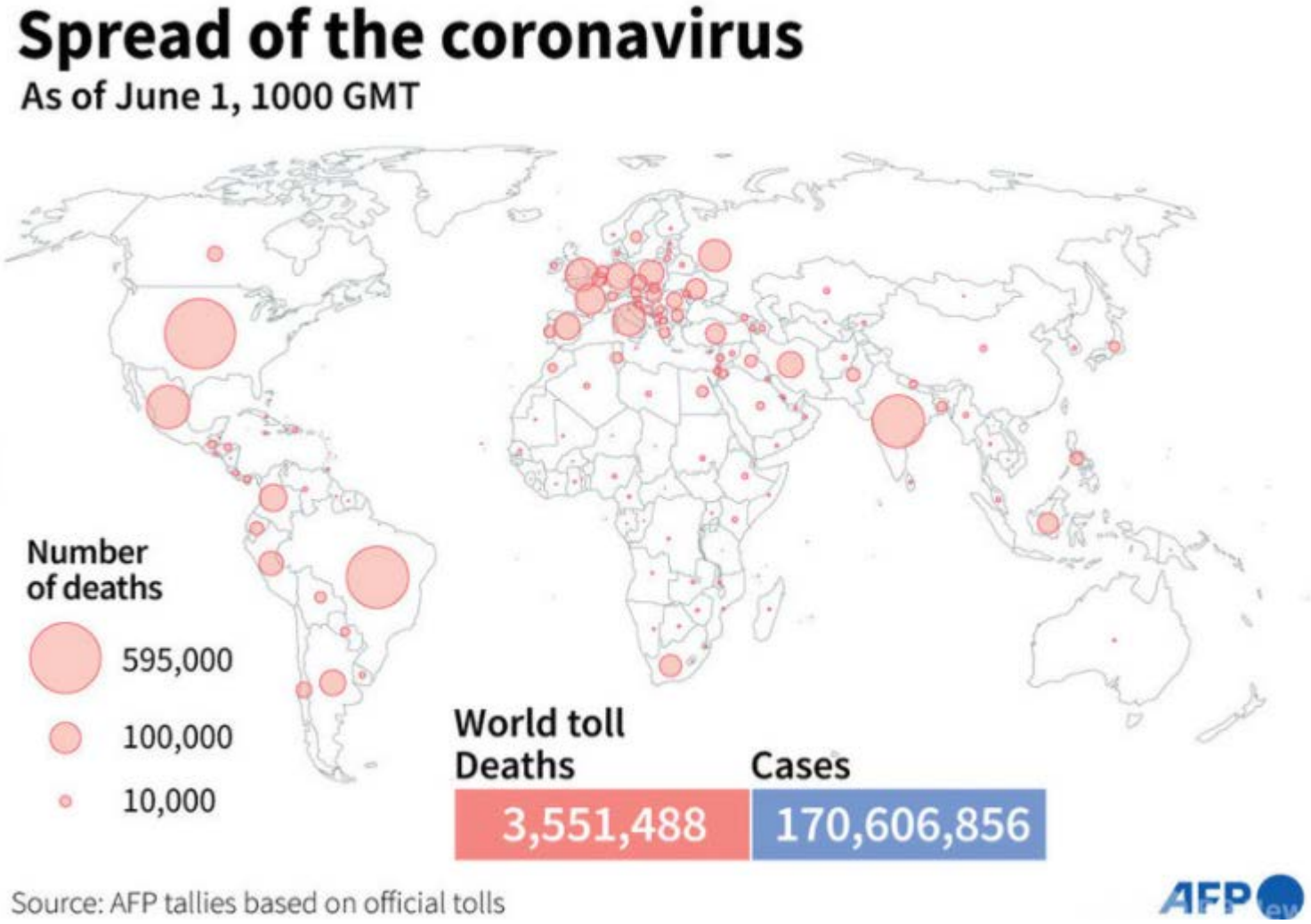
Redesigning trials to include fewer patients, providing conditional approval of drugs, and requiring post-marketing surveillance could have a profound effect, allowing smaller development programs to achieve greater success. ②

Cutting costs and time, while requiring high-quality and transparent patient registries for independent safety monitoring, would be a more informative and cost-effective approach. With the widespread adoption of electronic health records and the introduction of many low-cost data-analysis tools, it is now feasible to develop mandatory post-marketing surveillance programs that make thousand-patient trials obsolete. ③

Covid-19 Pandemic
First report from China in January 2020

https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/

The infection has spread rapidly around the world and is still spreading



Covid-19

World toll Tuesday, June 1 at 1000 GMT

Deaths	New	Cases	New
3,551,488	8,264	170,606,856	386,023

New: 24-hour increase on Monday, May 31

Hardest-hit countries*

	Deaths	New (latest report)	Cases
UNITED STATES	594,568	135	33,264,429
BRAZIL	462,791	860	16,545,554
INDIA	331,895	2,795	28,175,044
MEXICO	223,568	61	2,413,742
UNITED KINGDOM	127,782	1	4,487,339
ITALY	126,128	82	4,217,821
RUSSIA	121,873	372	5,081,417
FRANCE	109,557	126	5,667,324
COLOMBIA	88,774	492	3,406,456
GERMANY	88,595	153	3,682,911
IRAN	80,156	217	2,913,136
SPAIN**	79,953	48	3,678,390

*In Peru, a panel of experts put in place by health authorities has estimated that the real number of deaths in the country is more than 180,000

**Toll reported Monday includes new deaths since Friday

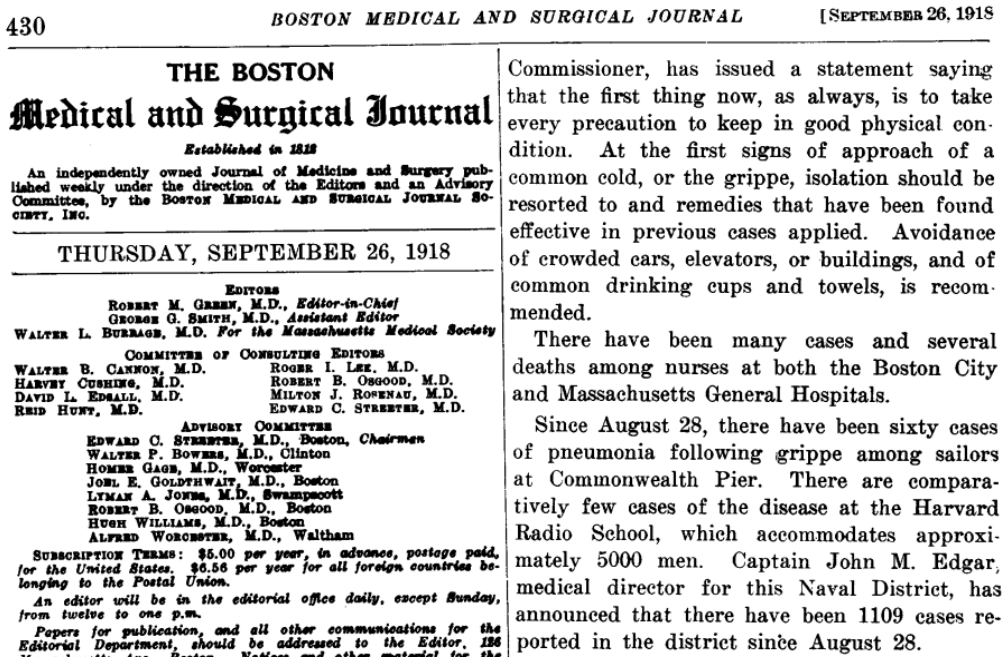
Increases over 24 hours may not tally exactly with previous day's total due to inavailability or late publication of data or corrections made by authorities

Source: AFP count based on official tolls

AFP

https://www.afpbb.com/articles/-/3349608

Pandemic that occurred 100 years ago (Spanish flu)



430 BOSTON MEDICAL AND SURGICAL JOURNAL [SEPTEMBER 26, 1918

THE BOSTON
Medical and Surgical Journal
Established in 1828

An independently owned Journal of Medicine and Surgery published weekly under the direction of the Editors and an Advisory Committee, by the BOSTON MEDICAL AND SURGICAL JOURNAL SOCIETY, INC.

THURSDAY, SEPTEMBER 26, 1918

EDITORS
ROBERT M. GREEN, M.D., *Editor-in-Chief*
GEORGE G. SMITH, M.D., *Assistant Editor*
WALTER L. BURRAGE, M.D. *For the Massachusetts Medical Society*

COMMITTEE OF CONSULTING EDITORS
WALTER B. CANNON, M.D. — ROGER I. LEE, M.D.
HARVEY CUSHING, M.D. — ROBERT B. OSGOOD, M.D.
DAVID L. EDSALL, M.D. — MILTON J. ROSENAU, M.D.
REID HUNT, M.D. — EDWARD C. STREETER, M.D.

ADVISORY COMMITTEE
EDWARD C. STREETER, M.D., Boston, *Chairman*
WALTER P. BOWERS, M.D., Clinton
HOMER GAGE, M.D., Worcester
JOEL E. GOLDTHWAIT, M.D., Boston
LYMAN A. JONES, M.D., Swampscott
ROBERT B. OSGOOD, M.D., Boston
HUGH WILLIAMS, M.D., Boston
ALFRED WORCESTER, M.D., Waltham

SUBSCRIPTION TERMS: $5.00 *per year, in advance, postage paid, for the United States.* $6.56 *per year for all foreign countries belonging to the Postal Union.*

An editor will be in the editorial office daily, except Sunday, from twelve to one p.m.

Papers for publication, and all other communications for the Editorial Department, should be addressed to the Editor. 126

Commissioner, has issued a statement saying that the first thing now, as always, is to take every precaution to keep in good physical condition. At the first signs of approach of a common cold, or the grippe, isolation should be resorted to and remedies that have been found effective in previous cases applied. Avoidance of crowded cars, elevators, or buildings, and of common drinking cups and towels, is recommended.

There have been many cases and several deaths among nurses at both the Boston City and Massachusetts General Hospitals.

Since August 28, there have been sixty cases of pneumonia following grippe among sailors at Commonwealth Pier. There are comparatively few cases of the disease at the Harvard Radio School, which accommodates approximately 5000 men. Captain John M. Edgar, medical director for this Naval District, has announced that there have been 1109 cases reported in the district since August 28.

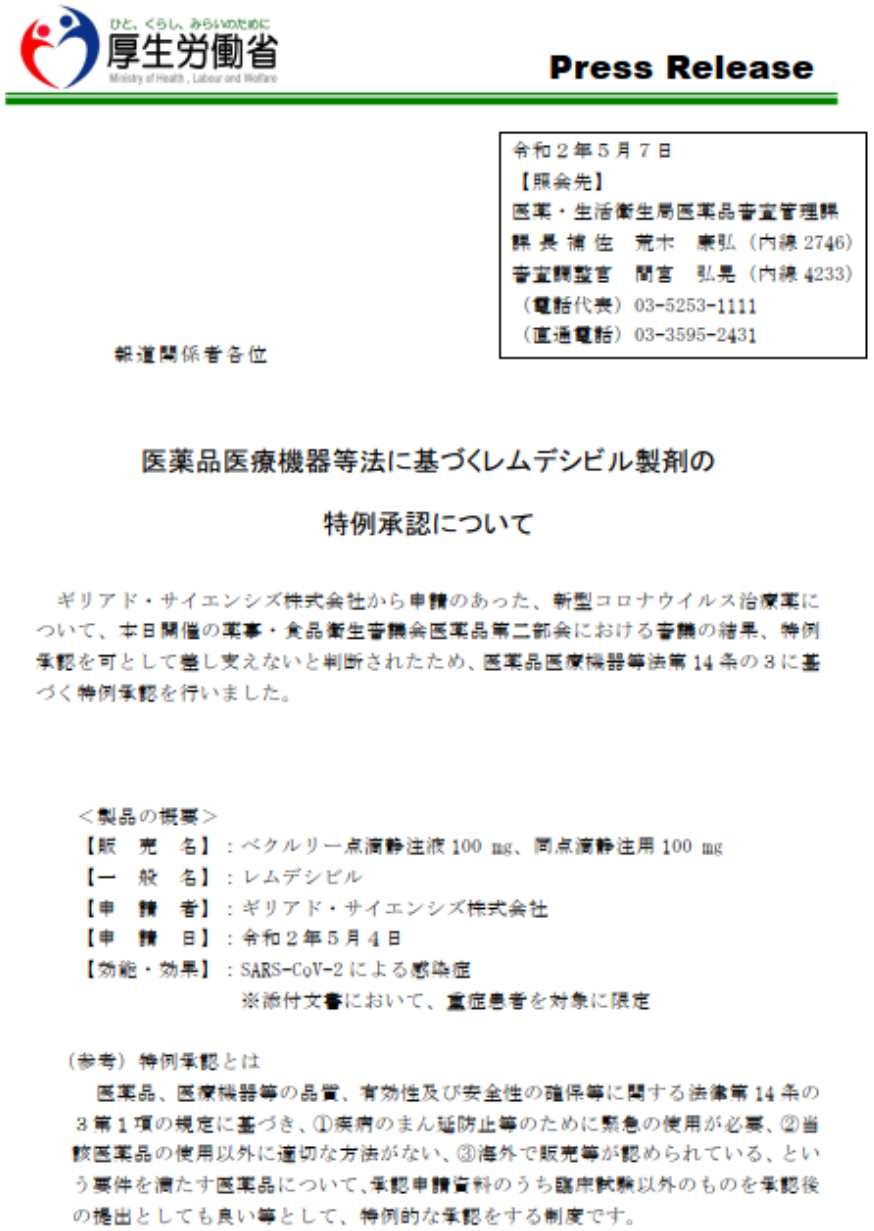
EPIDEMIC INFLUENZA.*

(SPANISH INFLUENZA.)

AN acute infectious disease (epidemic influenza) has prevailed in Europe this year similar in many respects to the diesease which prevailed in pandemic form in the winter of 1889-90. It seems probable that in 1918, as in 1889-90, the earliest appearance was in eastern Europe. By April cases were occurring on the western front. In Spain, according to reports, 30 per cent. of the population were attacked in May. The 1889 epidemic, starting in northern Europe, also fell heavily on Spain; the present ruler, then 3 years old, being one of the first attacked in Madrid. The King of Spain is

It is estimated that 500 million people have been infected worldwide and at least 17 million have died.

In Japan, about 24 million people are infected and about 390,000 die (case fatality rate 1.63%).



厚生労働省
Ministry of Health, Labour and Welfare

Press Release

令和２年５月７日
【照会先】
医薬・生活衛生局医薬品審査管理課
課長補佐　荒木　康弘（内線 2746）
審査調整官　関宮　弘晃（内線 4233）
（電話代表）03-5253-1111
（直通電話）03-3595-2431

報道関係者各位

医薬品医療機器等法に基づくレムデシビル製剤の

特例承認について

ギリアド・サイエンシズ株式会社から申請のあった、新型コロナウイルス治療薬について、本日開催の薬事・食品衛生審議会医薬品第二部会における審議の結果、特例承認を可として差し支えないと判断されたため、医薬品医療機器等法第 14 条の３に基づく特例承認を行いました。

＜製品の概要＞
【販　売　名】：ベクルリー点滴静注液 100 mg、同点滴静注用 100 mg
【一　般　名】：レムデシビル
【申　請　者】：ギリアド・サイエンシズ株式会社
【申　請　日】：令和２年５月４日
【効能・効果】：SARS-CoV-2 による感染症
※添付文書において、重症患者を対象に限定

（参考）特例承認とは
医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律第 14 条の３第１項の規定に基づき、①疾病のまん延防止等のために緊急の使用が必要、②当該医薬品の使用以外に適切な方法がない、③海外で販売等が認められている、という要件を満たす医薬品について、承認申請資料のうち臨床試験以外のものを承認後の提出としても良い等として、特例的な承認をする制度です。

Global drug development has begun to accelerate

- Special approval based on the Pharmaceuticals and Medical Devices Act
- **Application May 4, 2020**
- **Approval May 7, 2020**

- **May 1, 2020**, the United States FDA gave the Emergency Use Authorization

Ideas that support the entire prevention, diagnosis, and treatment system for Covid-19 infectious diseases are important

- Government support
  (https://www.mhlw.go.jp/stf/covid-19/seifunotorikumi.html#h2_6)
- Collaboration between academic societies and the medical community
  - Japan Medical Association covid-19 Expert Meeting
    (https://www.covid19-jma-medical-expert-meeting.jp/)
- The pharmaceutical industry's efforts
  (http://www.jpma.or.jp/coronavirus/)

Research and development on the new coronavirus infection (COVID-19) supported by AMED (https://www.amed.go.jp/news/topics/covid-19.html)

As of March 2, 2021(Japanese version)

*English version is as of August 11, 2020

(https://www.amed.go.jp/en/news/topics/covid-19.html)

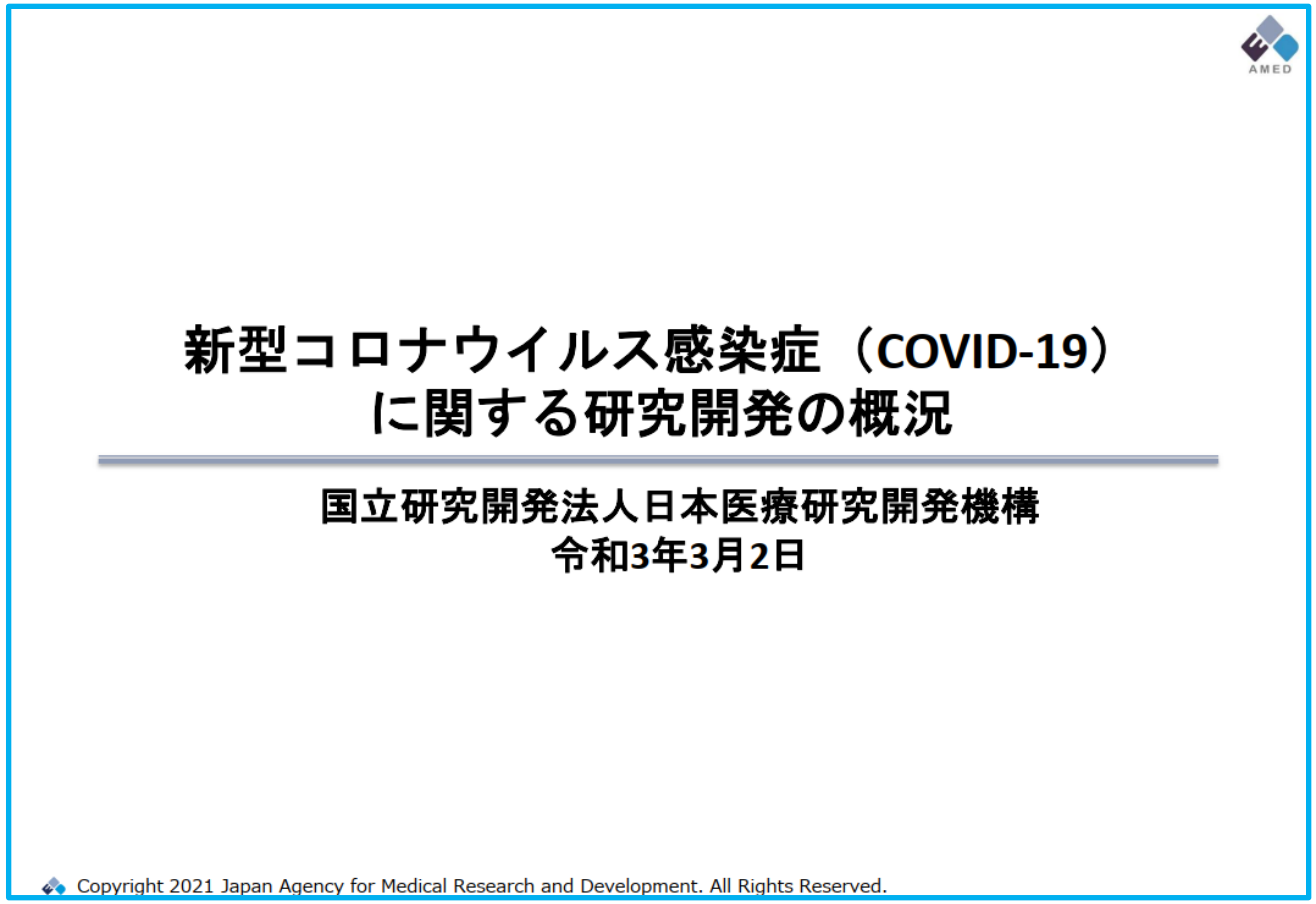
AMED expenses 138.6 billion yen out of the government budget of 193 billion yen

Treatment development: 9.88 billion yen

Vaccine development: 60.25 billion yen

Diagnostic method development: 240 million yen

Medical device / system development: 14.21 billion yen



The latest information on diagnostics, therapeutic drugs and medical devices on MHLW's HP

(https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/covid-19tiryouyaku_vaccine.html)

- Therapeutic agents for new coronavirus infections and their candidates **(As of May 26, 2021)**
  - **https://www.mhlw.go.jp/content/10900000/000784429.pdf**
  - already been approved for use ➡ 4 products
  - Under development or evaluation ➡12 products
- Approval / certification status of medical devices for new coronavirus infections or related symptoms **(As of May 28, 2021)**
  - **https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/000011639.html**
  - already been approved for use ➡ 32 products
- Approval information for in-vitro diagnostic drugs (test kits) for new coronavirus infections **(As of May 26, 2021)**
  - **https://www.mhlw.go.jp/stf/newpage_11331.html**
  - For PCR testing ➡ 30 products , For antigen testing ➡ 23 products

Therapeutic agents for new coronavirus infections and their candidates ①　May 26, 2021 Edition

1. Approved for use as a treatment for new coronavirus infections

1-1. Veklury (Remdesivir), Gilead Sciences

- RNA polymerase inhibitor and developed as a therapeutic agent for Ebola hemorrhagic fever.
- Special approval granted on 7 May 2020.

Special Approval on 7 May 2020

  - Administration should be performed for patients with SARS-CoV-2 pneumonia based on the main administration experience in clinical trials, etc.
  - The median time to recovery of patients receiving remdesivir was 10 days, which was significantly shorter than 15 days of placebo group from final result of the Japan-US international clinical trial (for moderate to severe cases).
  - EU: Conditional approval on July 3, 2020; US: Approved on October 22 2020.

1-2. . Decadron (Dexamethasone), Nichi-Iko and others

- Steroid, approved for severe infections and interstitial pneumonia.
- It was listed as a standard treatment method (medicine approved in Japan) in the “Guide for the Treatment of Coronavirus Infectious Diseases, Ver. 2.2".
  - Reduced the mortality rate for patients with covid-19 who needed ventilator and those who otherwise needed oxygen in a large-scale clinical study in the UK.

1-3. Heparin

- In patients with COVID-19, there is a risk of blood clots due to cytokine storms and vascular endothelias disorders. Autopsy cases have proven obstruction of alveoli capillaries. (Originally, in severe infections and respiratory failure, moderate risk factors for deep vein thrombosis.)
- The "New Coronavirus Infection Medical Care Guidelines" stated that it is recommended to perform anticoagulant therapy with heparin (including low molecular weight heparin) when there is a risk of blood clots (if the D-dimer exceeds the NUL).

1-4. Olumiant (Baricitinib), Eli Lilly

- Janus Kinase (JAK) inhibitor, approved for rheumatoid arthritis and other indications in Japan.
- Approved for concomitant use with Remdesivir on April 23, 2021.
  - Administered in hospital to patients requiring oxygen inhalation, artificial respiration management, or introduction of ECMO.
  - The median time to recovery was 7 days in the Baricitinib group and significantly shorter than 8 days in the placebo group in international joint clinical trials including Japan (moderate to severe subjects) (HR [95% CI]: 1.15 [1.00 to 1.31]).

Therapeutic agents for new coronavirus infections and their candidates ②　May 26, 2021 Edition

2. Approval application submitted

2-1. Avigan (Favipiravir), FUJIFILM Toyama Chemical

Application submitted on 16 Oct 2020

- RNA polymerase inhibitor, approved for new or re-emerging influenza in Japan.
- No Avigan in Japan market due to its teratogenicity and the JP government stocks.
- FUJIFILM Toyama Chemical submitted a partial change approval application for manufacturing and marketing approval on October 16 based on a clinical trial to mild and moderately patients, started from March 31, 2020. It is difficult to clearly judge the efficacy of this drug from the data obtained at present at the Pharmaceutical Affairs and Food Sanitation Council's Second Pharmaceutical Subcommittee on March 21, and the results of clinical trials currently underway, etc. After waiting for the early submission, it was decided to re-deliberate (continue deliberation). Currently, clinical trials are being conducted in Japan and overseas, and in Japan, a new clinical trial is being conducted in patients aged 50 years or older with early-onset COVID-19 patients with aggravation risk factors.
  - Observational studies have been conducted since February 22, 2020. In addition, specific clinical studies have been conducted with asymptomatic and mild patients (This started on March 2, 2020, ended on August 31st. No statistically significant difference was reached).

3. Clinical trial underway

3-1. Actemra (Tocilizumab (genetical recombination)), Chugai Pharm.

Clinical Trial started from 8 Apr 2020

- Molecular-targeted drug, approved for rheumatoid arthritis.
- A humanized anti-human IL-6 receptor monoclonal antibody that suppresses the action of IL-6, which is an inflammatory cytokine, and exhibits an anti-inflammatory effect. Cytokine storms have occurred as a hypothesis regarding the mechanism of severe pneumonia caused by coronavirus infection, which may lead to rapid aggravation, and are therefore being investigated as therapeutic agents.
- A company-led phase III study was conducted overseas in patients with severe pneumonia, but no statistically significant difference was observed with placebo in terms of improvement in clinical severity. In another phase III clinical trial, the proportion requiring mechanical ventilation was significantly reduced, but no significant improvement was observed in terms of mortality or the time to improvement of clinical symptoms.

3-2. Kevzara (Sarilumab (genetical recombination)), Sanofi

- A molecular-targeted drug, approved in Japan for rheumatoid arthritis.
- Company-led Phase II / III international clinical trials with severe patients did not show efficacy sufficiently.

Therapeutic agents for new coronavirus infections and their candidates ③　May 26, 2021 Edition

3. Clinical trial underway (continued)

3-3. Viracept (Nelfinavir), Japan Tabacco

Physician driven Clinical Trial started from 22 Jul 2020

- Protease inhibitor, approved for HIV infection (but no sales anymore)
- A basic study using cell lines conducted by the NIID suggested an antiviral effect on the new coronavirus.
- A physician driven clinical trial is being conducted mainly at Nagasaki Univ..

3-4. Stromectol (Ivermectin), MSD

- Approved in Japan for the treatment of intestinal fecal nematodes (a disease in which nematodes infect the intestines) and scabies (a disease in which a type of mite parasitizes the skin).
  - Overseas, it is used as a remedy for onchocerciasis (river blindness).

Physician driven Clinical Trial started from 16 Sep 2020

- Satoshi Omura received the Nobel Prize in Physiology or Medicine for the discovery of this drug (2015)
- In a basic study, an Australian group reported that it has a strong inhibitory effect on the growth of the new coronavirus.
- A physician-driven clinical trial is underway at Kitasato Univ. Hospital.

3-5. (Adrenomedullin) (ADM-L1-01)

Physician driven Clinical Trial started from 1 Sep 2020

- A bioactive peptide with a strong vasodilatory effect found in human pheochromocytoma tissue.
- Focusing on the fact that this drug is an essential factor that controls the health of blood vessels, it can be administered to patients with severe pneumonia due to coronavirus infection, in addition to its anti-inflammatory effect, to cause damage to blood vessels and lungs. The possibility of suppressing organ damage is being investigated.
- Miyazaki Univ. is conducting a physician-driven clinical trial.

3-6. Product name undecided (Sargramostim), Nobel pharma

Clinical Trial started from 30 Oct 2020

- A GM-CSF preparation developed as a therapeutic agent for autoimmune alveolar proteinosis.
- An interim analysis of a clinical trial of sargramostim inhalation currently being conducted in Belgium suggests that patients who inhale sargramostim have an improved alveolar-arterial oxygen partial pressure gradient compared to the standard treatment group.
- Nobel Pharma is conducting a clinical trial.

3. Clinical trial underway (continued)

3-7. Foipan (Camostat), Ono Pharm.

Clinical Trial started from 27 Oct 2020

- Protease inhibitor, approved for chronic pancreatitis.
- A German research group has set the first stage of infection with the new coronavirus, the outer membrane of the virus and the cell membrane of infected cells and was identified as a drug that could effectively block the viral invasion process by blocking fusion.
- Ono Pharm. is conducting a clinical trial.

4. Specific clinical research underway

4-1. Alvesco (Ciclesonide), Teijin Pharma

Specific Clinical Research started from 27 Mar 2020

- An inhaled steroid drug, approved for bronchial asthma.
- In addition to being expected to have anti-inflammatory effects as a steroid, antiviral activity against the new coronavirus has been confirmed in non-clinical studies.
- Kanagawa Prefectural Ashigarakami Hospital announced cases (3 cases) in which symptoms improved after administration to 3 patients with new coronavirus infection (March 2, 2020).
- National Center for Global Health and Medicine (NCGM) conducted a specific clinical study with asymptomatic to mild patients and preliminary report concluded that the pneumonia exacerbation was significantly higher in the ciclesonide inhalation group than in the symptomatic group. (December 23, 2020).

3-6. Futhan (Nafamostat), Nichi-Iko

Specific Clinical Research started from 1 May 2020

- Protease inhibitor, approved for acute pancreatitis.
- A research group at the University of Tokyo Identified as a potential drug which effectively blocks the virus invasion process in the first stage of infection with the new coronavirus.
- Conducting specific clinical research mainly at the University of Tokyo.
  - Observational studies were conducted from April 1, 2020 to March 31st, 2021.

5. Others

5-1. Kaletra (Lopinavir / Ritonavir), AbbVie

- Approved for HIV infection.
- It was also used clinically for SARS measures.
- It inhibits the activity of HIV protease and suppresses the production of infectious HIV.
- Structural analysis on a computer suggests a binding between the protease of the new coronavirus and the active ingredient of Kaletra.
- NEJM (International Medical Journal) reported that the mortality rate of the Kaletra-administered group was not significantly different from that of the placebo group.
    - * Observational studies were conducted from February 22, 2020 to March 31st, 2021.

5-2. (Product name undecided) (Plasma fractionation product), Takeda Pharm.

- An antibody specific to the new coronavirus is concentrated, collected from a patient who recovered from a new virus infection, and formulated.
- This study is being conducted mainly by the NCGM as an international joint clinical trial supported by NIH and reported that the primary that endpoint was not achieved.

新型コロナウイルス感染症治療薬の実用化のための支援事業の

採択事業における交付基準額の公表について

新型コロナウイルス感染症治療薬の実用化のための支援事業における採択事業について、交付基準額を公表します。

令和３年５月31日

厚生労働省健康局

新型コロナウイルス感染症治療薬の実用化のための支援事業の

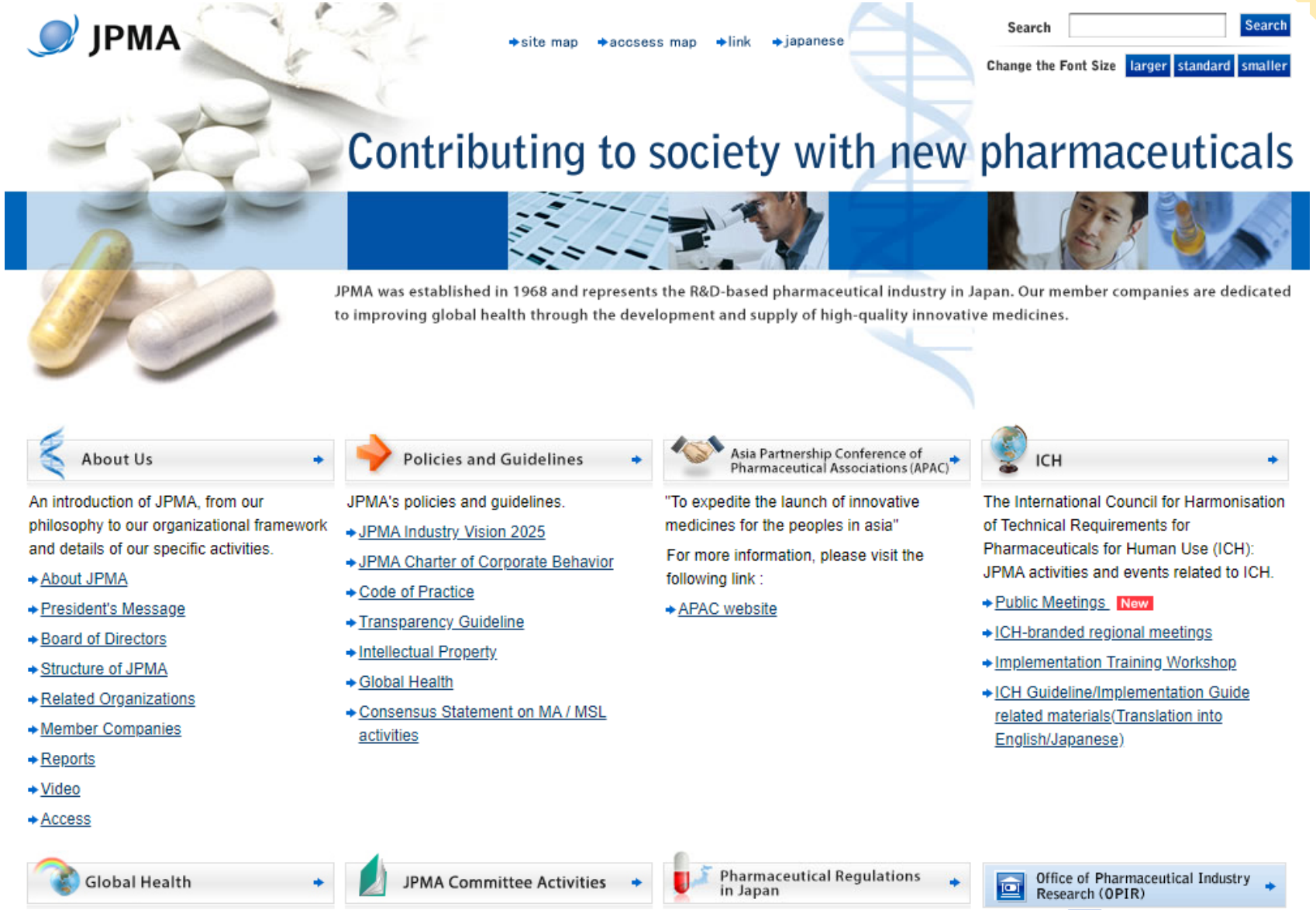
採択事業における交付基準額について

採択事業者名	治験薬名	交付基準額
小野薬品工業株式会社	カモスタット	600,209,000円
グラクソ・スミスクライン株式会社	GSK3196165IV	188,454,000円
	GSK4182136（VIR-7831）	258,533,000円
中外製薬株式会社	REGN-COV2	321,618,000円
	AT-527	458,129,000円
ファイザー株式会社	PF-07321332	72,509,000円
	PF-07304814	99,289,000円

（五十音順）

The amount of support for the therapeutic drug development support project was announced on May 31, 2021.

Adopted companies	Investigational drug name	Issued standard amount of money
Ono Pharmaceutical Co., Ltd.	Camostat	600,209,000 yen
GlaxoSmithKline Co., Ltd.	GSK3196165IV	188,454,000 yen
	GSK4182136（VIR-7831）	258,533,000 yen
Chugai Pharmaceutical Co., Ltd.	REGN-COV2	321,618,000 yen
	AT-527	458,129,000 yen
Pfizer Japan Inc.	PF-07321332	72,509,000 yen
	PF-07304814	99,289,000 yen



http://www.jpma.or.jp/english/

Providing development information on vaccines and therapeutic agents of pharmaceutical companies

新型コロナウイルス感染症に対する製薬協の取り組みについて

今般、国内外で新型コロナウイルス感染症に罹患され、亡くなられた方々に対し衷心よりお悔やみ申し上げますとともに、罹患され闘病中の皆様にも謹んでお見舞い申し上げます。
また、感染症対策や治療の最前線で尽力されているすべての医療関係者の皆様に心より感謝申し上げます。

日本製薬工業協会は、新型コロナウイルス感染症が世界規模で蔓延している中、有効で安全な治療薬およびワクチンの迅速な研究開発を進めることが収束に向かう重要な手段であると認識し、会員各社はこれにコミットし鋭意努力を続けております。
具体的な取り組みの方向性としては、既存薬の転用（ドラッグ・リポジショニング）、ワクチンの創出、新規治療薬の創出等が挙げられます。いずれの取り組みにおいても、その有効性と安全性を適切に評価することが必要であり、これらを迅速に進めるべく各社最善の努力を行っております。業界団体としては、それらの取り組みをより一層加速すべく、産学官の連携を働きかけていくなど取り組んでまいります。

この度、会員各社のこうした取り組みについて、特設サイト「新型コロナウイルス感染症対策への取り組みについて」を開設し、情報を提供させていただくこととといたしました。詳細につきましては、本サイトをご覧いただきますようお願いいたします。

以上

日本製薬工業協会
会長 岡田安史

※なお、各社の取り組みの最新情報等詳細については、各社にお問合せください。

随時更新中	随時更新中
製薬協加盟各社による、治療薬・ワクチンの研究開発の取り組みについて	製薬協加盟各社による、その他の取り組みについて

製薬協HPより　http://www.jpma.or.jp/coronavirus/

Follow-up after starting use is important

- Accelerated examination and approval are indispensable in public health emergencies, but follow-up of effectiveness and safety after approval is important.
  - Implementation of confirmatory clinical trial (validity verification)
  - Utilization of side effect reporting system and patient registry (safety verification)