Benefits and challenges:

How regulators can reduce time and efforts in the case of public health emergencies?

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Outline of presentation

- Challenges that regulators are facing
- Korea’s experience
- Vaccine evaluation in public health emergencies
- Way forward

Challenges that regulators are facing

- When a public health emergency of infectious disease is declared, the timelines for developing, evaluating and approving a candidate vaccine against the pathogen causing the epidemic are critical.
- Direct impact on the vaccine availability/deployment programme thus big impact on effective control of the epidemic/emergency.
- All processes need to be accelerated as much as possible.

  - regulatory process need to be in place to enable rapid evaluation of submissions as well as to allow, following careful benefit risk assessment, the use of vaccines for which a full regulatory package may not yet be available

  - need to fast track necessary regulatory procedures to make much needed vaccines available in a reasonable time whilst still maintaining Q, S, and E.

- How can an appropriate degree of regulatory oversight be provided to ensure the quality, safety and efficacy of a new vaccine in a timely manner in the face of an epidemic or pandemic?
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Ivana Knezevic MFDS symposium, 2016

Korea’s experience

- Outbreaks of new infectious diseases in Korea
- Regulatory pathways in public health emergency
- Preparedness of medicinal products against new infectious diseases

Outbreaks of new infectious diseases in Korea

- Global outbreaks of new infectious diseases caused by ebola virus, novel influenza virus, MERS-CoV, and zika virus, etc.
- Increased need for vaccines, and medicinal products to diagnose or treat such life-threatening diseases
- Novel influenza virus infection (2009-2010) and MERS cases reported (2015) in Korea

Novel influenza infection (2009-2010)

- Novel influenza (A/H1N1) in Korea
  - Anti viral drug (Peramivirs®) : permitted for emergency use
  - Vaccine(Greenflu-S) : consultation (whole development process) and accelerated review, approval, and lot release.
    - Acceptance of clinical trial protocol : August 20, 2009
    - Approval : October 21, 2009
    - Initiation of vaccination : October 27, 2009
- Thanks to WHO for giving us the information (Ag content, test method, etc.)

MERS-CoV outbreak in Korea, 2015

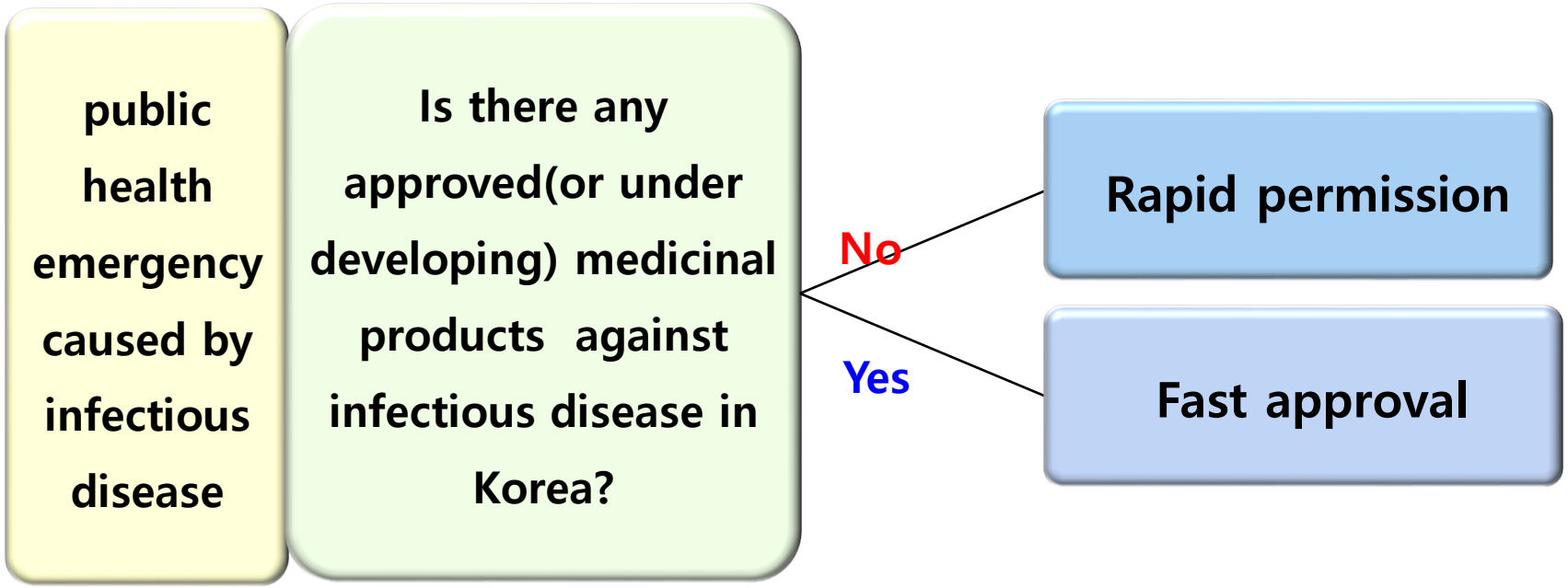
- May 20, 2015 ~December 23, 2015 (217 days)
- Patients 186, death 38, quarantine 16,693
- Anti-viral agent, ECMO(Extra Corporeal Membrane Oxygenation), plasma treatment

- No vaccine!!!

Regulatory pathways in public health emergency

1. Rapid permission system
2. Fast review & approval system

Strategies to access medicinal products for emergency use



1. Rapid permission

Legal Basis for Rapid Permission of Drugs for Emergency Use

Article 42 (Import approval of medicinal products)

② The minister of national defense or importers may import a pharmaceutical, etc. falling under any one of the following subparagraphs without having to receive item authorization or report in item

1. **The minister of national defense intends to import pharmaceuticals, etc, not manufactured in Korea** to be used urgently for military purposes after **consulting with minister of MFDS** regarding the item and quantity.

「Pharmaceutical Affairs Act」(March 30, 2011)

Article 85-2 (Special cases for medicinal products for disease prevention and treatment purpose)

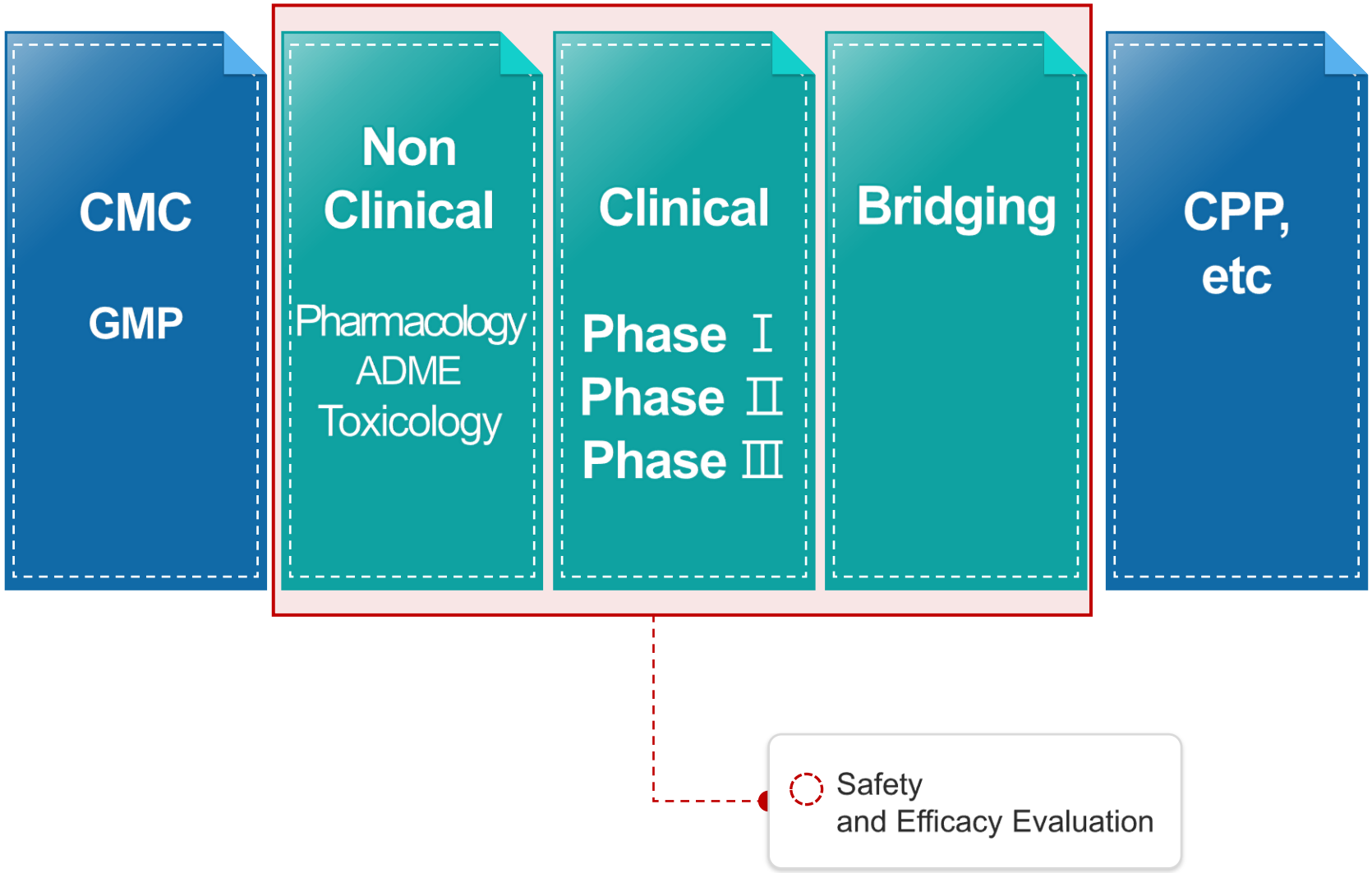
① The Minister of MFDS can take one of the following measures in order to appropriately respond to infectious disease pandemics.

1. permit drug **manufacturers to manufacture unapproved and/or unregistered drugs**.
2. permit **importers to import unapproved and/or unregistered drugs**
3. permit manufacturing or import of drugs, with **newly determined administration method, dose, efficacy, effectiveness, and duration of drug use differing from those approved and/or registered in Korea**.

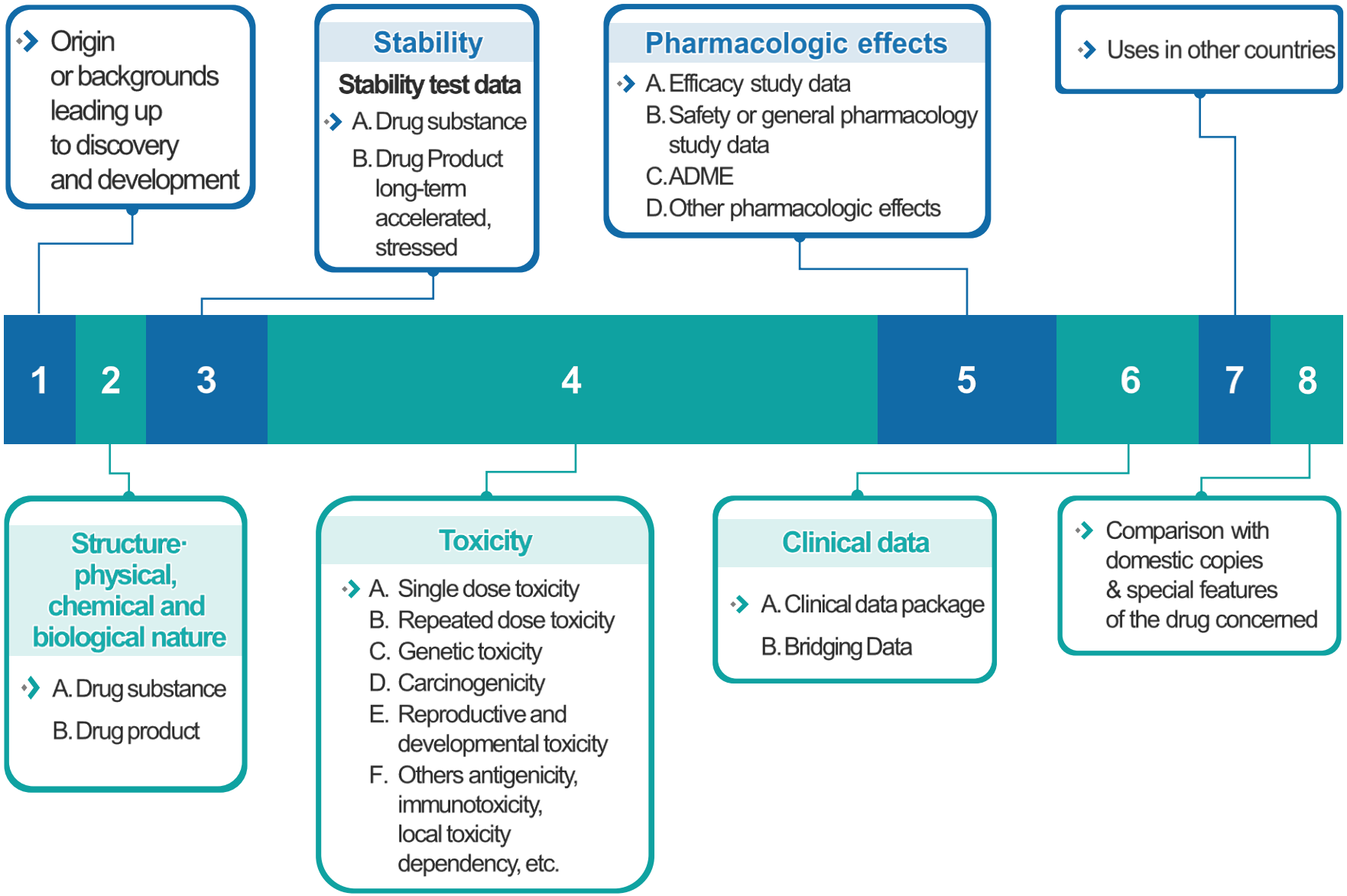
「Pharmaceutical Affairs Act」(Jan. 28, 2015)

2. Fast review & approval

Data Requirements for NDA



Dossier for Safety & Efficacy Evaluation



Regulations on Product Eligibility for Fast Review & Approval

Article 41 (**Fast Review Process**) MFDS may apply the fast review process. to

1. Medicinal products that may have **therapeutic effects against AIDS, cancers, or other life-threatening or serious diseases**.
2. Medicinal products of which fast introduction is deemed necessary because **treatment is not possible with existing therapies** (due to development of resistance or other reasons).
3. Medicinal products that may have **preventive or therapeutic effects against bioterror diseases and other pandemic infections**.
4. **Orphan Drugs**

「Regulation on Review and Authorization of Biological Products」(2008)

Detailed operation procedure including timeline for product designation and types of data required for review

MaPP for fast review and approval of vaccines against pandemic infections (published in Dec. 2016)

Animal rule?

- Article 24 (exemption of some part of data)
- Some data can be exempted, when those experiments are not possible to perform in theoretically and technically
- 1-4 Minister of MFDS think that this can not be possible to perform the test
- **「Regulation on Review and Authorization of Biological Products」**

Preparedness of medicinal products against New infectious diseases

1. National Research Strategies
2. Support Commercialization

National Research Strategies for Infectious Disease Crisis

- Background
  - Upward tendency of infectious disease events recently
  - Increasing public health costs as well as social costs due to infectious diseases
- Government-wide R&D support plan
  - 1st stage: 2012 – 2016
  - 2nd stage: 2017 -2021
- Goal
  - Maximizing effects of national R&D investment to infectious disease
  - Harmonizing R&D of each Ministry so that meet the need of the nation-wide disease prevention policy

National Research Strategies for Infectious Disease

▪ **Key Point**

Response Technologies for Emerging·New Strains from Overseas	Enhancing Response Capabilities to be conquered	National Safety Net against Infectious Diseases
• New and unidentified infectious diseases • Climate change-caused infectious diseases • Communicable diseases humans and animals • Influenza	• Multidrug-resistant bacteria • Tuberculosis • Chronic infectious diseases	• Preparation and control against disastrous infections • Preventable diseases & vaccines • Bioterrorism

Support for Commercialization of Domestic Vaccines (2010~)

- **Customized** One-stop consultation served to domestic companies
- To **raise domestic vaccine self sufficiency rate** & **support for NID vaccines development**

▪ **Outcome** of Support (2010~2015) ; 7 products approved

'10 ~ '13	'14 ~ '15	'16	'17
▪ LG('10) Hib vaccine ▪ Ilyang ('13) Influenza vaccine	▪ SK ('14) Cell-cultured Influenza vaccine ▪ Eubiologics('15); Cholera vaccine ▪ GreenCross & SK('15) 4-valent Influenza vaccine(15) ▪ GreenCross('15), Pre-pandemic influenza vaccine (H5N1)	Consulting on ▪ development of Zika vaccine(16.5) ▪ clinical study of MERS vaccine(16.6)	▪ IND(Phase I) MERS vaccine('17.8)

Vaccine evaluation in public health emergencies WHO

- Vaccine evaluation in public health emergencies –review of regulatory pathways in selected countries (draft 2015)
  -Some countries have well established, flexible and rapid regulatory pathways and some do not

- ICDRA 2016 identified a series of gaps in global and national regulatory preparedness for public health emergencies

- WHO informal consultation on regulatory preparedness to address public health emergencies, May, 2017

Key issues raised/comments received from consultations in 2015 (WHO)

- The difficulty of making decisions in emergency situations was well recognized, especially in developing countries where NRAs have limited resources and capacity
- Some countries have well-established, flexible and rapid regulatory pathways or mechanisms dealing with 'public health emergencies", while some do not have such in place
- Information of existing regulatory pathways/approaches especially from well-established NRAs might serve as examples for jurisdictions, for those that do not have appropriate procedures in place, to accelerate product development and licensure in response to a public health emergency.
- International collaboration and cooperation are important: collaborative approaches should be encouraged, with support from WHO and/or well-resourced NRAs, to support less-resourced NRAs.

Ivana Knezevic MFDS symposium, 2016

ICDRA meeting, South Africa. December 2016

- Many NRAs are weak and lack capacity and resources. Candidate products developed during a emergency may be cutting edge and are a challenge for even in the best-resourced NRAs to evaluate. Strengthening regulatory collaboration between countries and regions and capacity building
- Limited capacity and experience of communicating with stakeholders
- Stakeholders who are developing products do not always engage regulators early and often enough.

Regulatory preparedness key to addressing public health emergencies

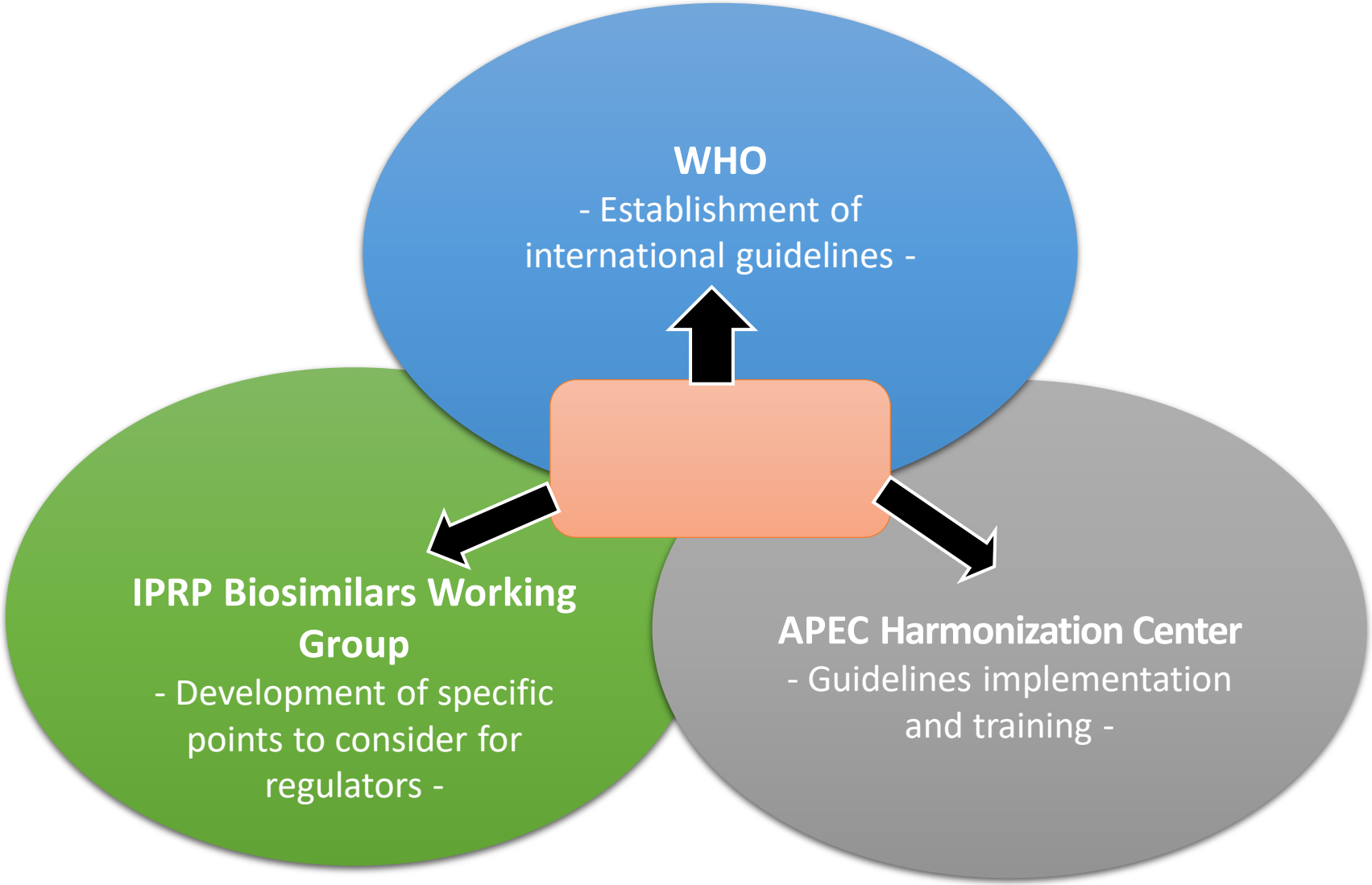
WHO informal consultation in Geneva 17-19 May, 2018

- Institute a pre-EUAL submission process : new physical standards, guidelines, companion diagnostics, etc.
- Information sharing with relevant NRAs and ethics committees/board
- Map/landscape the current emergency provisions(regulatory and legislative) in LMICs
- Develop a clear set of expected minimum competencies that NRAs and ethics committees/boards
- Develop guidance for the use of unlicensed medical products during a public health emergency
- Explore the use of other regional platforms and the feasibility of adapting models like AVAREF to other geographic area
- Explore 'mock-up' practice for expedited review of candidate products
- Develop measurement(physical) and written standards that serve as a basis for regulatory evaluation, collaboration with CEPI

Way forward

- International collaboration and cooperation are important: : collaborative approaches should be encouraged with support from WHO and/or well-resourced NRAs, to support less-resourced NRAs
- HOW???
  - International collaboration and cooperation
    - Ex. Biosimilar (WHO- APEC- IPRF)
  - Information sharing : EUA process, update of vaccine deveopment
  - Mock-up review,
  - Joint review
  - Capacity building

Collaboration Scheme of WHO, IPRP BWG and AHC



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Thank you.

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Vaccine Self-Sufficiency Plan

Total 28 vaccines(NIP/19, Non-NIP/5, Pandemic & Bioterror/4)

NIP

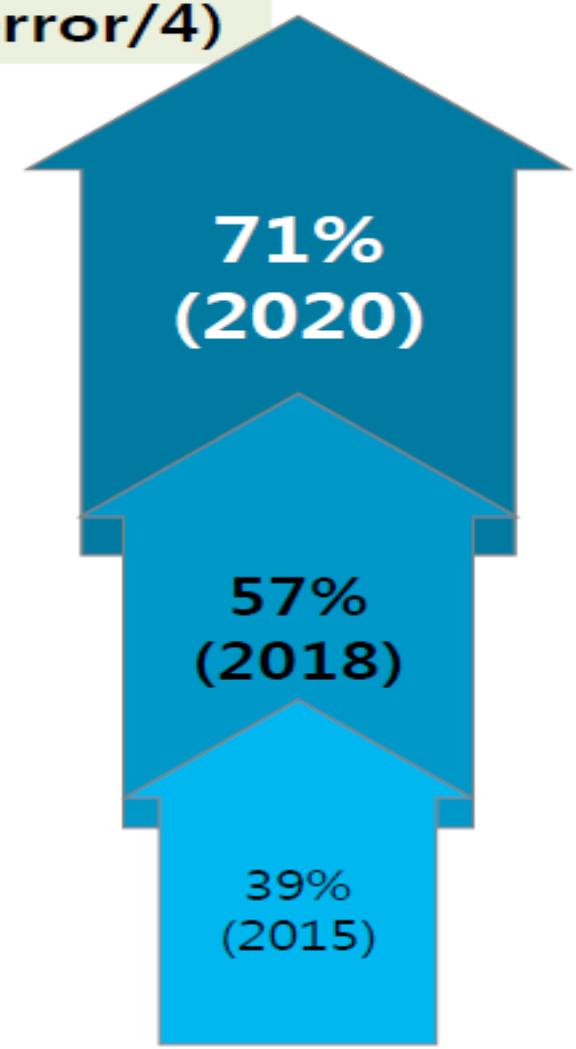
~2015 : HepB, JE(inactivated), HFRS, Varicella, Influenza, Typhoid, Hib
2016 : adult Td, Pneumonia(PCV)
2019 : IPV, adult Tdap
2020 : BCG(intradermal), IPV, adult Tdap, HPV

Non-NIP

2015: Cholera
2017: Zoster
2019: Rotavirus

Against pandemic, bioterror

2015: Smallpox, Cell culture influenza, Avian Influenza
2020: Anthrax



Output of collaboration

1. Publication and use of **PASIB** (Public Assessment of Summary Information of Biosimilars)

   - Development of a template with IPRP BWG for Member States to share information on the scientific basis for licensing biosimilars

   - Suggestion of **using PASIB as a template for joint review of ZaZiBoNa(Africa NRA)** in WHO implementation workshop, Ghana, Sept. 2015

2. Publication and use of **training manual for regulatory reviewers**

   [Subject : Analytical comparability of biosimilar monoclonal antibody]

3. Publication and use of **scientific reflection paper on extrapolation of biosimilars indications**