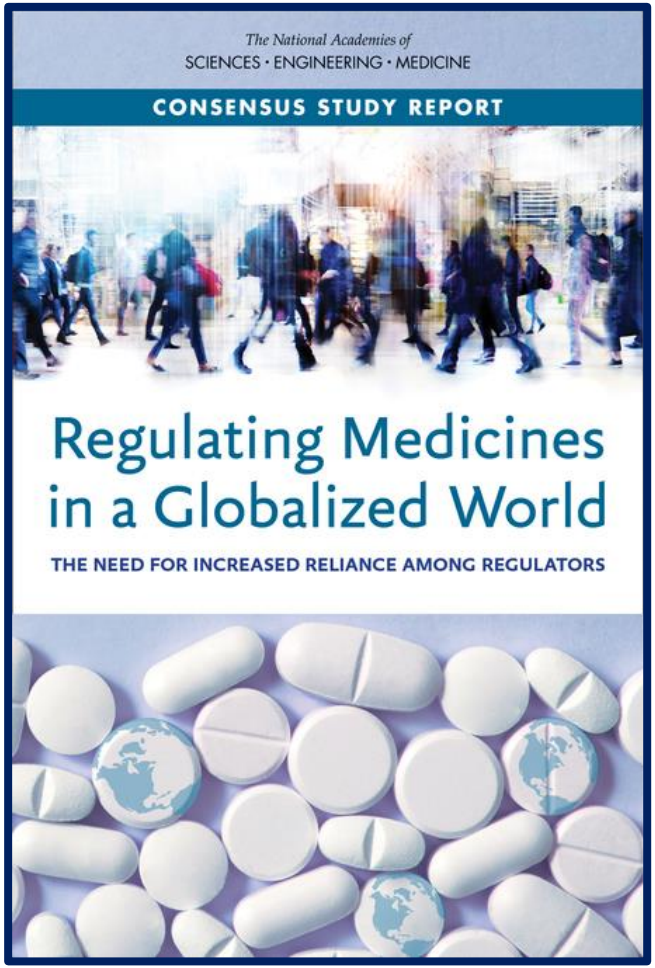


Welcome to the webinar on

Regulatory Reliance – If not now, when? What are the current barriers?

Friday, September 4th 10:30 am – 12:00 pm ET

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Regulatory Reliance – If not now, when? What are the current barriers?

Welcome and Background

Alastair JJ Wood, MB, ChB, FRCP, FACP (NAM)

Former Study Chair and Webinar Facilitator
Emeritus Professor,
Vanderbilt University Medical School

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Regulating Medicines in a Globalized World: The Need for Increased Reliance among Regulators

NASEM, 2020. Retrieved from https://doi.org/10.17226/25594

Study Context (PreCovid) But Prescient!!

- Globalization - people, disease and medicines cross borders
- Global pharmaceutical supply chains
  - Including settings with weaker oversight
- Increasing complexity of medicines
- Patients and consumers demanding similar access to medicines globally

https://doi.org/10.17226/25594

Context Changed PostCovid

- Report published in late 2019
- COVID-19 spreading within two months
- Before COVID topic might appear esoteric
- After COVID clear that mutual reliance among regulators is essential and urgent
  - Ineffective “approved” PPE
  - Invalid “approved” diagnostic tests
  - Untested/unapproved therapies used

https://doi.org/10.17226/25594

Two Types of Reliance Recognized in Report

- Horizontal/bidirectional reliance where similarly resourced regulators rely on one another
- Unidirectional reliance where a less resourced regulator relies on a well-resourced regulator for its reviews
  - Without giving up sovereignty

https://doi.org/10.17226/25594

Mutual Recognition Post COVID

- Redundant reviews an unaffordable luxury
- We are all exposed to global health risks
- For some novel therapeutics e.g. RNA vaccines regulatory experience is limited even in well resourced regulators and reliance will be essential
- Lessons from the repetitive PPE problems

https://doi.org/10.17226/25594

Goals for Today

- Recognize the advantages of reliance
  - For well resourced regulators
  - For less resourced regulators
- Identify the barriers to implementation
  - And determine how to remove them
- Define how we move forward for the good of global public health
  - Timeline driven by need to rapidly review new therapeutics for global health

https://doi.org/10.17226/25594

Regulatory Reliance –
If not now, when? What are the current barriers?

Session 1

Murray Lumpkin, MD, MS

Session 1 Moderator
Deputy Director,
Integrated Development and
Lead for Global Regulatory Systems Initiatives
Bill and Melinda Gates Foundation

Session 1:

What do you see as current barriers to greater use of reliance-based regulatory pathways and how might they be overcome?

Use the Q&A to ask questions

Moderator: Murray Lumpkin

- Guido Rasi, Chair of ICMRA & current Executive Director, EMA
- Emer Cooke, Director, Regulation of Medicines and other Health Technologies, WHO; & imminent Executive Director, EMA
- Janis Bernat, Director of Biotherapeutics & Scientific Affairs, IFPMA
- Mikel Arriola, Fmr Federal Commissioner, COFEPRIS, Mexico
- Margaret Hamburg, Fmr Commissioner of Food and Drugs, US FDA

https://doi.org/10.17226/25594

REGULATORY RELIANCE

21ST CENTURY "BEST REGULATORY PRACTICE"

CAN BE . . .

- USED BY WELL-RESOURCED AND LESS-RESOURCED REGULATORY AGENCIES
  - HELPS MANAGE HUMAN AND FINANCIAL RESOURCES SO THAT AVAILABLE RESOURCES CAN BE USED FOR REGULATORY ACTIVITIES WITH THE HIGHEST PUBLIC HEALTH IMPACT – NOT ON PERFORMING WHAT IN ESSENCE WOULD BE REDUNDANT REGULATORY ACTIVITIES ALREADY PERFORMED BY A TRUSTED REFERENCE AGENCY
- USED TO INCREASE AN AGENCY'S "EXPERTISE CAPACITY"
  - THE AGENCY HAS THE EXPERTISE, BUT JUST NOT ENOUGH OF IT TO MEET A NEED AT A CERTAIN TIME
- USED TO INCREASE AN AGENCY'S "EXPERTISE CAPABILITIES"
  - THE AGENCY DOES NOT HAVE THE REQUISITE EXPERTISE, AND THIS IS A WAY TO BRIDGE THAT "GAP"

REGULATORY RELIANCE

WHO DEFINITION:

THE ACT WHEREBY THE NRA IN ONE JURISDICTION MAY TAKE INTO ACCOUNT AND GIVE SIGNIFICANT WEIGHT TO ASSESSMENTS (INCLUDING INSPECTIONS) PERFORMED BY ANOTHER NRA OR TRUSTED INSTITUTION, OR TO ANY OTHER AUTHORITATIVE INFORMATION IN REACHING ITS OWN DECISION. THE RELYING AUTHORITY REMAINS INDEPENDENT, RESPONSIBLE AND ACCOUNTABLE REGARDING THE DECISIONS TAKEN, EVEN WHEN IT RELIES ON THE DECISIONS AND INFORMATION OF OTHERS.

- IT IS NOT "OUTSOURCING" ONE'S REGULATORY DECISION-MAKING.
- CAN BE USED FOR REGULATORY ACTIVITIES THROUGHOUT THE LIFE-CYCLE OF A PRODUCT (E.G., CTA, MARKETING AUTHORIZATION, INSPECTIONS, PV, VARIATIONS)

REGULATORY RELIANCE

REQUIRES THE PRODUCT ASSESSED BY THE REFERENCE AGENCY TO BE THE "SAME" PRODUCT AS BEING PRESENTED TO THE RELYING AGENCY.

- SAME QUALITATIVE AND QUANTITATIVE COMPOSITION, SAME STRENGTH / PHARMACEUTICAL FORM; SAME INTENDED USE; SAME MANUFACTURING PROCESSES AND SITES; SAME APIS / SUPPLIERS

REQUIRES ACCESS TO THE NECESSARY DOCUMENTS (ASSESSMENT REPORTS, INSPECTIONS REPORTS) TO ALLOW THE RELYING AGENCY TO BE FULLY INFORMED ABOUT THE ASSESSMENT PERFORMED BY THE REFERENCE AGENCY

- REDACTION CAN BE A BARRIER
- PUBLIC REPORTS OFTEN NOT FULLY HELPFUL BECAUSE OF DATA NOT INCLUDED

RELIANCE-BASED REGULATORY PATHWAYS

WORK-SHARING (VARIOUS PRACTICES)

- SHARING ACTIVITIES TO ACCOMPLISH A SPECIFIC REGULATORY TASK

VERIFICATION

- SAME PRODUCT AS ASSESSED BY REFERENCE COUNTRY

VERIFICATION WITH COUNTRY SUITABILITY ASSESSMENT

- SAME PRODUCT AS ASSESSED BY REFERENCE COUNTRY
- APPROPRIATE LABELING FOR RELYING COUNTRY
- APPROPRIATE FOR RELYING COUNTRY'S HEALTH CARE SYSTEM
- APPROPRIATE FOR RELYING COUNTRY'S POPULATION (CAN EFFICACY/SAFETY BE EXTRAPOLATED)
- APPROPRIATE FOR TRANSPORT, STORAGE, DISTRIBUTION IN RELYING COUNTRY

RELIANCE-BASED REGULATORY PATHWAYS

ABRIDGED ASSESSMENTS

- THE ASSESSMENT BY THE RELYING AUTHORITY IS WIDELY OR SOLELY BASED ON THE INFORMATION IN THE REFERENCE AGENCY'S ASSESSMENT REPORTS AND INSPECTION REPORTS.
    - NORMALLY IT WOULD ALSO INVOLVE SOME DEGREE OF ADDITIONAL WORK BY THE RELYING NRA, ESPECIALLY WITH RESPECT TO THE FORMULATION OF A BENEFIT-TO-RISK PROFILE WITH RESPECT TO THE SITUATION IN THE RELYING COUNTRY.
- SAVES RESOURCES BY NOT PERFORMING REDUNDANT ACTIVITIES
- SAVED RESOURCES CAN BE USED FOR REGULATORY ACTIVITIES WITH HIGHER PUBLIC HEALTH IMPACTS IN THE RELYING COUNTRY AND THUS MAKE THE OVERALL REGULATORY PROCESS BOTH MORE EFFICIENT AND MORE EFFECTIVE.

RECOGNITION

MAY BE SEEN AS A SPECIAL AND MORE FORMALIZED APPROACH TO RELIANCE IN THE BROADEST SENSE OF THE WORD

- WHO DEFINITION

  THE ACCEPTANCE OF THE REGULATORY DECISION OF ANOTHER REGULATOR OR TRUSTED INSTITUTION. RECOGNITION SHOULD BE BASED ON EVIDENCE THAT THE REGULATORY REQUIREMENTS OF THE REFERENCE REGULATORY AUTHORITY ARE SUFFICIENT TO MEET THE REGULATORY REQUIREMENTS OF THE RELYING AUTHORITY. RECOGNITION MAY BE UNILATERAL OR MUTUAL AND MAY, IN THE LATTER CASE, BE THE SUBJECT OF A MUTUAL RECOGNITION AGREEMENT.

- RECOGNITION USUALLY REQUIRES FORMAL AND BINDING LEGAL PROVISIONS, AS OPPOSED TO THE RELIANCE-BASED REGULATORY PATHWAYS PREVIOUSLY OUTLINED

- THIS IS MUCH MORE OF AN "OUTSOURCING" OF ONE'S REGULATORY DECISION-MAKING

QUESTIONS TO PANEL

- WHY AREN'T THESE RELIANCE-BASED REGULATORY PATHWAYS USED MORE FREQUENTLY?
- WHAT CAN BE DONE TO INCREASE THEIR USE AND THUS MAKE FOR MORE EFFICIENT AND MORE EFFECTIVE USE OF LIMITED REGULATORY HUMAN AND FINANCIAL RESOURCES?
- DOES THE CURRENT PANDEMIC PRESENT OPPORTUNITIES FOR THE REGULATORY COMMUNITY TO USE THESE PATHWAYS IN PLACES AND WAYS PERHAPS NOT USED PREVIOUSLY?

Regulatory Reliance –
If not now, when? What are the current barriers?

Session 1

Guido Rasi, MD

Session 1 Presenter
Chair of ICMRA
Current Executive Director, EMA

Reliance at times of COVID-19

US National Academy of Sciences, Engineering and Medicines
4 September 2020

Presented by Prof Guido Rasi
EMA Executive Director

'Making use of assessment from other authority while retaining decision'

Reliance

- Trust
- Equivalence of capabilities
- Bilateral or unilateral?
- Transparency
- Exchange of un-redacted information (*except for personal data*)
- **Benefits: resource use and earlier PATIENT access**

COVID-19

- ***ICMRA collaboration***
- *Sharing of experience and processes*
- *Unilateral*
- *Regulatory Convergence*
- *Transparency in real time*
- *Publication of assessment reports and re-start of EMA Clinical Data Publication*

Barriers to Reliance?

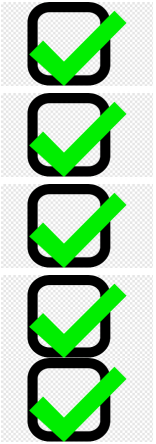
- *EU- US MRA implementation as an example*
- Willingness of parties or trust issues
- Legal framework (or alleged?)
- Different processes (convergence only, no need for 'harmonisation')
- So far, regulators and industry mostly concerned. Patients not engaged?

Additional barriers for COVID-19

- Political pressure
- National approaches

Reliance versus single authority

- Use of common tools (*compatible repositories rather than single*)
- Use of common (ICH) guidelines (*convergence by design*)
- Use of similar processes (*aligned for steps and requirements*)
- Sharing of unredacted reports and assessments
- Coordination by WHO



However, we need to retain **several independent assessments**
and possibility to learn from differences
(clear demonstrated added value of 2 rapporteurs in EU procedures)

Disclaimer

The presenter does not have any conflict of interests.

Further information

Contact me at guido.rasi@ema.europa.eu

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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Regulatory Reliance – If not now, when? What are the current barriers?

Session 1

Emer Cooke, MSc, MBA

Session 1 Presenter
Director, Regulation and Medicines and other Health Technologies
WHO
Imminent Executive Director
EMA

World Health Organization

Regulatory Reliance: if not now, when?

Emer Cooke Director, Regulation and Prequalification

04 September 2020

Reliance is not new

Reliance part of European pharmaceutical legislation since 1972

First Mutual Recognition Agreement on GMP signed 1998 (EU-Australia)

WHO uses reliance principles for Prequalification (PQ) where possible

Over 500 national authorizations based on Reliance on PQ since 2014 – Collaborative Registration Procedure

WHO first institution to publish guidance on “desktop inspections”

WHO’s National Control laboratory Network uses concepts of secure sharing of lot release testing and reliance

But Reliance is in the news..

NASEM report on Regulatory Reliance

WHO survey to IPRP* members – October 2018

Detailed responses originally from 17 regulators

Wealth of information and suggestions:

- Clear and consistent messages – reinforced by new inputs
- Some novel ideas and multiple examples
- Publication in press

WHO published draft Good Reliance Practices (GrelP) guideline August 2020 – deadline for comments 18th September

WHO promoting reliance concepts in context of COVID-19

What are the barriers – Imperfect Regulatory frameworks

- Since early 1960s, national regulations have been built as stand-alone systems
- But growing experience and realization that

  the future is about enabling cooperation
- “No regulator is an island”
- Challenge is how to build cooperation and reliance concepts into not just regulatory thinking, but economic and public health thinking

How does reliance fit within the regulatory framework?

What are the barriers - competencies, training and mindsets

Every distinct national regulatory requirement adds a cost and complexity to the global system

Consequences:

- Costs are passed onto the healthcare system and/or patient
- Global complexity direct relation with shortages
- For smaller markets in particular - additional requirements **hinder access and exacerbate shortages**

Reliance, work-sharing and cooperation can be a solution

But have we understood what competencies are needed to practice reliance? How do we change - especially in times of crisis?

What are the Barriers – transparency, trust, accountability and time

- Transparency vital in **building trust – also a key enabler**
  For example:
  - Unredacted reports shared with sponsor?
  - Information available on website?
  - Policy and procedures for sharing with other regulators?
  - Ability to interact with reference agencies?
- More emphasis needed on **understanding what *stands behind/supports regulatory outputs and decisions***, including good regulatory and review practices
- Reliance does not change accountability
- Too busy, too much national pressure to think globally?

Overcoming the barriers – making it happen

- Doesn’t happen by magic – requires framework and planning
- Advocacy and buy-in at the highest and lowest level
- Walking the Talk – someone has to go first
- Seizing the moment – use voluntary agreements and commitments
- Global success depends on strategic commitment and alignment – both top down and bottom up

Regulatory Reliance – If not now, when? What are the current barriers?

Session 1

Janis Bernat, MSc

Session 1 Presenter
Director of Biotherapetutics & Scientific Affairs
IFPMA

IFPMA

Regulatory Reliance

If Not Now, When?

What Are the Current Barriers?

Janis Bernat, IFPMA

September 4, 2020

Current Barriers

Key questions that need to be answered more fully:

what exactly is Regulatory Reliance

where does a national regulatory authority begin

to whom do you talk to

?

IFPMA

Potential Solutions

AWARENESS	ALIGNMENT	AGILITY
‘Sensitization’ on the topic of regulatory reliance	Implementation of WHO guidance on Good Reliance Practices	Context of Covid-19: ICMRA & WHO good vehicles for broader exchange and conversations

“Collaboration and dialogue between all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance.”

Considerations for effective regulatory reliance – an Industry perspective
IFPMA, 2019


IFPMA
Position Paper

IFPMA

Thank You

j.bernat@fpma.org
www.ifpma.org

Regulatory Reliance – If not now, when? What are the current barriers?

Session 1

Mikel Arriola, ML, MPP

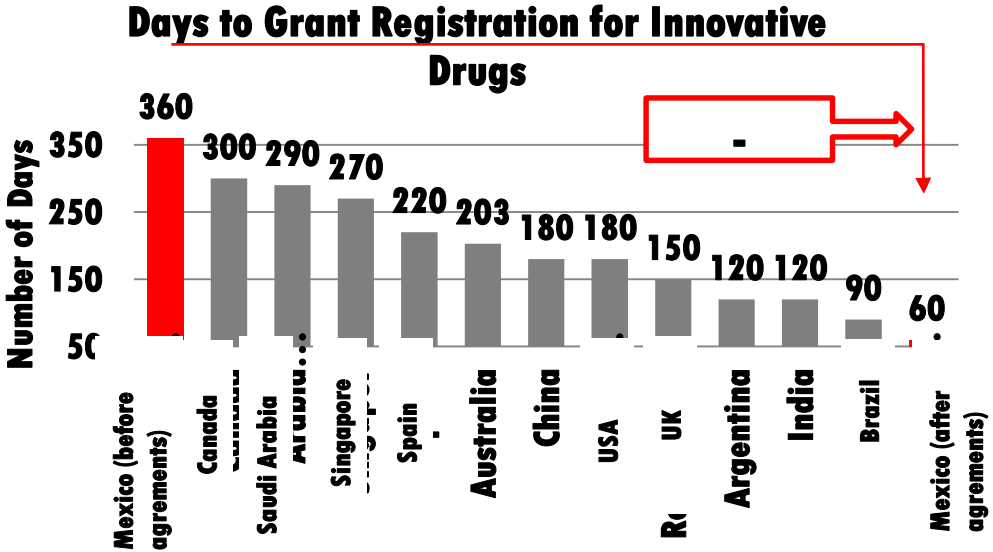
Session 1 Presenter
Former Federal Commissioner,
COFEPRIS, Mexico

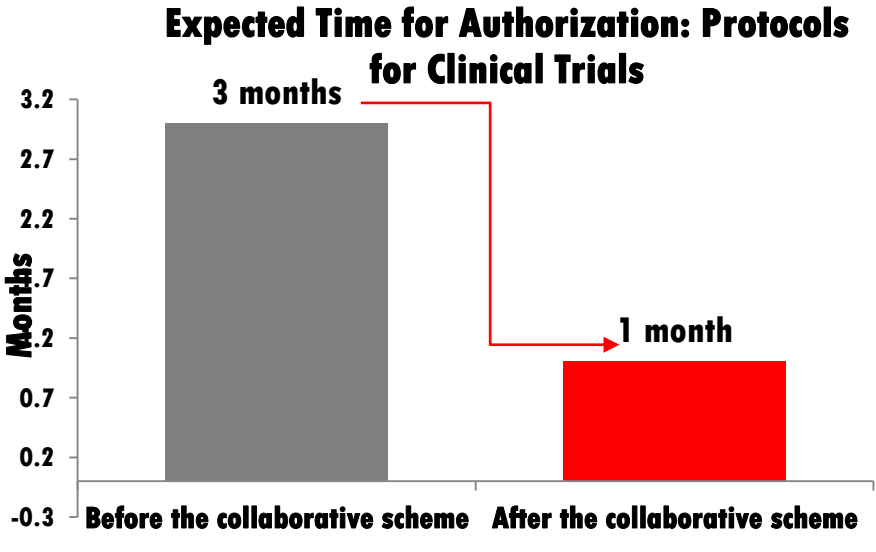
Innovation Policy Agreement Innovation Promotion

In 2011 Mexico adopted an innovation policy relying on Equivalence Agreements among different health agencies to expedite the entry of new drugs to the country. As a result, from 2012 to 2018, COFEPRIS issued 336 new marketing authorizations for innovative medicines. This represents an increase of 11,100% in medicine supplies with respect to the 3 registrations issued in 2010.

Pre-Approval of Clinical Trials Protocols

Worldwide R+D expenditures from the leading pharmaceutical companies is over 80 billion USD, and Mexico's indicator is close to only 262 million USD given long clinical trial approval times, Mexico was losing competitiveness. After new policies were implemented, approval length for clinical trials protocols was reduced by 66%, from 3 to 1 month. This efficiencies in time frames were on result of relying on international best practices.

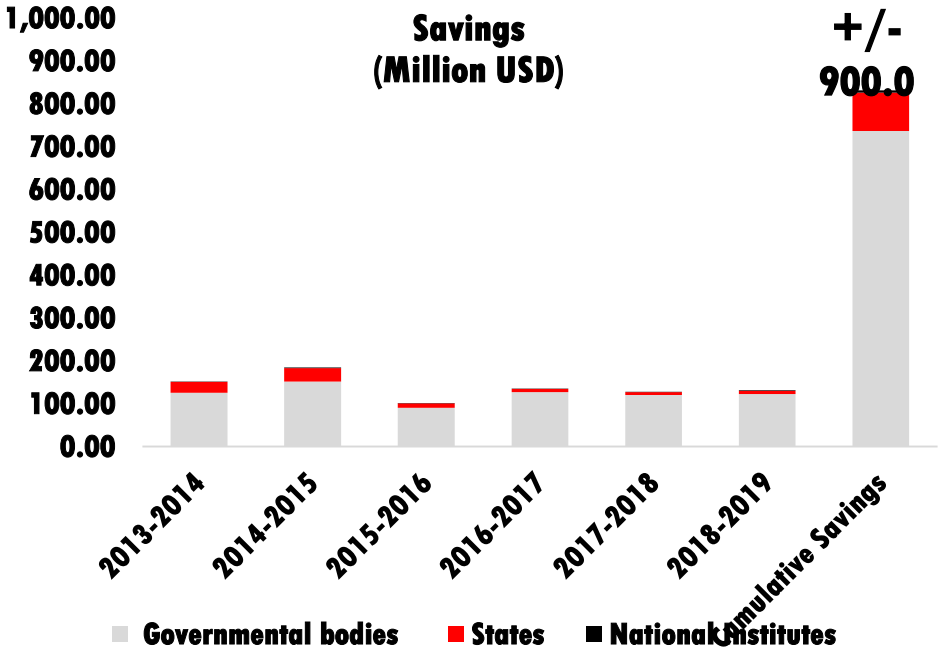




Benefits of Supporting Innovation

This policy increased the supply of medicines and the availability of new molecules for R+D.

Mexico accumulated 900 million USD savings in medicines at the end of 2019.

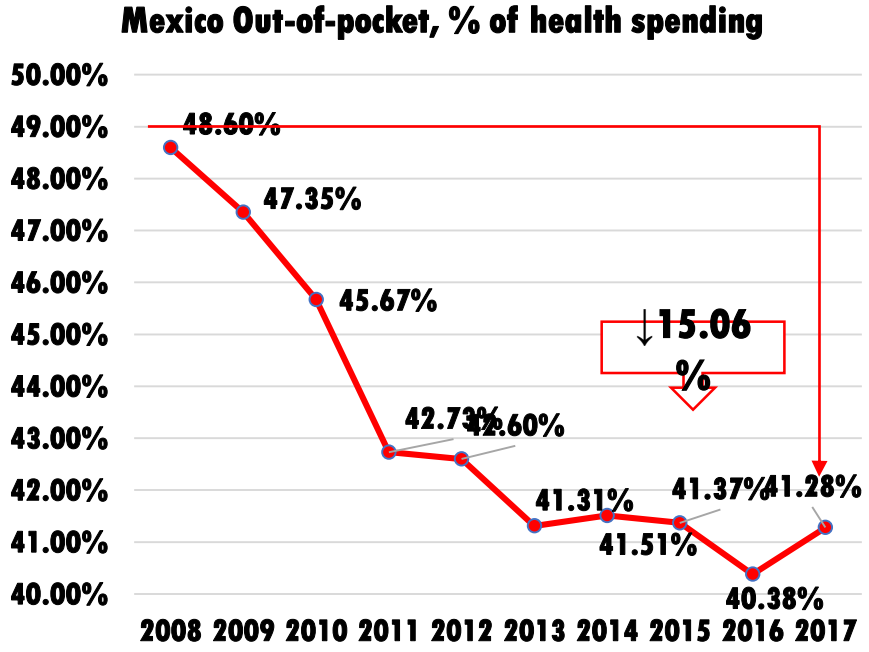


Source: COFEPRIS.

New Pharmaceutical Market Conditions in Mexico

The pharmaceutical policy implemented by COFEPRIS reduced out of pocket spending in Mexico.

From 2008 to 2017, out of pocket spending in Mexico has decreased from 48.6% to 41.28% of total health expenditures.



Source: OECD.

COVID-19 Vaccine Joint Review Process

World Health Organization

The competition for access to the Covid -19 vaccine among countries will exacerbate during 2020/21, considering that the demand of this product in the world is much greater than the world production capacity.

Currently there are around 25 COVID-19 vaccine projects developing in phases I, II and/ or III. Some of them are hosted by countries which agencies are not familiarized with the authorization of new vaccines (Russia, China).

The above mentioned projects could satisfy the world demand only in the case that they successfully complete phase III of their clinical trials. However if they are authorized only by their local agencies, access for other countries would face high transaction costs and would limit the recovery of the world economy, expanding poverty and inequality.

Therefore, the WHO should incorporate a COVID-19 vaccine joint review panel adopting international best practices and human expertise, in order to grant a global authorization by means of which every health agency in the world would grant an immediate local commercialization permit.

Regulatory Reliance –
If not now, when? What are the current barriers?

Session 1

Margaret Hamburg, MD

Session 1 Presenter
Former Commissioner of Food and Drugs
US FDA

Regulatory Reliance – If not now, when? What are the current barriers?

Panel Discussion

Moderators: Alastair Wood & Murray Lumpkin

Panelists:

- Jeffrey Drazen, Former Editor-in-Chief, The New England Journal of Medicine
- Margaret Hamburg, Former FDA
- Guido Rasi, ICMRA & EMA
- Emer Cooke, WHO & EMA
- Janis Bernat, IFPMA
- Mikel Arriola, Former COFEPRIS, Mexico

Regulatory Reliance – If not now, when? What are the current barriers?

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Jeffery Drazen, MD

Panel Discussion Presenter
Former Editor-in-Chief
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