



Public health and practical considerations on switching from seasonal to pandemic vaccine production

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'Switch' meetings in 2015 and 2016

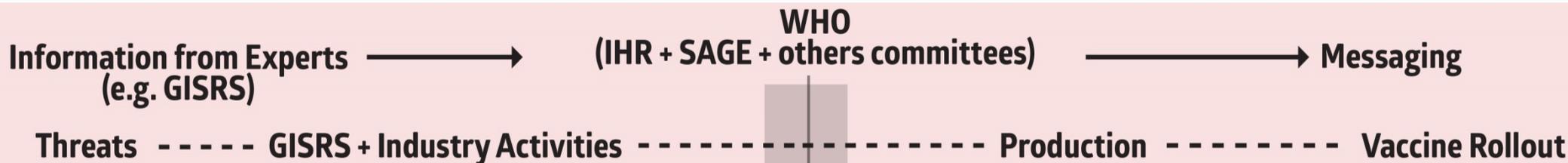
Challenges and timelines in producing a pandemic vaccine

- AIM: **Develop global strategy and operational mechanism** for pandemic vaccine response at the start of a pandemic when seasonal influenza vaccine may still be needed in many parts of the world
- **Timelines very tight - depend on interaction between many players**
 - GISRS, WHO CC, ERLs,
 - Candidate Vaccine Virus (CVV) reassorting laboratories,
 - Vaccine manufacturers,
 - Regulatory agencies,
 - Governments
 - Clinical trial experts
 - Vaccine program managers

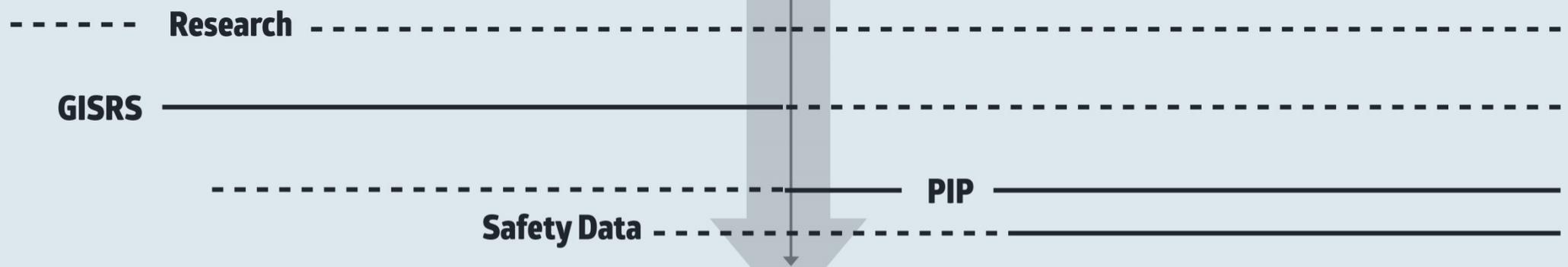
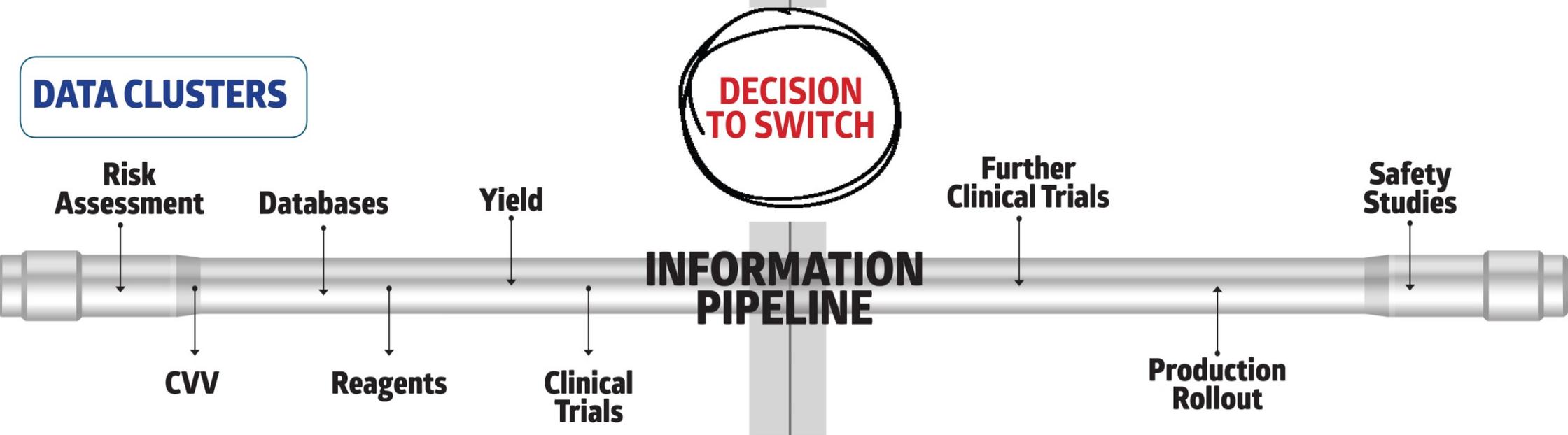
Mapping the pandemic vaccine production process

- Draft Operational Framework for Pandemic Vaccine Response – who?
- Timeline of pandemic vaccine production – when?
- Process for WHO pandemic vaccine response to pandemics – how?
- All to be an Annex to the PIRM
- 2015 Report: http://www.who.int/infuenza/resources/publications/infuenzavaccineresponse_meeting01/en/

INFORMATION LANDSCAPE FOR DECISION TO SWITCH FROM SEASONAL TO PANDEMIC PRODUCTION



DATA CLUSTERS



PRINCIPLES



Some outcomes of 'switch' meetings

- The timing of a switch to pandemic vaccine production has implications for manufacturers, program managers.
 - The switch will not necessarily be immediate. Contract implications.
 - The decision by countries to stop seasonal vaccine manufacturing has potential public health implications



Principles to guide Decision Making

- Any decision will be made on incomplete data. Early data may not be the same over time
- Needs to be flexibility to review the decision/recommendation to switch as new data arises, if no switch is recommended.
- Pandemic and Switch not co-dependant.. A Pandemic does not trigger a switch automatically; A switch to pandemic or novel vaccine is different to declaring a pandemic.. Time.. geography..
CVV



Principles to guide Decision Making

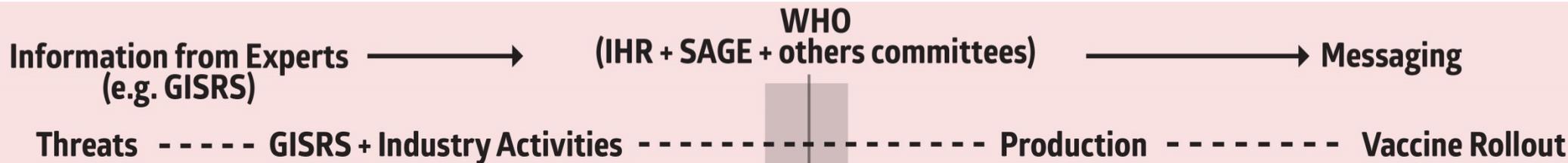
- The WHO recommendation should maximise global health and be guided by expert opinion
 - The risks of mortality, morbidity and economic consequences should be considered (minimising serious impact, minimising spread, risk reduction)
- The consequences and health implications of the switch, or not switching, should be considered.
 - Impact of not having seasonal vaccine available.
- Any decision or recommendation should be evidence based
 - The process should be transparent
 - Any recommendation should be defensible
- There should be clarity of roles and activities (Operational Plan)

Practical considerations

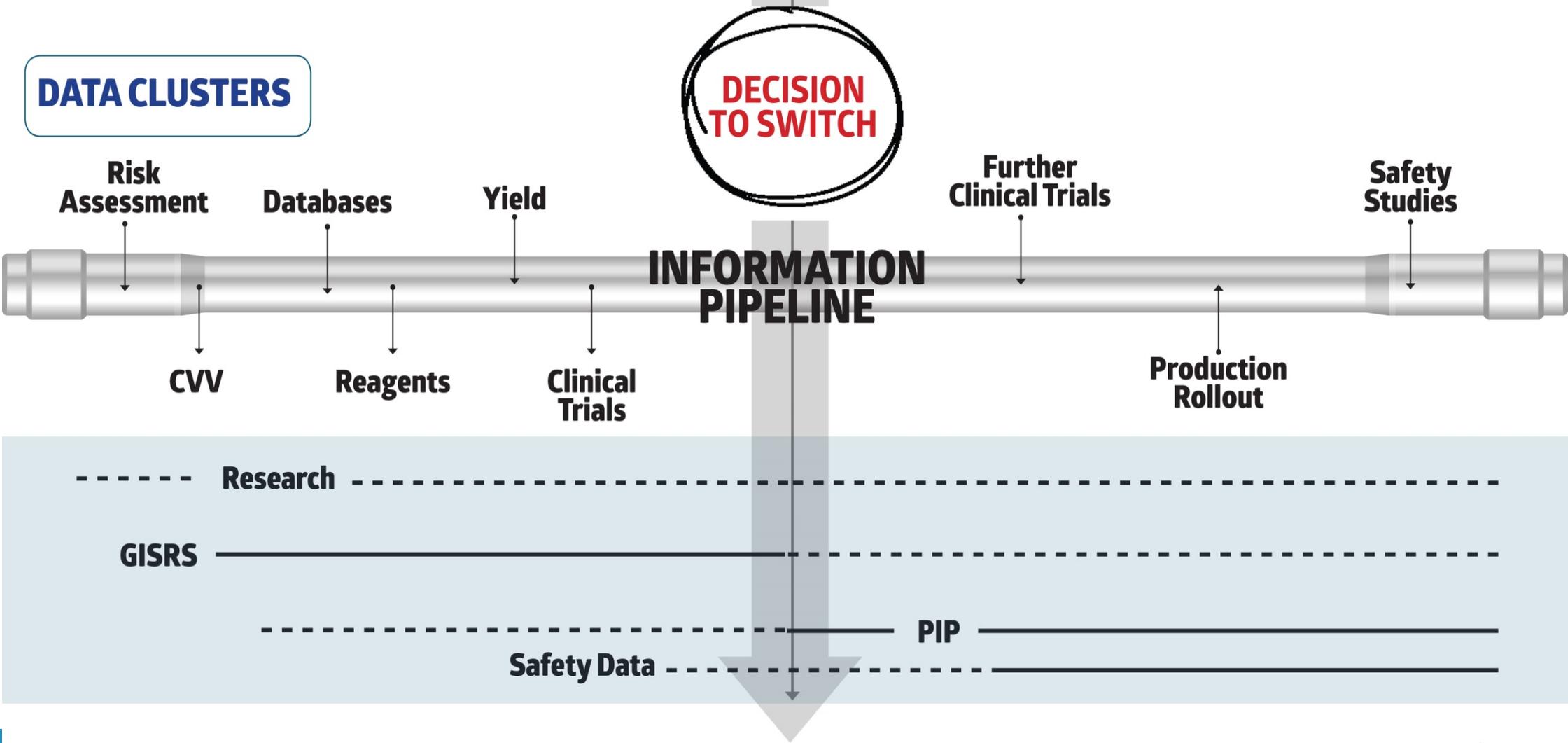
- **There are threats and bottlenecks** in the manufacturing process which can cause a domino effect & affect both seasonal and pandemic vaccine production and availability. These need further identification, exploration and resolution:
 - CVVs, Biocontainment level.
 - Reagent preparation
 - Vaccine production (yields etc)
 - Registration issues.



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Bottlenecks

Risk assessment

Bottleneck	Data needed	Solutions
<p data-bbox="11 359 638 790">Delay in making a risk assessment whether or not to make a vaccine switch</p>  <p data-bbox="246 1404 537 1508">World Health Organization</p>	<ul data-bbox="761 359 1456 1500" style="list-style-type: none">• Assess potential impact of new virus versus that of seasonal virus, including:<ul data-bbox="851 742 1299 1260" style="list-style-type: none">○ Epidemiology○ Severity○ Modelling○ Impact○ Ability to manufacture vaccine• Update risk assessment as more data available	<ul data-bbox="1512 359 2206 1268" style="list-style-type: none">• WHO to prepare formal output from all risk assessments including rationale for decisions• Review of risk assessment methodology<ul data-bbox="1601 973 2195 1117" style="list-style-type: none">○ Need to distinguish high and low risk• Develop decision making tool

Bottlenecks

CVV production/availability

Bottleneck	Data needed	Solutions
Lack of suitable BSL3/GMP laboratories for early small scale work	<ul style="list-style-type: none"> Review number of suitable labs available 	<ul style="list-style-type: none"> Dedicated publically-funded pilot BSL3/GMP labs
Not enough labs producing CVVs especially from highly pathogenic viruses	<ul style="list-style-type: none"> None identified 	<ul style="list-style-type: none"> WHO to identify and establish more pandemic CVV labs
Not enough high containment labs for making LAIV CVVs	<ul style="list-style-type: none"> Review number of suitable labs available 	<ul style="list-style-type: none"> Dedicated publically-funded pilot BSL3/GMP labs
Slow decision on CVV status for Nagoya Protocol or SMTA2	<ul style="list-style-type: none"> Prepare a review of the type of CVVs to be produced and their use 	<ul style="list-style-type: none"> WHO to obtain clarification
Uncertainty about manufacturers' obligations to share synthetic seed viruses and shipping requirements	<ul style="list-style-type: none"> None identified 	<ul style="list-style-type: none"> Manufacturers to start dialogue with WHO
Delays in shipping	<ul style="list-style-type: none"> None identified 	<ul style="list-style-type: none"> Manufacturers to obtain import permits (including GMO CVV) in advance; obtain agreement(s) with courier(s)



Bottlenecks

Yield and manufacturing of CVVs

Bottleneck	Data needed	Solutions
Identification of the type of safety tests needed; availability of wt virus comparator; the need for ferret safety tests	<ul style="list-style-type: none"> • wt virus risk assessment • Criteria for attenuation and biosafety and utility of safety tests 	<ul style="list-style-type: none"> • WHO to review guidance on safety testing of CVVs
Continued need for chicken pathogenicity tests of CVVs derived from hp viruses	<ul style="list-style-type: none"> • Historical review of chicken test data • Review in vitro test data 	<ul style="list-style-type: none"> • WHO/WHO CCs request that either USDA remove requirement for chicken pathogenicity test or remove hp influenza viruses from Select Agent status
Slow decision on biosafety and USDA Select Agent status; biosafety status could be country-specific	<ul style="list-style-type: none"> • Information on pathogenicity • Sequence especially HA/NA gene segments and including both egg and cell isolates 	<ul style="list-style-type: none"> • All CVV labs aiming to work with hp viruses should register with USDA in advance • WHO to lead and coordinate biosafety assessment and to speed up assessment • WHO to provide feedback on IFPMA 'white paper' on CVV biocontainment • Better coordination of CVV labs • Better communication between CVV labs and manufacturers • CVV labs to standardized lab release documents for CVVs • Future use of synthetic HA/NA CVVs
Uncertainty about biosafety status of synthetic CVVs especially with USDA Select Agent status	<ul style="list-style-type: none"> • Information on pathogenicity • Sequence especially HA/NA gene segments and including both egg and cell isolates 	<ul style="list-style-type: none"> • Manufacturers to clarify status with human and agricultural safety authorities • WHO to coordinate

Bottlenecks

Clinical trials for the first pandemic vaccines

Bottleneck	Data needed	Solutions
Delay in availability of clinical trial vaccine lots, specifically related to vaccine potency assays	<ul style="list-style-type: none"> Data from SRID and alternative potency assays 	WHO and ERLs to review and recommend alternative potency assays
Delay due to GMO issues	<ul style="list-style-type: none"> Certificate of analysis 	<ul style="list-style-type: none"> None identified
Delay due to country-specific vaccine lot release	<ul style="list-style-type: none"> Lot release data 	<ul style="list-style-type: none"> WHO to coordinate pandemic vaccine lot release globally
Delay in clinical trial protocol review	<ul style="list-style-type: none"> None identified 	<ul style="list-style-type: none"> Harmonize clinical trial procedures
Delay in serology assays	<ul style="list-style-type: none"> Robustness and reproducibility of assays 	<ul style="list-style-type: none"> Improvement, standardization and acceptance of assays

Bottlenecks

Timing of SRID reagents for vaccine potency testing

Bottleneck	Data needed	Solutions
Delays in reagent supply will delay vaccine lot release and vaccine supply	<ul style="list-style-type: none">• Availability of antigen and antiserum for use in reagent production• Biosafety status of antigen• Which CVV is being used?• Suitability of existing reagents i.e. are new ones really needed?<ul style="list-style-type: none">○ Is use of heterologous reagents realistic?	<ul style="list-style-type: none">• Reagent supply needs better coordination and harmonization• Alternative validated potency tests• Early start of antiserum production (before CVV availability)• Allow use of heterologous reagent• Consider making panel of reagents at risk



Bottlenecks

Regulatory harmonization

Bottleneck	Data needed	Solutions
<p>Lack of mutual recognition of regulatory procedures leading to delays in vaccine supply</p>	<ul style="list-style-type: none"> • Review regulatory requirements in different countries • Identify a basic set of criteria for seasonal and pandemic vaccine Prequalification • What requirements are there for donated vaccines in an emergency • Do country NRAs meet published criteria for functionality • Robustness of pandemic vaccine capability in countries • Review of data on vaccine effectiveness • Explore labelling requirements for emergency use of pandemic vaccine • Review pandemic vaccine lot release requirement in different countries 	<ul style="list-style-type: none"> • Cross communication between regulatory authorities • WHO to introduce Prequalification for seasonal and pandemic influenza vaccines • Continue to support regional regulatory harmonization in low and middle income countries • Establish or strengthen NRA's: <ul style="list-style-type: none"> ○ Regulatory systems ○ Marketing Authorization • Agreement on criteria for assessment of vaccine effectiveness • Harmonization of labels and package inserts for pandemic vaccines • Harmonization of pandemic vaccine lot release

Bottlenecks

Fill and finish capacity

Bottleneck	Data needed	Solutions
<p>If pre-filled syringes are used, filling is slower and uses more antigen;</p> <p>if multidose vials are used, thiomersal will be used and this limits its use</p>	<ul style="list-style-type: none"> • Criteria used by countries for selecting final presentation • What is formulation requirement to ensure required shelf life • An understanding of the need for prefilled syringes for some groups e.g. pregnant women, children 	<ul style="list-style-type: none"> • Evaluate different delivery methods • Education on benefits of use of multidose vials • Use USA model of a fill/finish network to optimize global filling capacity

Key Outcomes of the Meetings and Next Steps

- There are many components of the decision to switch and they will involve nearly all aspects of the influenza community.
- Such an integrated approach could be achieved by bringing together an **international expert group** tasked with making such a decision.
- The expert group should follow the principles for a vaccine switch outlined during this consultation and should meet to work through switch scenarios in order to establish a good working relationship.



Key Outcomes of the Meeting and Next Steps

- A main focus of the second consultation was to **propose solutions to bottlenecks and problems** that would interfere with making a switch and making pandemic vaccine available quickly.
- The next steps would be in deciding ownership of these proposals and then if needed, convening expert groups in order to bring solutions closer. It was agreed at the consultation that **small working groups would take this forward, organised by WHO.**



Key Outcomes of the Meeting and Next Steps

- One proposal that was placed in the parking lot during the first consultation was to establish a publically-funded small scale GMP pilot lot vaccine production facility would be used for influenza vaccine evaluation.
 - Training, future GAP support?
- Following finalization of the operational framework for pandemic vaccine response, it will now be possible to finalize the PIRM Framework document.
 - Following that, there should be consultation with member states on its implementation and periodically it should be reviewed and updated.



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