THE WORKSHOP ON THE JOINT PROCUREMENT OF PANDEMIC VACCINES

Luxembourg, 29-30 April 2015

Disclaimer: This is a technical document prepared for the purpose of supporting a discussion on the Joint Procurement Agreement. Any views expressed in this document are purely those of the authors and may not in any circumstances be regarded as stating an official position of the European Commission.
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The European Commission would like to thank all participants to the workshop on joint procurement for pandemic vaccines for their active contributions to a rich debate on numerous aspects of the joint procurement of pandemic vaccines under the Joint Procurement Agreement for medical countermeasures. Particular thanks go to all speakers for their outstanding presentations.
1. INTRODUCTION

J. F. Ryan, acting Director of Directorate C of DG SANTE, opened the workshop on the joint procurement of pandemic influenza vaccines highlighting the specificities of the joint procurement mechanism. He recalled that the joint procurement is an innovative and unique mechanism:

- in institutional terms, it is a budgetary implementing measure;

- in terms of management, the mechanism is piloted by participating Member States with the administrative and technical support of the Commission services working together in a specific and independent steering committee;

- in procurement and contractual law terms, it creates a European framework allowing participating Member States to free themselves, when wanting to procure in common, of the existing national differences/specificities/barriers,

- participation of the Member States to the joint procurement agreement, and/or to a specific procedure that will be launched under it, is on a voluntary basis.

The joint procurement mechanism provides to participating Member States the facility for the procurement of medical countermeasures used to mitigate serious cross-border threats to health, creates the conditions for more balanced procurement procedures both in the interest of public health administrations and in the interest of the industry.

J. F. Ryan noted also that the joint procurement agreement might play a role in enabling wider use of the 'innovative partnership' introduced under Directive 2014/24, it creates the frame for a pro-active pooling of needs, competences, knowledge and resources (scientific, technical and financial) to foster, in the medium to long term, the development of innovative new treatments/vaccines to significantly improve public health in still unexplored areas.

In the context of the joint procurement for pandemic vaccines, signing contracts for the reservation of significant quantities of vaccines "in peace time" is a challenge, and not only because the vaccine will not exist before the pandemic will be declared. It is of utmost importance to ensure that all stakeholders in the process of procuring pandemic vaccines have as complete and as transparent as possible understanding of all aspects that will significantly influence the procedure.

This is the reason why on 29-30 April a workshop on joint procurement of pandemic vaccines was organised and both public health administrations representatives and representatives of the industry were invited. Additionally, the institutional stakeholders like WHO, EMA and ECDC were invited to elaborate on all elements that might help to improve the preparation of the specifications and preparedness for the next pandemic.
2. Historical and Political Background of the Joint Procurement Initiative

Daniel Reynders, Head of General Services International Relations and Public Health Emergencies, Belgium Ministry of Health, gave the key note speech on the historical and political context which led to the setting up of the joint procurement mechanism at the initiative of the Belgian Presidency in 2010.

Since 1998, the EU had a political and legal framework for communicable diseases. The Decision 2119/98 established the requirements regarding monitoring, notification of potential outbreak of communicable disease across the Union and the exchange of information on public health measures to control the spread of these diseases.

In 2003 Belgium was hit as the Netherlands and Germany by an outbreak of avian flu due to H7N7.

In 2005 the fear of a new pandemic increased worldwide due to the new strain influenza A/H5N1 and the WHO as well as the EU advocated for a better preparation of their Member States which brought the pandemic influenza preparedness high on the agenda.

The new International Health Regulations were adopted by the WHO World Health Assembly the same year.

To face this new threat, the EU Member States discussed several times during the years 2005-2006 the need for better preparedness. The idea of an EU stockpiling of pandemic vaccine and antivirals came also on the agenda of the council and the Commission prepared proposals to address this challenge. The EPSCO Council of 12 December 2005 concluded “that there should be further consideration of the available options for dealing with an outbreak including the feasibility and added value of the EU holding a targeted strategic stockpile of antivirals” but due to a lack of consensus this initiative was abandoned rapidly. Several member states started to discuss with the industry in order to secure their own national stockpile (through “advanced purchase agreement”) should the pandemic become a reality.

In 2007 the mandate of the Health security committee was extended to address the pandemic preparedness. But at that time we were only perceiving the threat as a potential one. Therefore, and this represent only my personal opinion, this “virtual threat was not strong enough to lead to decision.

In 2009 the new strain influenza A/H1N1 emerged in Mexico. Rapidly this new strain, after having spread to the USA was imported in UK and in Spain. It was now a reality which was touching directly citizens of EU Member States. Many Member States signed contract with the industry without having time or opportunity to really negotiate the procurement of new vaccines or large amount of antivirals which was at that time the only counter-measure available. We all know what the perception of the public and the media was about these measures while the pandemic appeared to be less hard than expected.

The 2010 'Assessment Report on EU-wide Pandemic Vaccine Strategies' and the EU/Belgian Presidency 'Conference on lessons learnt from the A(H1N1) pandemic' identified a number of weaknesses in the procurement of pandemic influenza vaccines and antivirals by Member States during the influenza A H1N1 pandemic in relation to
price, liability, confidentiality and flexibility to adjust the quantities ordered to actual needs.

Belgium, after the H1N1 Pandemic, took the opportunity, during its presidency of the European Union, to work on the Conclusions of the European Council to highlight the need for greater cooperation and coordination at European level.

The informal EPSCO Council in its conclusions of 13 September 2010 invited the Commission to develop a mechanism for vaccines and antiviral medication which would allow Member States, on a voluntary basis, common acquisition of these products or common approaches to contract negotiations with the industry, clearly addressing issues such as liability. This was confirmed by formal conclusions in December 2010.

It underlined the need to introduce a common procedure for the joint procurement of medical countermeasures, and in particular of pandemic vaccines, to allow member states, on a voluntary basis, to improve their purchasing power and have equitable access to vaccines and antivirals. The joint procurement mechanism will benefit to all EU countries, in particular the ones which encountered difficulties in purchasing vaccines developed for the H1N1 pandemic in 2009.

By the end of 2011, to draw lessons from previous crises and meet these Council Conclusions, the Commission presented a proposal to the European Parliament and the European Council on serious cross-border threats to health including providing a legal basis for a joint mechanism for the purchase of medical countermeasures on a voluntary basis. This proposal led to the adoption of the 1082/2013 Decision published on the 5 November 2013.

With this legal provision, all Member States participating in the JP will have a tool which allows member states and the Commission to procure commonly medical countermeasures to serious cross-border threats to health.

In June 2014, Belgium represented by the Secretary of State Philippe Courard and 14 other representatives of Member States signed the proposed agreement for joint procurement in Luxembourg. In addition, 8 Member States signed at that time a letter of intent.

The majority\(^1\) of the Member States have signed the JPA so far and others are on the process to join the JPA. The final tool, which we now have in hands, is suitable for any medical countermeasures addressing serious cross-border threats to health.

There is still a formal request from Member States, through their conclusions of the EPSCO Council, to start discussions on pandemic vaccine.

Nevertheless, the choice on the medical countermeasure to be firstly procured has already been discussed during the first meeting of the Steering Committee of the Joint Procurement Agreement. Depending on the needs expressed by the Member States the first medical countermeasure may be different than pandemic vaccines and we are now on the way to develop a call for tender for personal protective equipment to face the threat of Ebola.

\(^1\)The list of the Member States that signed the Joint Procurement Agreement can be found under the following address: [http://ec.europa.eu/wipo/wcm/3vare.ccc.eu.int/8080/health/preparedness_response/joint_procurement/jpa_signature_en.htm](http://ec.europa.eu/wipo/wcm/3vare.ccc.eu.int/8080/health/preparedness_response/joint_procurement/jpa_signature_en.htm)
This tool provides Member States with a better negotiation position but at the industry level, the agreement has also an interest in allowing for better planning of investments and thus improving the security of supply and will certainly lead to a reduction in costs.

It was a long way to get here, and we are still far from the goal of better solidarity and equity in the European Union but it is an important step forward.

M. Reynders concluded that it is now up to the Member States to decide what they will do with this tool. There are still some reluctances in the mind of some of them and only the practice will be able to demonstrate its added value.

Take home messages:

- The joint procurement mechanism provides the Member States a facility for the common procurement of medical countermeasures used to mitigate serious cross-border threats to health.
- It is now up to the Member States to decide what they will do with the tool. All decisions in the framework of the joint procurement mechanism are taken by the Member States through the Steering Committees.

3. THE JOINT PROCUREMENT – STATE OF PLAY, ORGANISATION AND FUNCTIONING OF THE MECHANISM

Magdalena Kolowca and Jean-Luc Sion, policy officers from Health Threats Unit, DG SANTE, provided background information on the Joint Procurement mechanism and explained its organisation and functioning. They also outlined what the preparation of the specifications for a call for tender would mean and the different steps that will lead to the signature of a contract.

The political and legal origin of the mechanism was described recalling that he Joint Procurement Agreement is a framework agreement laying down common rules for practical organisation of joint procurement procedures with a view to the advance purchase of medical countermeasures for serious cross-border threats to health.

On 20 June 2014, the Commission and 15 Member States signed the Joint Procurement Agreement at the end of the EPSCO Council.2

The Joint Procurement Agreement enables Member States and the Commission to organise joint procurement procedures with a view of to acquire medical countermeasures. The participation of a Member State in any procurement procedure organised pursuant to JPA remains voluntary and Member States may choose not to participate in a particular procurement procedure.

2 Until April 2015 19 Member States signed the Agreement. The updated list of the Member States that signed the Joint Procurement Agreement can be found under the following address: http://wcmcom-ec-europa.eu-wip.wcm3vue.cec.eu.int:8080/health/preparedness_response/joint_procurement/jpa_signature_en.htm
Moreover, participation in a particular procurement procedure does not prevent Member States from carrying out independent procurement procedures, also when they involve the same medical countermeasures or the same operators.

The whole process of the joint procurement is managed by two types of Steering Committees:

- the permanent Joint Procurement Agreement Steering Committee (JPASC) that is in charge of all the matters relating to the JPA as such; it is composed of one representative of each Contracting Party (Member States and the Commission);

- the Specific Procurement Procedure Steering Committee(s) (SPPSC(s)) that will be in charge of the matters relating to specific procurement procedures organised under JPA. The SPPSC will be composed of one representative of each Contracting Party (Member States and the Commission) participating in a specific procurement procedure. For each specific procurement procedure, a separate SPPSC will be established.

It was underlined that all decisions in the framework of the joint procurement mechanism are taken by the Member States - Contracting Parties to the JPA. The Commission (SANTE C3) ensures the secretariat and chair the Steering Committees.

The role of each of the committees in the mechanism was further developed:

The tasks of the JPASC include:

- decisions on the type of medical countermeasures to be procured;
- decisions on the order in which the procurements will be organised in time;
- preparation of amendments to the JPA;
- matters related to incompliance by a Contracting Party with the JPA, disputes between two or more Contracting Parties, or legal proceedings under the joint procurement procedure concerning all Contracting Parties.

Each SPPSC will be responsible for matters relating to the specific joint procurement procedure, including:

- technical specifications;
- determination and application of the criteria for allocation of medical countermeasures, including temporary deviations from such criteria;
- the award decision on the basis of the opinion of the evaluation committee;
- any legal proceedings under the framework contract.

M. Kolowca underlined that the core of the mechanism is its voluntary nature. It is up to the Member States to decide whether they want to join a specific procurement procedure.
The subsequent steps for the organisation of the specific joint procurement procedure were developed by JL. Sion.

4. POTENTIAL USE OF THE JOINT PROCUREMENT MECHANISM

4.1. Legal considerations - the scope of the Joint Procurement Agreement

Agnieszka Mielczarek, a legal officer from the Legal Affairs Unit, DG SANTE, gave a comprehensive presentation on the scope of the Joint Procurement Agreement (JPA) under Decision 1082/2013/EU.

Decision 1082/2013/EU defines a serious cross-border threat to health as "a life threatening or otherwise serious hazard to health of biological, chemical, environmental or unknown origin which spreads or entails a significant risk of spreading across the national borders of Member States, and which may necessitate coordination at Union level in order to ensure a high level of human health protection".

Decision 1082/2013/EU specifies the following categories of serious cross-border threats to health:

1. threats of biological origin, consisting of: communicable diseases; antimicrobial resistance and healthcare associated infections related to communicable diseases; biotoxins or other harmful biological agents not related to communicable diseases;
2. threats of chemical origin;
3. threats of environmental origin;
4. threats of unknown origin;
5. events which may constitute public health emergencies of international concern under the IHR, provided that they fall under one of the categories of threats set out in points (a) to (d).

A communicable disease is defined in Decision 1082/2013/EU as an "infectious disease caused by a contagious agent transmitted from person to person by direct contact with an infected individual or by indirect means such as exposure to a vector, animal, fomite, product or environment, or exchange of fluid, which is contaminated with the contagious agent".

Therefore, the JPA allows jointly procuring of any medical countermeasures against communicable diseases that can be considered as serious cross-border threats to health.

A. Mielczarek explained that according to the JPA, the medical countermeasures are "any medicines, medical devices, other goods or services that are aimed at combating serious cross-border threats to health, as referred to in Decision 1082/2013/EU". The term should be interpreted in the light of the aim of the Decision 1082/2013/EU, which, in accordance with its Article 1(2), is "to support cooperation and coordination between the Member States in order to improve the prevention and control of the spread of severe human diseases across the borders of the Member States, and to combat other serious cross-

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3 An indicative list of such communicable diseases can be found in the Commission Decision 2000/96/EC of 22 December 1999 on the communicable diseases to be progressively covered by the Community network under Decision No 2119/98/EC of the European Parliament and of the Council (Annex I, point 2). Nevertheless, the Joint Procurement mechanism is not limited to that list.
border threats to health in order to contribute to a high level of public health protection in the Union”.

Where medicines, medical products or other goods or services can prove necessary to prevent or to control the spread of severe human diseases across the borders of the Member States, or to combat other serious cross-border threats to health, they should be covered by the term "medical countermeasure".

Case-by-case, the examples of such medical countermeasures could include laboratory tests, diagnostic tools/kits for seasonal or pandemic influenza, influenza vaccines, antivirals, decontamination products, masks and personal protective equipment or other goods and services, depending on the need triggered by a serious cross-border threat to health.

4.2. Other considerations - access to high-cost medicines

Dirk Van den Steen, Team Leader from Healthcare Systems Unit of DG SANTE reported on access to High-Cost Medicines.

He reminded that the focus of EU-level policy is on ensuring accessible and affordable treatments for all EU citizens and minimizing unintended effects from current pricing systems in Member States, by improving cooperation and coordination at EU-level. In line with this focus, the Commission has referred to the possible use of the JPA in a recent statement made during an EP Plenary session.

Research has shown that economic considerations, such as price level and market size, determine the effective availability of medicines for patients in the EU. Current price setting mechanisms, whereby prices in a given EU Member State are benchmarked with those in other Member States, may further exacerbate the lagging accessibility of medicinal care in lower-price / smaller markets.

The EU-level mandate to intervene is limited, in line with Article 168(7) of the Treaty stating that Member States are responsible for the definition of their health policies as well as for the organisation and delivery of health services. This includes measures regulating the prices of medicines and their inclusion in health insurance systems. Nevertheless, Article 168(2) states that the Union shall encourage cooperation between the Member States.

D. Van den Steen noted that in keeping with its mandate and the observation that cross-country coordination challenges are hampering patient access, the Commission has formulated the intention to help foster the cost-effective use of medicines in view of improving access to medicinal care across the EU. In the Communication from the Commission on cost-effective use of medicines issued in 2014 the Commission stated that: "The EU needs a competitive pharmaceutical industry. With this background, Member States and the Commission should reflect further on how to reconcile the policy objectives of ensuring accessible healthcare for all EU citizens with the need for cost containment. Consideration should be given to improved cooperation on building mechanisms for increased transparency and better coordination to minimise any unintended effects that current national pricing systems may have in terms of accessibility throughout the EU".
This policy agenda was confirmed in the mission letters by President Juncker to Commissioners Andriukaitis and Bienkowska indicating that medicines are "not goods like any others".

EU-level initiatives on pricing models in relation to the accessibility of medicines are further underpinned by calls from Member States as formulated in a recent series of Council Conclusions. Planned initiatives include the use of the Public Health Programme to support relevant research tools and information sharing capacity in coming years.

D. Van den Steen stressed that when comparing the variability in living standards between EU Member States as well as applicable price levels, it is noted that GDP per capita varies considerably more than price levels for medicinal products. Given practices such as price benchmarking between Member States and parallel export flows from low-price to high-price Member States this relative price convergence does not surprise. However, it should be noted that differences in purchasing power per Member States will impact the comparative accessibility of medicines between Member States.

In view of the above observations, he questioned whether a unitary (EU-wide) price that is affordable across all Member States can be achieved, how the issue of "price" should be addressed under the Joint Procurement Agreement and how the Joint Procurement Agreement could be fine-tuned to overcome this challenge.

Jean-Luc Sion, Health Threats Unit, DG SANTE, further informed about requests by Member States through the Health Security Committee to reflect on the possibility to use the joint procurement agreement to ease the difficulties in procuring pertussis and BCG vaccines.

**Take home messages:**

- The Joint Procurement Agreement is a framework agreement laying down common rules for practical organisation of joint procurement procedures with a view to the advance purchase of medical countermeasures for serious cross-border threats to health.

- All potential medicines, medical devices, other services and goods that could be used to mitigate/treat a life threatening or otherwise serious hazard to health of biological, chemical, environmental or unknown origin which spreads, or entails a significant risk of spreading across the national borders of Member States, and which may necessitate coordination at Union level in order to ensure a high level of human health protection, can be procured in common under the Joint Procurement Agreement.

- The political focus at EU-level is on ensuring accessible and affordable treatments for all EU citizens and minimizing unintended effects from current pricing systems in Member States, by improving cooperation and coordination at EU-level.

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4 The Health Programme 2014-2020 to support the policy debate, build up a sound evidence base and explore possible policy avenues: a project grant to improve information sharing on the prices of medicinal products (expected to start in 2015 for a duration of 3 years); a study exploring alternative pricing approaches as well as related cooperation mechanisms in view of possible impacts, including on patient access (delivery by the end of 2015).
5. RESEARCH AND DEVELOPMENT ON NEW VACCINES

5.1. Horizon 2020 funding for research and innovation in vaccines

Cornelius Schmaltz, Deputy Head of Unit, Infectious Diseases and Public Health, DG RTD, presented Horizon 2020 funding for research and innovation in vaccines.

M. Schmaltz recalled that Horizon 2020 is the new EU funding programme for research and innovation running from 2014 to 2020 with a €79 billion budget.

Vaccine research is mentioned prominently in the legal basis of the 'Specific Programme' for the Horizon 2020 Societal Challenge 1 'Health, Demographic Change and Well-being'.

The EU supports research and innovation for vaccines to reach the following policy objectives:

- high social and economic impact on disease eradication and to avoid pandemics;
- cost-effectiveness for health systems and society;
- reduction of the risk of antimicrobial resistance;
- maintain European leadership in vaccine R&D and manufacturing

and to meet scientific challenges such as:

- increased effectiveness;
- easy to use in developing countries;
- serious gaps related to the fact that protective vaccines are available only for some diseases; gaps related to the elderly population.

M. Schmaltz presented several major vaccine research projects that had already started under H2020: Integrated Monitoring of Vaccines Effects in Europe (I-MOVE+) which is a scientific public health platform to identify, pilot test, use and disseminate the best study designs to measure the effectiveness (direct effect) and the impact (indirect and overall effect) of influenza and pneumococcal vaccines against clinical and laboratory confirmed outcomes in the elderly population. TBVAC2020 and EMI-TB are two major platforms for the early development of new TB vaccines funded with an EU contribution of 18.2 and 8 million EUR respectively.

In the last part of his presentation C. Schmaltz presented the major funding opportunities for vaccine research in Horizon 2020 and related sources of further information. In addition to the 'classical' 'Collaborative Research', a new SME instrument allows for the support of single SME in the pursuit of competitive, market-oriented projects with an EU dimension.

The Innovative Medicines Initiative 2 (IMI2) is Europe’s public-private partnership for health, co-funded by The European Federation of Pharmaceutical Industries and Associations (EFPIA) together with other life science industries and the European Commission with over 1.6 billion EUR respectively. The aim of IMI2 is to enable an

5 http://cordis.europa.eu/project/rcn/193288_en.html
appropriate European-level research and innovation response that will make a crucial contribution to delivering better health and well-being for all, while positioning Europe as a leader in the rapidly expanding global markets for health and well-being innovations. Vaccines are one of the priorities of the IMI 2 Strategic Research Agenda.

The third initiative on which information was provided is the European and Developing Countries Clinical Trials Partnership (EDCTP), a public-public partnership between 14 European countries, 14 countries in sub-Saharan Africa and the European Union. EDCTP’s mission is to support collaborative research that accelerates the clinical development of new or improved interventions to prevent or treat HIV/AIDS, tuberculosis, malaria and neglected infectious diseases in sub-Saharan Africa. The scope of activities was extended to include neglected infectious diseases, all clinical phases, diagnostics and delivery optimization. The initial duration of the EDCTP was extended up to 10 Years (2014-2024). The European Union provides co-funding of €683 million from Horizon 2020 (2014-2020) matching contributions from the European participating states.

5.2. Plant-Made VLP Vaccines – Innovative Measures against Pandemic Influenza

Dr Sonia Trepanier, Senior Director Clinical studies at Medicago Inc. Canada introduced her company’s last innovations in the field of vaccine research/production/administration with a particular attention to progresses made that could affect vaccines against pandemic influenza.

Medicago is a clinical-stage biopharmaceutical company developing novel vaccines and therapeutic proteins to address a broad range of infectious diseases worldwide. The company is committed to providing highly effective and competitive products based on its proprietary Virus-Like Particles (VLPs) and manufacturing plant-based technologies. This technology provides a first responder solution and has the potential to offer vaccines and therapeutics with speed and cost advantages over competitive technologies, enabling the development of products for testing within approximately 1 month after the identification and reception of genetic sequences. This production time frame has the potential to rapidly vaccinate or treat populations and supply large volumes of product to the global market and can allow treatment of primary health care providers during the first wave of a pandemic. This technology demonstrated its potential for responding to global pandemics when it produced candidate influenza vaccines for H1N1 in 2009 and H7N9 in 2013 in 19 days, compared to the several months required to produce vaccines using eggs. This platform also has the potential to respond to strain mismatch.

In 2010, Medicago was awarded a $21M grant from DARPA in US to develop a commercial vaccine facility within 12 months and to demonstrate its capacity to produce more than 10M doses within a month of pandemic H1 VLP influenza, which was successfully achieved. Medicago was also recently awarded a contract by the U.S. government to manufacture Ebola antibodies for a study in non-human primates.

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7 http://www.edctp.org/
Medicago is the most clinically advanced vaccine company using a plant-based production platform with eight clinical trials conducted so far with influenza VLP vaccines against pandemic and seasonal strains. These trials showed that the VLP vaccines are safe and well-tolerated in adults and elderly and generated strong immunogenicity responses meeting licensure criteria. Moreover, cell-mediated immunity studies indicated strong stimulation of cross-reactive polyfunctional T cells, important for protection against antigenic drift and to better protect the elderly population. These vaccines induced durable antibody and cellular immune responses.

In conclusion, Medicago’s VLP platform has the capacity to manufacture efficacious vaccines harboring unique intrinsic properties providing optimal humoral and cellular immune responses, long lasting immunity and broad protection against multiple Influenza strains. This platform can provide more potent vaccines with speed and cost advantages over competitive technologies and can allow vaccination of the population before the first wave of a pandemic strike.

Take home messages:

- Horizon 2020 is the new EU funding programme for research and innovation running from 2014 to 2020 with a €79 billion budget.
- Technologies are being developed and tested that could allow quicker deployment of vaccines than existing processes.

6. MARKETING AUTHORISATION PROCEDURES FOR PANDEMIC VACCINES

6.1. Regulatory aspects of the marketing authorisation procedures

Agnes Mathieu from Medicinal products – authorisations, European Medicines Agency Unit of DG SANTE, recalled the regulatory framework for granting a marketing authorisation for pandemic vaccines including conditional marketing authorisation and marketing authorisation under exceptional circumstances.

A. Mathieu reminded that a medicinal product may only be placed on the market in the European Union when a marketing authorisation has been issued either by the competent authority of a Member State (national authorisations) or when an authorisation has been granted for the whole EU (union authorisation).

She informed that there are four procedures for granting marketing authorisation:

1. Centralised Procedure\(^8\) - scientific assessment is made by the EMA while the authorisation is granted by the European Commission, after consulting a

\(^8\) The procedure is compulsory for: products derived from biotechnology, e.g. reverse genetics techniques or recombinant DNA technology in influenza vaccines, orphan medicinal products, treatment of AIDS, cancer, neurodegenerative disorders or diabetes, for veterinary medicinal products to promote growth or to increase yields from treated animals. It is optional for: new active substance in non-mandatory therapeutic area, significant therapeutic, scientific or technical innovation or interest of patients at Union level.
committee of Member States (comitology). The centralised authorisation means that there is one marketing authorisation valid in all Member States and one product name identical in all Member States.

2. Mutual Recognition Procedure – based on the principle of recognition of an already existing national marketing authorisation by one or more Member States.

3. Decentralised Procedure - application for the marketing authorisation is submitted simultaneously in several Member States, one Member State is chosen as the Reference Member State - national marketing authorisations are granted in the Reference and in the Concerned Member States.

4. Purely national procedure - for products authorised in one Member State only - decision is taken by the national authorities.

She informed that there are two pathways to place medicinal products earlier on the market under very strict circumstances: conditional marketing authorisation and marketing authorisation under exceptional circumstances.

<table>
<thead>
<tr>
<th>Conditional marketing authorisation</th>
<th>Marketing authorisation under exceptional circumstances</th>
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<tr>
<td>Less clinical data on the efficacy and safety</td>
<td>Less clinical data on the efficacy and safety</td>
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<tr>
<td>Scope: e.g. medicines to be used in emergency situations in response to public health treats, unmet medical needs of patients, in the interests of public health, demonstrate positive benefit-risk balance</td>
<td>Scope: in those cases where the indication is very rare, where comprehensive information cannot be provided &quot;in the present state of scientific knowledge&quot; or where it is contrary to generally accepted principles of medical ethics to collect such information, it is unlikely that a full data package will ever be obtained</td>
</tr>
<tr>
<td>Less pre-clinical or pharmaceutical data in emergency situations e.g. pandemic</td>
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<tr>
<td>Authorization valid for one year, on a renewable basis, opinion of EMA prior to expiry, annual renewal</td>
<td>Authorization valid for 5 years, reviewed annually</td>
</tr>
<tr>
<td>Once the pending studies are provided, it can become a &quot;normal&quot; marketing authorization</td>
<td>Will normally not lead to the completion of a full dossier</td>
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A. Mathieu indicated that the influenza vaccines that may be authorised are the following:

- seasonal influenza vaccines (to be used during the annual influenza season);

- pre-pandemic influenza vaccines (or zoonotic vaccines) (pre-pandemic situation to immunise specific populations at risk, emerging animal strain with pandemic potential);

- pandemic vaccines (pandemic situation, pandemic influenza strain officially recognised by the Union or the WHO, to be authorised during a pandemic situation or in advance to prepare against a potential health threat).

There are also three options of the pathways for pandemic vaccines that are possible:
1. Marketing authorisation that is granted prior to the recognition of pandemic situation (‘pandemic preparedness vaccine’);

2. Marketing authorisation granted during a pandemic situation;

3. Variation of a relevant seasonal and prepandemic vaccine.

6.2. European Medicines Agency revised guidelines applicable to pandemic vaccines

Manuela Mura and Thomas Girard from the European Medicines Agency informed on EMA revised guidelines for the approval of a marketing authorisation in the European Union for pandemic influenza vaccines. They also recalled about existing marketing authorisations and on-going procedures in the centralised procedure in respect of pandemic vaccines.

They informed that public consultation for both the regulatory and procedural module and the Clinical and Non-Clinical Module of the guideline is already closed and currently the comments are being revised. The approximate date of publication of the regulatory module is July 2015\(^9\) whilst for the last module of the guideline (non-clinical and clinical) is foreseen for the end of 2015 or beginning of 2016.

The changes of the document aim at improving clarity: covering all types of flu vaccines and all epidemiological scenarios in one document, as well as at improving evaluation of future vaccines: revised requirements based on current knowledge and past experience.

They elaborated on the new elements introduced in the document with respect to the requirements for the authorisation for pandemic preparedness vaccines (former ‘mock-up vaccines’), which are the following:

- The target population it remains to generate immunogenicity data from healthy adults >18 years; however it is now recommended that at least some data is generated in elderly subjects >60 years;
- as far as may be possible, data should be obtained also from other age and population groups, particularly healthy children;
- the total size of the safety population should consist of at least 3000 individuals (for rare AEs - as for any influenza vaccine) – and the follow up should be for at least 6 months post-primary dose;
- existing data for the same vaccine construct generated with other pandemic/zoonotic/seasonal strains should be submitted as supportive – the investigation of two or more strains is strongly recommended to further enlarge the knowledge around the efficacy of the vaccine.

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\(^9\) Strain with pandemic potential, Non-comprehensive dossier = conditional MA, data to be submitted after MA; possible exemption to place the product on the market (sunset clause), Variation when a pandemic situation is dully recognized (variation reviewed under an accelerated timeframe.

\(^{10}\) Please note that the guidelines for the regulatory module was published 02/07/2015 on EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000407.jsp&mid=WCOB01ac058002958b
Concerning the applications to change vaccine composition (‘pandemic strain change variation’), it is recommended that some clinical data indicative of the likely immunogenicity of the pandemic strain are included in the strain change variation dossier.

Other important changes that are foreseen in the guideline with the aim of improving the evaluation of future influenza vaccines as whole are the following:

- efforts during clinical development are encouraged to support identification of correlates for protection (CoPs);
- immunity against HA: HI/SRH and VN should be used to test the immunogenicity of new vaccines; an HI titre of 1:40 is no longer considered sufficient per se for approval, but a distribution of titres across population and % of vaccinees above specified cut off levels appropriately justified should be presented in addition to the usual GMTs, SC, pre/post-vaccination comparisons;
- overall a broader investigation of immune responses by measure of anti-NA and CMI is recommended;
- specifically for pandemic vaccines: % of vaccinees achieving predefined justified antibody threshold levels, plus additional analysis to evaluate titres distribution across population should be investigated, including potential of vaccines to cross-protect against similar viruses.

### Take home messages:

- Pandemic Preparedness Vaccines (PPVs) are so far the best tool to prepare for a pandemic in advance.
- 3 Pandemic Preparedness Vaccines are authorised; one procedure is ongoing.
- Pandemic Preparedness Vaccines are not ‘empty’ virtual files; the dossiers are authorised based on adequate amounts of data to allow for posology and safety recommendations.
- New guideline aims at improving evaluation of future influenza vaccines, including Pandemic Preparedness Vaccines.

### 7. EBOLA VACCINE DEVELOPMENT – AN EMERGENCY RESPONSE

Francois Roman, Director for Clinical Research and Translational Science Vaccine Discovery and Development from GSK informed on Ebola vaccine development by the company as an example of an emergency response. In order to accelerate vaccine development in response to the WHO-declared public health emergency a partnership was set up.

F. Roman reminded that after WHO declared that the Western African Ebola outbreak was considered a Public Health Emergency of International Concern (on August 8, 2014), WHO also stated during a virtual press conference (held on August 12, 2014) that: “There is unanimous agreement among the experts that given the special circumstances
of this Ebola outbreak it is ethical to offer unregistered interventions as potential treatments or prevention."

On August 13, 2014, WHO formally requested GSK’s help to make a vaccine available to assist in the control of the outbreak, with a specific focus on high-risk health care workers (HCWs). To help this effort, an international initiative was rapidly established that involved The Wellcome Trust, UK Government Department for International Development, UK Medical Research Council, the European Commission, Government of Switzerland, Bill & Melinda Gates Foundation, and the US Government (NIH, CDC, BARDA).

The objective of the partnership was for all parties to work together to finalize the most rapid approach for developing and making safe and efficacious vaccines available to the affected populations.

8. PACKAGING AND LABELLING ISSUES

8.1. Lessons learned on the review of the labelling of pandemic vaccines

Thomas Girard, Regulatory Affairs Officer from the European Medicines Agency, reported on the lessons learned on the labelling of pandemic vaccines after 2009.

He recalled that several problems were identified during the review of pandemic vaccines labelling in 2009 outbreak indicating the remedies that could be foreseen in the future to mitigate such issues:

- timing for printing of final labelling material
  Recommendation: mock-ups labelling should be submitted for review prior to the printing of final labelling material, the Agency will offer earlier slots for the submission of mock-ups labelling, as well as accelerated review.

- use of common labelling
  Recommendation: critical information such as the invented name or the type of vaccines should be specifically indicated on the labelling.

- English only labelling
  Recommendation: possibility to request for a translation exemption at national level.

- prominence of key information on the outer labelling
  Recommendation: in addition to the critical information (invented name, common name, pharmaceutical form) the following key information should also appear prominently displayed on the main panel: route of administration, total volume, statement on multi-dose vial (if appropriate), shelf-life after mixing/reconstitution, mixing/reconstitution instructions (e.g. “suspension to be mixed with X before use”).
- readability of the information displayed on small immediate labelling, use of multi-dose vials
  Recommendation: it is acknowledged that containers used for vaccines are generally very small. However, the biggest size label suitable for the concerned containers should always be used; other types of labels should be investigated e.g. concertina type of labels; some simplification to the text used to display the minimum requirements (Art.55(33) of Directive 2001/83/EC) have been performed by the EMA and could be used provided the information appears on the outer labelling; possibility to request exemption of some particulars (article 63(1) of Directive 2001/83/EC) to be addressed to the Agency.

- use of multi-dose vials
  Recommendation: specific key information about the correct handling of multi-dose vial should be included; early discussions with competent authorities on the adequacy of the information/instruction for the handling of the vaccines, ideally with the participation of healthcare professionals.

- labelling impact for a posology change from full dose to half dose
  Recommendation: because of the specific nature of multi-dose vials, the information about the possible use of a half dose would be clearly stated in the SmPC and in the package leaflet while the vial/pre-filled syringe would only display the total volume; for pre-filled syringes, in view of the possibility that a half dose could be administered, the pre-filled syringe barrel should be graduated.

- outdate of the package leaflet
  Recommendation: the above approach to refer to the EMA website in addition to the standard life-cycle of the package leaflet is maintained; the QRD standard statement “Detailed information on this medicine is available on the European Medicines agency website http://ema.europa.eu” should be included.

**8.2. Public health benefits could be secured by using a generic packaging for pandemic vaccines**

Sophie Marszalek, Regulatory Affairs Director, Flu Franchise from Sanofi Pasteur spoke about industry's view on what public health benefits could be secured by using a generic packaging for pandemic vaccines.

She reported on the challenges regarding the labelling in particular in emergency situations recalling that during the H1N1 influenza pandemic, companies had difficulties in making available the most up to date package leaflets (PILs) to the patients. She informed that introducing a change in the labelling requires a minimum lead time of 4 weeks from design to actual printing without taking into account the time necessary to include these “new” materials into the production line. The inclusion of separate sheets with peel-off stickers in (or with) boxes of multi-dose vials is not considered an ideal approach to minimise risks of misreporting safety issues because it adds a level of complexity in the production/supply chain and therefore may affect delivery timelines and it may be an additional source of errors and confusion.

In a pandemic context, the responsibility of the industry is to develop, produce and deliver as many safe and effective vaccines doses as possible in a timely manner to meet public health expectations and to respond to government's requests.
Anticipated and simplified packaging and labelling regulatory process could save 6 to 8 weeks for dose availability.

Early availability of the vaccine doses to vaccinate the target population is crucial to fight against the disease and to have better chances to smoothen/delay the pandemic peak.

A universal packaging and labelling would be an approach to be considered to reduce the timelines and increase the supply chain flexibility in and outside Europe meaning a simplified labelling content for outer packaging, labels and the package leaflet (shortened package leaflet based on a “Specific QRD template for pandemic vaccines”) for which an early approval by EU authorities would be granted.

**Take home messages:**

- Lessons learnt after the 2009 pandemic lead to the identification of several possibilities of tackling the issue of packaging in a more common approach.
- Anticipated and simplified packaging and labelling regulatory process could save 6 to 8 weeks for dose availability.

## 9. Liability issues

### 9.1. The lessons learnt from the H1N1 pandemic

Herta Adam, Deputy Head of Health Threats Unit, DG SANTE, informed on the lessons learnt from the H1N1 pandemic in respect of liability issues.

She informed that in case of a pandemic vaccine, the issue of liability/responsibility and the way the risks are covered can have a significant impact on the conditions under which a contract is signed.

As regards the question of liability there are three levels of liability/risk in case of a pandemic vaccine:

1. the risk related to manufacturing of the product → to be covered by the producers who are in charge of the implementation of Good Manufacturing Practices;

2. the risk related to the implementation of a mass vaccination campaign taking into account that the number of people to be vaccinated in such circumstances is much higher than in normal vaccination instances (ex. the risk related to the management of the cold-chain by public health authorities, the organisation of vaccination clinics) → to be covered by the public health authorities organizing such a campaign;

3. the risk related to the use of the product (i.e. the risk that the vaccine will not demonstrate sufficient efficacy and safety or that it will generate unexpected adverse side effects)
There is no pre-defined solution that could be implemented in all cases. This significant and sensitive issue needs to be tackled taking into account the particularities of each Member State’s situation.

The risk linked to the potential occurrence of unexpected adverse side effects is much more difficult to assess and to mitigate.

In 2009 the insurance industry refused to insure the product risk related to H1N1 vaccine, as this risk could not be quantified and therefore became uninsurable.

In the EU, the full risk was covered by the governments that purchased pandemic vaccines. After the end of the pandemic, several public assessments of the response to the pandemic concluded that this could not be considered optimal and that there is a need for industry to take full responsibility for adverse side effects of pandemic vaccines in the future.

Medical countermeasures such as vaccines that are given to healthy people are held to higher standards of safety than treatments given to people who are sick.

The current public health attitude requires that pharmaceutical companies demonstrate the absence of rare to very rare side effects before any vaccine is authorized.

Obtaining a proof of absence of side effects is impossible in the timeframe required for useful immunization. The absence of rare to very rare side effects can only be demonstrated by large clinical trials and in normal cases this is achieved by large trials and a post-marketing pharmacovigilance system.

However, in a pandemic situation there is no time to conduct large trials nor to get results from a post-marketing pharmacovigilance system.

9.2. Narcolepsy

Kari Johansen from the European Centre for Disease Prevention and Control gave the state of play on the issue of the narcolepsy after the 2009 H1N1 pandemic.

She informed that in advance of vaccination campaigns among many activities EMA defined adverse events of special interest (AESI)\textsuperscript{11} while ECDC requested their newly formed vaccine safety network VAESCO able to conduct studies to investigate background incidence for the possible AESIs including Guillain-Barré syndrome.

It was recalled that as in August 2010 the cases of narcolepsy were reported in vaccinated children in Sweden and Finland. Than EMA reviewed data and concluded that "available evidence insufficient …further studies necessary". Vaccine Adverse Event Surveillance and Communication\textsuperscript{12} developed case definition and submitted study protocol. In parallel, national initiatives were conducted. Soon Finland reported 9-fold increased risk while Sweden reported 4-fold increased risk. VAESCO confirmed signal in Finland and Sweden. In July 2011 EMA recommended restricted use of Pandemrix in persons under 20 years of age. However, overall benefit-risk remains positive.

\textsuperscript{11} Neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell’s palsy, demyelinating disorders, laboratory-confirmed vaccination failure.

\textsuperscript{12} \url{http://vaesco.net/vaesco.html}
Kari Johansen described the symptoms of narcolepsy disease that are: disabling chronic sleep disorder, excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, disrupted nocturnal sleep, insidious onset, commonly long time between onset and diagnosis and genetically susceptible individuals - strong association with HLA haplotype DQB1*0602.

She concluded summarizing the lessons learned from the H1N1 pandemic underlying the need for routine monitoring of vaccine programmes and the products used. She also pointed out that in case of unexpected safety signal arises several stakeholders are needed (ex. manufacturers responsible for respective product, regulatory agencies responsible for authorisation, public health responsible for the programmes). However, it is important to distinguish and agree on roles and responsibilities, to have proper SOPs in place for signal detection / signal verification for hypothesis generation / epidemiologic study for hypothesis testing / funding.

She also drew attention to the fact that compensation for narcolepsy varies significantly from countries with organised schemes to countries where each family has to file complaint in court.

Sari Ekholm, Senior Medical Officer, Finland Ministry of Health, informed on the Finnish experience and response to narcolepsy after the 2009 H1N1 pandemic.

The Finnish Pharmaceutical Insurance Pool has received 258 claims for narcolepsy since 2009-2010 following the vaccination done with Pandemrix.

The compensation is paid by the Insurance Pool to 216 individuals. To this date around 4-5 million were paid. There are still 21 pending decisions.

9.3. Manufacturers of influenza pandemic vaccines and liability

Magdalena R. de Azero, Vaccines Europe Executive Director, presented the views of the vaccine manufacturers regarding liability in case of pandemics. She explained that in the case of an influenza pandemic stakeholders across all sectors are pressured to urgently develop and authorise a pandemic vaccine to immunise a large part of the population as quickly as possible and that the mass vaccination programs are likely to involve populations across different ages, some with underlying medical conditions, within very short timelines.

The speed and conditions under which a pandemic vaccine is developed, authorised, and administered differ from the interpandemic period posing greater challenges. Therefore, in such circumstances all stakeholders need to work together and jointly in order to achieve the intended public health goals.

M. Azero explained in more detail what are some of the challenges that could be faced in a pandemic situation. For example, she mentioned that the pharmacovigilance systems might not be able to detect a safety signal quickly:

- in case of certain adverse events, regulatory authorities may not have enough time to revise the vaccine’s use and implement any risk minimisation strategies;
• adverse event reporting may be suboptimal given the likely limited number of HCPs available during a pandemic;

In addition, potential incorrect vaccine administration by insufficiently trained personnel (either due to illness among HCPs or unprecedented demand for vaccine) may occur leading to potential misuse such as dosing errors and a risk of different vaccines being injected to the same vaccine with no patient documentation.

Potential local storage challenges can also be faced in emergency circumstances.

M. Azero stated that all of the above make the pandemic influenza vaccine exposure to liability different from normally marketed vaccines.

She explained that industry positions are not monolithic and risk may be approached by different manufacturers in different ways as well as change over time. However, individual manufacturers may not be prepared to assume all risks. It is crucial to look at other models around the world as government acceptance for liability for use of pandemic vaccines has been widely accepted by national and supranational authorities, such as the WHO and the USA. She also underlined that to preserve options for the procurement of pandemic vaccines or other emergency countermeasures a flexible approach is important.

Finally, she stated that companies are open to working on a legal frame for public health emergency situations and to discuss how this can be implemented in the case of Joint Procurement, taking into account such stated need for a flexible approach.

9.4. Liability issues – situation in Europe

M. Zwozdziak-Carbonne, Assistant to the Director of Directorate C – Public Health, DG SANTE, provided an overview of the main rules which are relevant for medicinal products under EU law reminding that in order to correctly assess the applicable provisions, it is important to establish when and where an incident takes place that may lead to potential liability claims. For investigational medicinal products, which are used in the context of a clinical trial, different rules apply compared to authorised products. Likewise for authorised products, it is important to establish whether the concerned product is authorised in the EU and whether the events take place inside or outside the EU.

According to the current applicable rules on clinical trials (Directive 2001/20/EC) a clinical trial may be undertaken only if “provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor” (Article 3(2) of Directive 2001/20/EC). Hence, that Directive introduced for clinical trials conducted in the EU an obligatory insurance/indemnity.
For the post-authorisation phase the EU pharmaceutical legislation, i.e. Directive 2001/83 and Regulation 726/2004 do not contain any general sector specific provisions regarding liability.

Article 25 of Directive 2001/83/EC states that the granting of a marketing authorisation for medicinal products shall not affect the civil or criminal liability of the manufacturer and, where applicable, of the holder of the marketing authorisation. Reference is further made to Directive 85/374/EEC, which harmonises the applicable provisions in Member States concerning the liability for defective products.

Directive 85/374/EEC is a piece of consumer protection law, which imposes strict liability in respect of defective products subject to certain defences. Those rules are in principle applicable to medicinal products, too, provided that the product can be shown to be ‘defective’. This being said, the Directive also contains a grandfather clause, which allowed Member States to maintain special liability systems, which were in existence prior to the adoption of the product liability directive. For that reason, some Member States have specific liability schemes for medicinal products, which differ from those of Directive 85/374/EEC.

M. Zwozdziak-Carbonne underlined that liability claims under civil law may not only be based on national consumer protection law. Claims may also arise as a cause of action in the tort of negligence or for breach of warranty in contract. Those further possibilities depend on national law.

According to Article 5(3) of Directive 2001/83/EC Member States shall lay down provisions in order to ensure that marketing authorisation holders are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product otherwise than for the authorised indications or from the use of an unauthorised medicinal product, when such use is recommended or required by a competent authority in response to serious and major public health threat.

Health policy, as well as the organisation and delivery of healthcare, is a Member State’s competence under Article 168 of the Treaty on the Functioning of the European Union. As such, injury compensation schemes are not a matter of EU competence.

She added that the above provisions under EU or national law are normally not applicable to events that take place in third countries. It would be for any claimant to prove that a national or EU court has nevertheless exceptionally jurisdiction in the specific case.

9.5. US way of tackling the issue of liability for adverse side effects

Maria Julia Marinissen, Director of the Division of International Health Security in the Office of the Assistant Secretary for Preparedness and Response (ASPR) from the U.S. Department of Health and Human Services, described the example of US way of tackling the issue of liability for adverse side effects.

She pointed out that drug and vaccine development is an expensive, high risk undertaking. The priorities of the private capital markets, instead of the priorities of government, tend to drive the development of pharmaceuticals.
Historically, it is not unusual for a manufacturer of emergency medical countermeasures to find that, under ordinary tort law and liability models, developing, manufacturing, and deploying a product is far more economically risky than the potential economic gain from the sale of the product. Therefore, in cases where the governmental national security and public health interest in availability of emergency medical countermeasures is sufficiently high, liability protections and compensation models have been considered to reduce risk for manufacturers and to compensate those that might be injured as result of the administration or use of medical countermeasures.

She underlined that in the context of administration of medical countermeasures during a public health emergency, liability protections for potentially liable entities (e.g., vaccine manufacturers, donor countries, etc.) may be implemented as “indemnification” and/or “immunity”.

M. Marinissen developed on the immunity approach introducing The Public Readiness and Emergency Preparedness Act (The U.S. PREP Act) that provides liability immunity in US courts related to the manufacture, testing, development, distribution, administration and use of medical countermeasures against chemical, biological, radiological and nuclear agents of terrorism, epidemics, and pandemics.

The legislation also authorized the establishment of a program to compensate eligible individuals who suffer injuries from administration or use of products covered by the PREP Act’s immunity provisions.

Immunity means that courts must dismiss claims brought against any entity or individual covered by the PREP Act.

Under a PREP Act Declaration the immunity may be afforded to manufacturers and distributors of countermeasures, program planners, (i.e., individuals and entities involved in planning, administering, or supervising programs for distribution of a countermeasure), qualified persons (i.e., persons who prescribe, administer, or dispense countermeasures such as healthcare and other providers), officials, agents, and employees of any of these entities or persons; and the United States.

In the US the countermeasures that may be covered by immunity from liability are:

- a qualified pandemic or epidemic product;
- a security countermeasure;
- an unapproved drug, biological product, or device used under an Emergency Use Authorization (EUA) issued by FDA;
- an approved drug, biological product, or device used pursuant to Federal law in conditions that are in consistent with its approval; or

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13 Claimants can initiate legal claims for loss or damage in a jurisdiction against liable entities (e.g. manufacturers, etc.). If a court determines that the liable entities owe the claimants, those liable entities pay the claimants for loss or damage.

14 Potentially liable entities are granted immunity by a particular jurisdiction (e.g. by the United States) and cannot be sued in that jurisdiction as specified under the terms of immunity (e.g., the law and implementing regulations/declarations).
• an unapproved drug, biological product, or device, or an approved drug, biological product, or device intended for an unapproved use, that is intended for emergency use and shipped and held by a government agency or someone working on that agency’s behalf for use only when that use is authorized.

In addition to liability protections, the PREP Act established the Countermeasures Injury Compensation Program (CICP) to provide compensation to eligible individuals for serious physical injuries or death directly caused by the administration or use of countermeasures identified in declarations issued by the Secretary of Health and Human Services.

If an individual qualifies for CICP\(^\text{15}\) benefits, that person may be compensated for:

- medical expenses (unreimbursed/out-of-pocket medical expenses that are reasonable and necessary to diagnose or treat your covered injury and to diagnose, treat, or prevent its health complications);
- lost employment income; survivor death benefits.

M. Marinissen, recalled that since enactment in 2005, PREP Act Declarations have been issued for pandemic influenza vaccines, antivirals (Relenza®, Tamiflu®, Peramivir®), respiratory protection devices, respiratory support devices, and diagnostics; and all countermeasures against anthrax, smallpox, acute radiation syndrome, and botulinum toxin.

Moreover, PREP Act Declarations have served as an incentive to researchers and manufacturers to develop countermeasures that may be procured by the Biomedical Advanced Research and Development Authority (BARDA) for the Strategic National Stockpile (SNS).

Further, declarations for pandemic influenza countermeasures were relied on by manufacturers, States, localities, health care providers, and others to respond to the 2009 H1N1 influenza pandemic. In two lawsuits filed after the H1N1 influenza pandemic PREP Act protection was upheld by the court.

She mentioned that the HHS Secretary has made a declaration under the PREP Act to facilitate the development and availability of experimental Ebola vaccines and therapeutics. The declarations are intended to assist in the global effort to help combat the current epidemic in West Africa and help prevent future outbreaks there.

### 9.6. The impact of Ebola crisis so far on the issue of the liability for side effects

Dr Isis E. Pluut, from the Ebola vaccine deployment team at WHO presented the potential legal implications in terms of liability on the use of unlicensed or fully regulatory approved vaccines.

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\(^{15}\) The CICP has paid claims arising from the H1N1 pandemic influenza response, largely for claims related to vaccination. The CICP has paid 21 claims for injuries from the 2009 H1N1 vaccine and one claim for injuries from the smallpox vaccine.
She reminded that following the Ebola outbreak in West Africa and once Ebola outbreak in West Africa was declared a Public Health Emergency, WHO called on the international vaccine community to accelerate development of high quality, safe and effective Ebola vaccines and they called for an international partnership to bring forward availability of high quality safety and immunogenicity data.

In principle, vaccine manufacturers and the National Regulatory Authorities (NRAs) should have in place mechanisms to indemnify adverse events/side effects derived from the clinical studies.

Ethics Review Committees, implementation of Informed Consent and insurance are the processes to be used to protect and cover participants in the clinical studies.

Once the vaccine has been tested, but not yet fully approved, given the emergency, NRAs and governments should judge the cost and benefits of the intervention with unlicensed vaccines and assume liability of their use.

Take home messages:

- EU has limited competence in the area of liability and the liability issues for use of a medicinal product are regulated by national law in all MS.
- The industry positions are not monolithic and risk may be approached by different manufacturers in different ways as well as change over time.
- The companies are open to working on a legal frame for public health emergency situations and to discuss how this can be implemented in the case of the Joint Procurement.
- Once the vaccine has been tested, but not yet fully approved, given the emergency, NRAs and governments should assess the cost and benefits of the intervention with unlicensed vaccines and ways to cover liability of their use.

10. THE SECURITY OF SUPPLY

Atika Abelin, Senior Director for Vaccination Policy and Advocacy from Sanofi Pasteur, described how governments can ensure proper security of supply of pandemic vaccines. She also addressed the role of preparedness/reservation fees in advance purchase agreements.

A. Abelin recalled that during an influenza pandemic, the primary responsibility of manufacturers will be to produce vaccines in a timely fashion and in order to fulfil this responsibility the industry must continue to invest in pandemic influenza preparedness studying new influenza viruses with pandemic potential as they emerge, establishing and maintaining pandemic surge capacity, ensuring pandemic readiness for critical supplies and components and maintaining market authorisation.

She underlined that the European Union is in a unique situation regarding influenza vaccination. Unlike several countries which are almost exclusively producing influenza
vaccines for their own population, the large European manufacturers produce most of the global influenza vaccine supply.

Further, considering that most of the world’s major influenza vaccine companies are located in Europe, EU procurement requests must consider manufacturers’ responsibility to other countries and WHO commitments (PIP SMTA2).

A. Abelin informed that much of the influenza manufacturing capacity remains Europe-based (48%) but it has declined over time (down from ~65% in 2008). Between 2009 - 2011 global capacity has grown significantly (60%), but the number of doses actually produced for 2011 - 2012 used less than half of actual capacity. Increased capacity is not matched by sustained demand.

Without uptake in National Immunisation Programmes (NIPs) and sustained demand, production capacity is at risk of shrinking to better fit with annual uptake with negative impact on pandemic preparedness. She recalled that during H1N1 there were 5 companies producing pandemic vaccines while in 2015 there are 3 companies producing pandemic vaccines in Europe.

Comprehensive global mechanism is needed as it is unclear who decides to switch from seasonal to pandemic influenza vaccine production.

A. Abelin also referred to the issue of preparedness fees stressing that securing supply requires continuous investment for an indeterminate period of time. She underlined that it refers to investment on three levels:

- vaccine development (studying new influenza viruses with pandemic potential as they emerge (pre-clinical and clinical trials), developing or acquiring adjuvants through licenses and monitoring product stability
- vaccine manufacturing (establishing pandemic surge capacity, maintaining trained staff skilled in areas of production not routinely used (increased resources), ensuring pandemic readiness for critical supplies and components (stockpiles, etc.), maintaining contingency plans for critical staff, supplies, and services
- vaccine distribution (establishing and maintaining readiness of emergency distribution capabilities, maintaining market authorisation, establishing rapid regulatory processes for registration of emergency vaccines).

**Take home messages:**

- Increased capacity is not matched by sustained demand. Without uptake in NIPs and sustained demand, production capacity is at risk of shrinking to better fit with annual uptake with negative impact on pandemic preparedness.

- It is unclear who decides to switch from seasonal to pandemic influenza vaccine production – a comprehensive global mechanism is needed.

- Securing supply requires continuous investment for an indeterminate period of time → the preparedness fees are critical to secure readiness.
11. THE SPECIFICITIES OF THE PANDEMIC VACCINE MARKET

Axel Lambert de Rouvroit, TDV Europe, provided information on the specificities of the pandemic vaccine market.

M. Lambert recalled that vaccine production economics are characterized by high fixed costs. A vaccine production factory needs to be activated in its entirety, regardless of the quantity of vaccine produced (even for one dose, hypothetically). This implies a fixed cost, independent of the number of vaccine produced, that include the cost of capital needed to build the factory, depreciation, etc.

He pointed out that capacity is one of the most important competitive advantages in the industry, for several (and interconnected) reasons. The first reason is the very high effect of economies of scale, which benefits large players by lowering their costs and constitutes an effective barrier to entry. The second reason is the use of capacity as a strategic weapon. In a capital-intensive industry with overcapacity, producing little-differentiated products (commodities), everyone is chasing volume and price wars erupt readily, even more so in the case of vaccines where buyers (governments) mostly use auction-type purchasing. The net effect has indeed been as predicted, with smaller players exiting the field (Crucell/J&J’s Inflexal V) or transferring assets to existing players aiming to reach a critical size (Novartis to bioCSL).

In a market in overcapacity and commoditized products, the only way for new entrants is to offer differentiated products that will command prices high enough to justify entry. New entrants cannot compete with the large firms because of the economies of scale described above. Therefore, their innovation strategies must address above all the production process, aiming to reduce the time between the selection of strains and the production of the first dose. Similarly, new production methods will disrupt the status quo if they do not require the large fixed-costs of traditional vaccine production, and even allow factories to be used under-capacity, therefore providing a crucial advantage in pandemic preparedness. This is where reverse-genetics, recombinant protein, plant production systems etc. will be developed.

M. Lambert concluded by stating that Member States considering joint procurement of pandemic vaccines must refrain from exerting price pressure if they recognize that current products are insufficient to solve the pandemic challenge, and that innovative solutions will only be developed if these can fetch a premium price.

12. THE IMPLEMENTATION OF WHO GUIDELINES FOR TRIGGERING A PANDEMIC AND ITS POTENTIAL IMPACT ON THE SWITCH FROM SEASONAL VACCINE PRODUCTION TO PANDEMIC VACCINE PRODUCTION

Jean-Luc Sion from DG SANTE briefly informed on behalf of Dr Wenqing Zhang Coordinator a.i. Global Influenza Programme and Pandemic Influenza Preparedness Framework Pandemic and Epidemic Department of WHO, on the on-going thinking about the implementation of WHO guidelines for triggering a pandemic and its potential impact on the switch from seasonal vaccine production to pandemic vaccine production.
M. Sion pointed out that among all pandemic response measures, influenza pandemic vaccine response is critical, and complicated. One of many factors is that same facilities being used for seasonal vaccines will be used for pandemic vaccines.

WHO since last year started interactions informally with countries and industries to better understand the issue and best way forward, for example a meeting with two Advisory Groups of WHO took place in April 2015 as side meeting of the Pandemic Influenza Preparedness General Assembly meeting with International Federation of Pharmaceutical Manufacturers and Associations. Issues discussed included the pandemic vaccine switch.

The first informal consultation with stakeholders took place at the end of June in Geneva. Based on the outcome of the first consultation, a second meeting at policy level is envisioned.

The first consultation is planned to analyse the “complexities” of vaccine response during the period around the start of a pandemic, via scenarios. Corresponding operational processes of response to various scenarios, when/who/what/how, will be developed. For the meeting, expert representatives of industries, national policy makers, Global Influenza Surveillance and Response System, regulatory agencies, and experts on Risk Assessment etc. will be invited.

It was underlined that while all issues will have to be discussed in the consultation, the cross-linkage of agreements/frameworks is well acknowledged, and issues like large-scale production of pandemic vaccines shall be coordinated globally.

Bruce Gellin MD, MPH, Deputy Assistant Secretary for Health and Director, National Vaccine Program Office of the US Department of Health and Human Services, informed on on-going reflections on the implementation of WHO guidelines for triggering a pandemic and its potential impact on the switch from seasonal vaccine production to pandemic vaccine production.

Dr. Gellin referred to the 2013 Pandemic Influenza Risk Management WHO Interim Guidance that introduces a risk based approach to pandemic influenza risk management and encourages member states to develop flexible plans, based on national risk assessment, taking into account the global risk assessment conducted by WHO.

Dr. Gellin noted that prior planning for vaccine production was based on a pandemic declaration (WHO Phase 6) however with the emphasis on national responses to national risk assessments, the trigger for vaccine manufacturers to stop seasonal influenza vaccine production and switch to pandemic vaccine production is unclear.

Following consultations with influenza vaccine manufacturers few conclusions were drawn:

- pandemic vaccine will be made by the same companies in the same facilities as seasonal vaccine, both can’t be accomplished maximally

- manufacturers are unclear about how they will respond to requests for pandemic vaccines against advance purchase agreements especially when the countries and/or regions with large orders request pandemic vaccine, knowing that this is a call for seasonal vaccination to stop.
• manufacturers are exposed to financial and reputational losses for non-delivery of seasonal vaccines, depending on the timing of the requests and the stage of seasonal vaccine production.

Dr. Gellin further noted that informed that as a next step WHO is organizing an informal stakeholder consultation at the end of June 2015 in order to analyse the “complexities” of vaccine response during the period around the start of a pandemic, via scenarios. He added that corresponding operational processes of response to various scenarios, when/who/what/how will be developed.

Take home messages:

• The Pandemic Influenza Risk Management WHO Interim Guidance can be used to inform and harmonize national and international pandemic preparedness and response.

• The guidance introduces a risk based approach to pandemic influenza risk management and encourages member states to develop flexible plans, based on national risk assessment, taking into account the global risk assessment conducted by WHO.

• Further work is being conducted by WHO to better understand the issue of triggering the switch between seasonal and pandemic vaccine production.

13. THE NEXT STEPS

• The Member States will be asked to designate its representatives to the Specific Procurement Procedure Steering Committee for pandemic vaccines as well as to provide their updated needs analysis.

• Several issues related to the procurement of pandemic vaccines for which decisions must be taken by the Member States before the call for tender can be published will be further discussed and followed (types of vaccines, type of procedure, regulatory aspects related to the type of approval of the vaccines to be procured, packaging, liability for side effects; preparedness fee, key performance indicators, security of supply, triggering of the switch from seasonal to pandemic vaccine production).

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16 WHO Informal Consultation on Influenza Vaccine Response during the Start of a Pandemic was held on 29 June – 1 July 2015 in Geneva.