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Regulatory process for the authorisation of antiviral medicines and vaccines in the protection against Pandemic Influenza (H1N1) 2009

Accompanying document to the

**COMMUNICATION FROM THE COMMISSION TO THE COUNCIL,
THE EUROPEAN PARLIAMENT AND THE EUROPEAN ECONOMIC AND
SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS**

Pandemic Influenza A (H1N1) 2009

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EXECUTIVE SUMMARY AND CONCLUSIONS

On 11 June 2009 the WHO declared the influenza pandemic. Moreover the Strategic Advisory Group of Experts (SAGE) of the WHO recommended that healthcare workers should be vaccinated as a first priority to protect the essential health infrastructure. SAGE suggested the following order of priority encompassing the whole population: pregnant women, those aged above 6 months with one or several chronic medical conditions, healthy young adults of 15 to 49 years of age, healthy children, healthy adults of 50 to 64 years of age, and healthy adults of 65 years of age and above. WHO endorsed these recommendations on 11 July 2009.¹ The EU Member States are responsible for the definition and implementation of any strategy for vaccination, while both the EU and the Member States are carrying responsibilities for the authorisation of vaccines and for the needed pharmacovigilance. On this basis, Member States developed a shared approach for priority groups for vaccination, which was published on 25 August 2009.²

The EU has already started taken action to tackle the pandemic. While various anti-viral medicines received approval for marketing in the past and are available for treatment of pandemic influenza in the EU, new measures have been concentrated on an accelerated assessment of new applications for marketing authorisations of Influenza A (H1N1) vaccines and variations thereof. Both the European Medicines Agency (EMA) and Member States have received or are expecting applications for market authorisations and variations thereof. Community legislation provides for a sound legal framework to address the challenges of a pandemic influenza. For defined categories of medicinal products, such as vaccines manufactured using a biotechnological process, the central authorisation process for marketing is mandatory. The national authorisation procedure is applicable to all other procedures and under certain conditions there is a choice between the two procedures. On the basis of these provisions, swift scientific assessment of Influenza A (H1N1) 2009 vaccines by the EMA and a swift subsequent Commission Decision on the marketing authorisation will be ensured with the objective to have substantial amounts of safe vaccines available across the EU 27.

Moreover, Community legislation has specific legal provisions in the case of a declared pandemic influenza. The Commission has underpinned legislation by regulatory guidelines and the EMA has, through its scientific committees, adopted scientific guidelines including guidelines for pandemic vaccines. Specifically designed processes for the scientific evaluation of a variation of pandemic vaccines are intended to allow for best possible planning reliability in the case companies intend to start early production. In addition, the EMA is in close contact on an exchange and sharing of strategies for drug development, assessment and scientific information with major international partners, with which a confidentiality agreement exists (US, Canada, Japan).

Scientific assessment of the risk-benefit balance of any vaccine to be authorised for the protection against Influenza A (H1N1) 2009 will be important on the basis of available data in the current pandemic situation. In any case depending on the evolvement of the real situation the EU has all means at its disposal to act as rapidly as needed. Equally important for public trust and confidence is pharmacovigilance. After an authorisation for marketing of vaccines

¹ http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090713/en/index.html

² http://ec.europa.eu/health/ph_threats/com/Influenza/docs/HSC_EWRS_statement_en.pdf

has been granted, companies will be subject to intensive pharmacovigilance monitoring and reporting obligations. When deemed necessary from a risk-benefit perspective, competent authorities will take the necessary actions with respect to the marketing authorisation granted. This may include, but is not limited to, a widening or a restriction of the scope of the marketing authorisation with respect to patient population, contraindications and posology amongst others.

The Commission will facilitate as much as possible cooperation and the exchange of information.

Cooperation with WHO is crucial. In order to develop vaccines against novel influenza, manufacturers depend on the isolation and supply of the relevant virus strains by the World Health Organization, which provided the Influenza A (H1N1) 2009 strains in May 2009. In addition, the WHO may proceed to issue specific recommendations for the development of this vaccine and on the continued production of seasonal vaccines.

Furthermore, after the declaration of the pandemic by WHO there are specific provisions which allow certain flexibility on the extent of data requirements to support a marketing authorisation application and variations thereof, and the subsequent timeframe for its regulatory assessment. In any case the risk-benefit assessment has to be positive for each vaccine.

1. TYPES OF MARKETING AUTHORISATIONS FOR MEDICINAL PRODUCTS

Anti-viral medication and vaccines are legally defined as medicinal products.³

In the EU, medicinal products and their variations are subject to authorisation for marketing either at a national level ("**national authorisation**") or at Community level, through Commission Decision, on the basis of a scientific opinion coordinated by the European Medicines Agency EMEA ("**central authorisation**"). The latter is mandatory, *inter alia*, when a biotechnological process such as reverse genetics techniques for the manufacturing of vaccines is involved. Otherwise, under certain conditions, the manufacturer is free to choose whether to go for national or Community authorisation. The challenge is to ensure that both routes are providing for efficient and fast solutions which respond to citizen's concerns.

2. AUTHORISED ANTIVIRAL MEDICATION IN THE EU TO ADDRESS THE NEW INFLUENZA

2.1. Authorised antiviral medicinal products

There are presently four antiviral drugs authorised and available for treatment and post-exposure prevention of influenza⁴ and these belong to two classes: adamantane (M2) inhibitors (Amantadine and Rimantadine) and neuraminidase inhibitors (Oseltamivir and Zanamivir).

The novel influenza viruses first detected in humans in Mexico were however found to be resistant to Amantadine and Rimantadine. Instead laboratory testing indicated that these viruses may be susceptible to Oseltamivir and Zanamivir.

³ Article 1 of Directive 2001/83/EC

⁴

Based on current information, the WHO evaluates that cases of resistance of Influenza A (H1N1) 2009 to neuraminidase inhibitors recently reported appear to be sporadic. At this time, there is no evidence to indicate the development of widespread antiviral resistance against neuraminidase inhibitors. Therefore, the WHO concluded that antiviral drugs remain a key component of the public health response when used as recommended.

2.2. Regulatory status of medicines containing Oseltamivir and Zanamivir

A medicinal product with the active substance **Oseltamivir** has been centrally authorised as **Tamiflu®** with a marketing authorisation valid since 20 June 2002. **Oseltamivir** is indicated in the treatment of influenza in patients one year of age and older who present with symptoms typical of influenza, when influenza virus is circulating in the Community. Oseltamivir is also indicated in post-exposure prevention in individuals one year of age or older. Oseltamivir is approved as hard capsules and powder for oral suspension.

A medicinal product with the active substance **Zanamivir** has been authorised nationally via the mutual recognition procedure as **Relenza®** since June 1999.⁵ Zanamivir is indicated for treatment of influenza in patients above 5 years of age who present with symptoms typical of influenza when influenza is circulating in the community. Zanamivir is also indicated for post-exposure prevention in individuals 5 years of age or older. Zanamivir is approved as oral inhalation powder administered through a diskhaler device.

2.3. Variation of Tamiflu® (Oseltamivir) and Relenza® (Zanamivir)

Tamiflu®

In May 2009, the European Commission approved a variation of the marketing authorisation for Tamiflu® concerning the shelf life extension from 5 to 7 years on the basis of a scientific opinion by the CHMP.

In addition, on 31 July 2009, the Committee for Medicinal Products for Human Use (CHMP)⁶ adopted scientific recommendations to vary the marketing authorisation for Tamiflu® with an update of the Summary of Product Characteristics (SPC) and the package leaflet:⁷

- For children aged from 6-12 months, the CHMP has concluded that during an influenza pandemic the benefits of the use of Tamiflu® outweigh the risks and recommended the extension of the currently approved indication to include this age group while providing specific dosing recommendations.
- For pregnant and breastfeeding women, the CHMP recommended the use of Tamiflu® for treatment and post-exposure prophylaxis.

The European Commission is currently evaluating these scientific recommendations in order to decide on the variation of the relevant marketing authorisation.

⁵ Relenza® has been authorised via Mutual Recognition Procedure in all Member States except Romania and Bulgaria.

⁶ **CHMP**: Scientific Committee of the European Medicines Agency (EMA) responsible for adopting a scientific opinion on the evaluation of an application for a **central** marketing authorisation and variations thereof.

⁷ <http://www.emea.europa.eu/htms/human/pandemicinfluenza/novelflu.htm#Updateon31July2009>

Relenza®

In May 2009, a variation to extend the shelf life of Relenza® from 5 to 7 years was approved by Member States via Mutual Recognition Procedure. This approval needs to be followed by a formal decision by each Member State, in which Relenza® has been authorised. This process is still ongoing.

In addition to scientific opinions in preparation of a variation the CHMP and the Coordination Group for Mutual Recognition and Decentralised Procedures – Human CMD(h)⁸ adopted scientific recommendations for Tamiflu® and Relenza® respectively. For details see Annex 1.

3. REGULATORY PROCEDURE FOR THE AUTHORISATION OF VACCINES IN THE EU

Special features of Influenza vaccines are described in Annex 2.

The EU is working on several possibilities to tackle the H1N1 Influenza on the basis of the development of new vaccines, further development of mock up vaccines or variations of mock up vaccines.

3.1. New vaccines

The procedure for assessing an application and preparing a marketing authorisation of a new vaccine is subject to legal timelines: **210 days** both for **national and central authorisations**⁹ covering the scientific assessment of comprehensive data for quality, safety and efficacy¹⁰. For those applications for a **central authorisation**, which are of major interest from the point of view of public health, this process can be further accelerated and the period reduced to **150 days**. Furthermore, competent authorities may decide, on a case-by-case basis, to accelerate their assessment and approval procedures depending on the urgency compared to the legal timelines.¹¹

In **exceptional circumstances** and for objective, verifiable reasons, a **central authorisation** may be granted subject to certain requirements, e.g. specific procedures concerning the safety

⁸ **CMD(h)**: Scientific Committee of the Member States tasked with the preparation and adoption of a scientific opinion on the evaluation of an application for a **national** marketing authorisation and variations thereof.

⁹ Article 17 of Directive 2001/83/EC; Article 6 (3) and 14 (9) of Regulation (EC) 726/2004

¹⁰ **Quality** is defined by the inherent product characteristics (e.g. nature of the active ingredient, manufacturing process, results of analytical testing, formulation, dosage form, stability, level of impurities); **efficacy** relates to the clinical effects of a medicinal product – specifically for vaccines it relates to the ability of inducing an immune response (**immunogenicity**); **safety** relates to any adverse reactions.

¹¹ Note: For **national procedures** Member States have to ensure that the procedure for granting the marketing authorisation is completed within a maximum of 210 days after submission of a valid application. For **central authorisations** the CHMP is obliged to provide its scientific opinion within 210 (or 150) days. In preparation of a Commission Decision with reference to the Comitology procedure (Decision 1999/468/EC) the European Commission submits the draft opinion for a vote to the Standing Committee representing Member States. The vote is followed by a *droit de regard* of one month by the European Parliament; specific arrangements are being agreed with the newly elected Parliament, on the basis of the Inter-institutional agreement between the Parliament and the Commission on procedures for implementing the Council decision 1999/468/EC [to reduce this period for reasons of public health](#)

of the medicinal product, notification to the competent authorities of any incident relating to its use and action to be taken. Continuation of the authorisation is linked to an annual reassessment of these conditions.¹²

For medicinal products used in emergency situations in response to public health threats, duly recognised either by the WHO or the Community (including the declaration of a pandemic), a **central conditional marketing authorisation**¹³ may be granted when there is sufficient proof of a positive risk-benefit balance on the basis of less comprehensive data for the safety and efficacy compared to a regular authorisation and when unmet medical needs will need to be fulfilled. Conditional marketing authorisations are made subject to specific obligations. They have a limited validity of one year and can be renewed. Furthermore, the applicant must provide comprehensive additional data and may be subject to specific obligations for collecting data on pharmacovigilance.

For such emergency situations such as the pandemic influenza a "rolling review procedure" has been developed to accelerate the review of any applications received. This means that during the phase of data development the company exchanges scientific data with the EMEA, as soon as available.

The procedures for application by companies and assessment by competent authorities are underpinned by specific technical guidelines developed by the EMEA, also covering the special aspects related to pandemic vaccines.¹⁴

In addition, it is possible to submit a new vaccine for a **national authorisation** by Member States who may also apply accelerated review timetables to speed up availability of authorised vaccines.

3.2. Authorised vaccines (under exceptional circumstances)

To date, the Commission has centrally authorised **one non-adjuvanted** and **three adjuvanted monovalent** influenza vaccines as pandemic *mock-up* dossiers under exceptional circumstances.¹⁵ These vaccines have been authorised for the prophylaxis of an influenza in an officially declared pandemic situation.

The adjuvant enhances the immunogenic effect of a vaccine and thereby allows a reduction in the amount of virus antigen in a given dose. This has an impact on the number of doses which can be produced with a defined amount of virus-antigen.

The intention of the mock-up concept is to have an approved model which can be swiftly changed to include the actual influenza virus strain identified for the pandemic and provided by the WHO. A pandemic vaccine can only be marketed in the case of a declared pandemic by WHO or the Community.

¹² Article 14 (8) of Regulation 726/2004

¹³ Article 14 (7) of Regulation (EC) 726/2004; Commission Regulation (EC) 507/2006

¹⁴ <http://www.emea.europa.eu/htms/human/pandemicinfluenza/guidance.htm>

¹⁵ <http://www.emea.europa.eu/htms/human/pandemicinfluenza/vaccines.htm>;
<http://ec.europa.eu/enterprise/pharmaceuticals/register/alfregister.htm>

3.3. Variations of authorised vaccines

Any adjustment of existing vaccines to include the strains to the Influenza A (H1N1) 2009 will trigger a variation of the mock-up vaccine marketing authorisation. Legislation stipulates for accelerated procedures both for the variation of seasonal vaccines and for the variation of vaccines in a pandemic situation.

A regular procedure for major variations takes **approximately 100 days**.¹⁶ Building on the experience of previous seasons, a typical variation for seasonal vaccines following the abbreviated scientific and regulatory assessment procedure may be started on the basis of *quality* data. However, the applicant is obliged to submit clinical data for the *immunogenicity*¹⁷ and *safety* during and before completion of the process. The procedure takes **approximately 70 days**.¹⁸

This procedure may exceptionally and temporarily be further abbreviated in case of a pandemic situation recognised by the WHO or the Community, building on the basis of a significantly reduced package of data. These specific provisions for variations of human influenza vaccines in a pandemic situation apply for centrally authorised products and for nationally authorised products via MRP and DCP procedure (see chapter 1). Its application for purely national variation procedures is at the discretion of the Member States.¹⁹ Such variation procedures normally address changes to the virus strains included in the vaccine, as with the exception of the virus strain the formulation would remain the same as for the mock-up. Subsequently, competent authorities may exceptionally and temporarily **consider the variation accepted after receipt of the application** before the full procedure of scientific and regulatory assessment has been completed. This concept builds on the fact that pandemic mock-up vaccines have been authorised on the basis of a certain amount of *quality* and clinical data for *safety* and *immunogenicity* of the proposed formulation of the mock-up vaccine. Therefore, to expedite the process compared to a variation of a seasonal vaccine, additional comprehensive clinical safety and efficacy data from adults and children can be submitted after the variation has been authorised by the competent authority. Changes to the formulation and inclusion of adjuvants to such vaccines would go beyond these specific variation procedures and be considered a major variation requiring additional scientific data to support the change.

In addition, in the event of declared pandemic competent authorities strive to speed up processes significantly and utilise various accelerated regulatory options available for the development of a vaccine.

3.4. Specific considerations for specific population groups

The overall risk-benefit balance of any vaccine authorised for protection against Influenza A (H1N1) 2009 and any variation to an authorised mock-up vaccine has to be positive. Taking the above mentioned priorities into account, there is the need for a careful scientific assessment on risks and benefits for defined special population groups for all vaccines. The

¹⁶ Type II variation as defined in Commission Regulation 1084/2003 and 1085/2003

¹⁷ **Immunogenicity** is the ability to provoke an immune response and is a **key criterion for the efficacy** of a vaccine.

¹⁸ Article 7 of Commission Regulation (EC) 1084/2003 and of Commission Regulation 1085/2003

¹⁹ Article 8 of Commission Regulation (EC) 1084/2003 and of Commission Regulation 1085/2003

outcome of this assessment should be reflected in the Summary of Product Characteristics (SPC) which is part of the authorisation of each vaccine.

Should new data be generated over time, the SPC may be further limited or widened through further variations. These principles are in line with the objectives and provisions of the Paediatric Regulation.²⁰

Based on the Community paediatric legislation the EMEA has developed principles for a harmonised approach to be applied for the development of Paediatric Investigation Plans (PIP) outlining the generation of scientific data for use of a Influenza A (H1N1) Vaccine in the paediatric population during a pandemic.²¹ Each PIP is subject to a scientific assessment by the Paediatric Committee and a decision by the EMEA.²² This should help national authorities when recommending or using vaccines notably for children

3.5. Specific legal provisions for the distribution by Member States

As a general rule, marketing authorisation holders are subject to liability for the use of their products as long as they are used within the terms of the marketing authorisation.

Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents. This encompasses pandemic situations, such as the Influenza A (H1N1) 2009 pandemic. In such a case marketing authorisation holders, manufacturers and health professionals are not subject to civil or administrative liability for any consequences resulting from the use of a vaccine when such use of an unauthorised vaccine is recommended or required by a competent authority in response to the pandemic situation. This also applies when the use of an authorised medicinal product, such as an antiviral medicine and a vaccine, is recommended beyond authorised conditions (e.g. indications, age groups). These provisions apply independently whether a national or Community authorisation has been granted.²³

4. ACCELERATED PROCEDURES FOR THE INFLUENZA A (H1N1) VACCINES)

4.1. Authorisation and variation of vaccines

In a situation, where the disease continues to evolve, the outcome of the assessment and the date of authorisation of Influenza A (H1N1) vaccines is currently difficult to predict. For the time being, any timelines must be considered indicative.

Several mutually non-exclusive **options** for national and central authorisations exist to allow a scientific development of a monovalent vaccine²⁴ against Influenza A (H1N1) 2009 according to the pandemic situation and subsequent regulatory approval. Regardless whether national or Community authorisation is chosen, it is important to ensure the efficient use of limited manufacturing capacities inside and outside the EU and for flexibility to assign batches according to the specific needs in various Member States.

²⁰ Regulation 1901/2006

²¹ <http://www.emea.europa.eu/pdfs/human/paediatrics/40577909en.pdf>

²² Regulation 1901/2006

²³ Article 5 of Directive 2001/83/EC

²⁴ monovalent vaccine – vaccine against one virus strain

A **variation of centrally authorised mock-up dossiers** is expected to allow fast assessment and authorisation and subsequent availability of vaccines for the market. Currently, it is expected that the majority of quality data considered key for preparing a scientific opinion on the variation of such mock-up vaccines will be available from September 2009 onwards allowing a Commission Decision on the variation to the terms of the marketing authorisation shortly thereafter.²⁵

The development of relevant data by interested companies and the scientific assessment for a **new vaccine** is more comprehensive. Therefore, in the case of applications for central authorisations it is expected that the scientific assessment will take longer. The Commission will swiftly take a Decision on the marketing authorisation after adoption of a scientific opinion. In the case of a national authorisation it is up to Member States to decide on the acceleration of the regular procedure.

Specific information is detailed in Annex 3 on the application of an accelerated procedure:

- (1) for the **variation** of centrally authorized **pandemic mock-up** dossiers for a strain update,
- (2) for a central **conditional marketing authorisation** in emergency situations
- (3) for the national authorisation of **new vaccines**

4.2. Official Control Authority Batch Release (OCABR)

On the basis of Community provisions and in the interest of public health Member States have put in place a system according to which Official Medicinal Control Laboratories (OMCLs) examine batches of specific medicinal products before the competent authority will allow those batches to be released onto the market (Official Control Authority Batch Release) after a medicinal product has been authorised. The examination is intended to determine the conformity of a batch with the approved specifications as laid down in the marketing authorisation.²⁶ This system also applies to immunological medicinal products used in public health immunisation programmes, such as against Influenza A (H1N1) 2009 independently whether they have been authorised centrally or at a national level.²⁷ Through this system it is intended to verify whether the quality control testing of the manufacturer is capable of ensuring the quality of the product. It may also serve to objective to evaluate the robustness of the manufacturing process, including quality control.

In the case of vaccines against Influenza A (H1N1) 2009 OMCLs of the Member States strive to accelerate the process of the above mentioned Official Control Authority Batch Release and to complete it coincidentally with the authorisation for marketing.

²⁵ <http://www.emea.europa.eu/pdfs/human/press/pr/46856809en.pdf>

²⁶ It covers at least the assessment of documents, including control reports by the qualified person, and may also include a re-testing by Official Medicinal Control Laboratories established by the Member States. Medicinal Products perform the re-testing in line with procedures and guidelines published by the European Directorate for the Quality of Medicines (EDQM); (http://www.edqm.eu/en/Human_Biologicals_OCABR-611.html)

²⁷ Article 112-114 of Directive 2001/83/EC

5. PHARMACOVIGILANCE

The European Union has in place a comprehensive and effective safety monitoring system for the reporting and assessment of the safety and efficacy of a medicinal product after it has been authorised.²⁸ These provisions sufficiently address the situation of pandemic influenza vaccines. In addition, the EMEA has published specific guidance.²⁹ As with all medicinal products for pandemic vaccines and anti-viral medicines, public confidence will depend on the proper functioning of the pharmacovigilance system in the EU.

When Member States launch an Influenza A (H1N1) vaccination campaign, it will be therefore essential to monitor closely any unexpected serious adverse reactions to allow the risk/benefit to be reassessed scientifically if necessary. Marketing authorisation holders are obliged to have procedures in place for adverse event reporting as part of their pharmacovigilance system. They may be required by competent authorities to propose additional pharmacovigilance activities. Marketing authorisation holders also have to submit Periodic Safety Update Reports (PSURs) documenting all adverse reactions including a scientific evaluation of the risk-benefit balance. In addition, the results of further post authorisation safety studies in adults and children will be systematically required. Close cooperation and the exchange of information between all competent authorities is therefore important.

In the case of centrally authorised pandemic vaccines, the CHMP has adopted scientific recommendations on the expected requirements which will be imposed on marketing authorisation holders as part of the marketing authorisation.³⁰ These include an earlier and more frequent submission of PSURs compared to the usual procedure. In addition, companies will be obliged to launch prospective epidemiological cohort studies for each authorised vaccine with a focus on safety and encompassing a minimum sample of 9000 subjects involving all age groups from 2 months up. For rare events, such as the Guillain-Barré syndrome³¹ marketing authorisation holders will be obliged to investigate the possibility of collecting data through participation of specialist centres or clinics.

If, after an assessment of these data and information, the view is taken that the risk-benefit balance of the vaccine is not positive under normal conditions of use, competent authorities are expected to suspend, revoke, withdraw or vary a marketing authorisation or prohibit the supply. These measures may also be taken for specific conditions of the authorisation, such as recommendations of use for specific age groups or patient populations.³²

Furthermore, the Commission will support studies on establishing a cross-border vaccine monitoring system for Influenza A (H1N1) vaccines based on a common protocol or the pooling of a critical set of validated data for rare and severe neurological adverse events from Member States. One of the expected deliverables is the development of a reliable methodology which can be routinely applied to the investigation of other rare adverse events.

²⁸ Title IX of Directive 2001/83/EC, Chapter 3 of Regulation 726/2004; Eudralex Volume 9 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm)

²⁹ <http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/35938109en.pdf>

³⁰ CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009); <http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/35938109en.pdf>

³¹ Guillain Barré Syndrome is a disorder in which the body's immune system attacks part of the peripheral nervous system. Vaccinations have been reported to trigger the syndrome.

³² Article 116 and 177 of Directive 2001/83/EC

For further details concerning legal and operational pharmacovigilance provisions see Annex 4.

6. COOPERATION WITH INTERNATIONAL PARTNERS

For the preparation of strategies for the assessment and authorisation of vaccines the European Commission and the EMEA are in close contact with the WHO and *via* the WHO also with other regulatory authorities worldwide.

Furthermore, the Commission and the EMEA concluded bilateral confidentiality arrangements with regulatory agencies of three third countries for the regulatory and scientific collaboration, in particular exchange of information between the parties as part of their regulatory and scientific processes, both before and after a medicine has been approved.³³ The exchange encompasses information related to applications for marketing authorisations, pharmacovigilance data and impending regulatory actions. Such arrangements have been concluded with the **US Food and Drug Administration (FDA)**, the Health Products and Food Branch of **Health Canada**, and for **Japan** with the Japanese Ministry of Health, Labour and Welfare (MHLW) and the Japanese Pharmaceuticals and Medicinal Devices Agency (PMDA).

In the current situation these arrangements are being used for an exchange of information and views concerning the scientific assessment and the regulatory procedure for the authorisation of vaccines against Influenza A (H1N1) 2009 and further close cooperation on this issue.

³³ <http://ec.europa.eu/enterprise/pharmaceuticals/international/intercoopbi.htm>

ANNEX 1: SCIENTIFIC RECOMMENDATIONS OF THE CHMP CONCERNING THE USE OF TAMIFLU® AND OF THE CMD(H) CONCERNING RELENZA®

(1) Scientific recommendations of the CHMP regarding the use of Tamiflu® and Relenza® in an influenza pandemic³⁴

As an early response to a potential health threat after the first cases of Influenza A (H1N1) 2009 have been reported the CHMP adopted scientific recommendations independently of any preparation for a variation of the marketing authorisation³⁵

In case of a pandemic influenza is declared by the WHO in the context of the Influenza A (H1N1) 2009 outbreak Tamiflu® may be used in children below one year of age under medical supervision. The recommendation also referenced to data suggesting that using Tamiflu® and Relenza® in pregnant and breast-feeding women may outweigh the risks in the context of an Influenza A (H1N1) 2009 in a pandemic situation. Finally, the CHMP recommended that boxes of Tamiflu® capsules should not be discarded where the expiry date has already passed and a further period of 2 years could be added to the stated expiry date when stored below 25°C.

(2) Scientific recommendations of the CMD(h) (Coordination Group for Mutual Recognition and Decentralised Procedures – Human) regarding the national distribution of Relenza® during influenza pandemic³⁶

In July 2009, the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)) concluded that a distribution of an additional device would be appropriate as a temporary measure during the Influenza A (H1N1) 2009 pandemic, considering limited production capacity of the approved diskhaler. Following this assessment it is now up to the national competent authorities to take a decision on temporary distribution in the absence of a specific authorisation of this additional device during the pandemic by making reference to specific legal provisions (see Section 3.5).

³⁴ <http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/32609509en.pdf>

³⁵ Article 5 (3) of Regulation 726/2004

³⁶ See the CMD(h) meeting report for more information:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/cmdh_pressreleases/2009_07.pdf

ANNEX 2: SPECIAL FEATURES OF INFLUENZA VACCINES

Influenza vaccines may be developed for the protection against seasonal influenza or for the protection against a pandemic with a specific influenza virus. For the protection in the case of an upcoming or recognised pandemic, two concepts have been developed in the European Union: pre-pandemic vaccines and pandemic "mock-up" vaccines. Currently, such vaccines have been approved against Influenza A (H5N1).

Vaccines may be monovalent or polyvalent, which means they may include antigens of one or several virus-types. While vaccines for seasonal influenza are typically polyvalent, existing concepts for vaccines for use in a (pre)-pandemic situation are currently based on a monovalent composition.

Two routes are possible for the manufacturing³⁷ of an influenza vaccine: a classical reassortant technique³⁸ and a biotechnological process involving a reverse genetics technique. Vaccines may be manufactured with or without an adjuvant.³⁹ The adjuvant enhances the immunogenic effect of a vaccine and thereby allows a reduction in the amount of virus antigen in a given dose. This has an impact on the number of doses which can be produced with a defined amount of virus-antigen.

³⁷ Using hen eggs or cells for the growth of the virus

³⁸ Reassortment: mixing of genetic material of viruses

³⁹ Adjuvants used include aluminium phosphate and hydrated aluminium hydroxide, MF 59, AS03

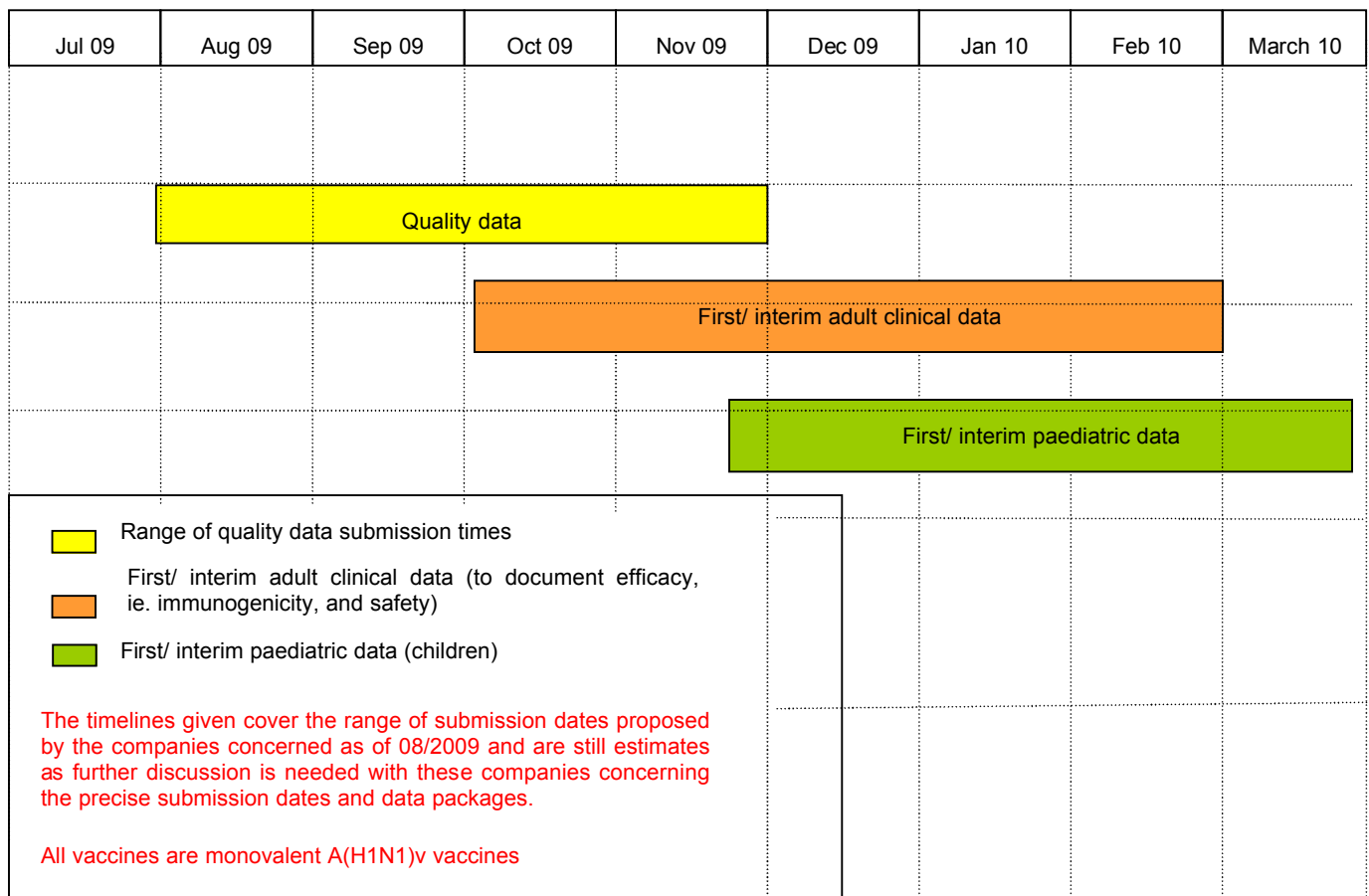
ANNEX 3: ACCELERATED PROCEDURES FOR THE AUTHORISATION AND VARIATION OF VACCINES

(1) Variation of centrally authorized pandemic mock-up dossiers for a strain update

As for the assessment of the variation of pandemic mock-up vaccines to include the actual pandemic virus strain, specific accelerated procedures can be applied. The evaluation of the CHMP, under which conditions a vaccine is expected to have a positive risk-benefit balance and the assessment of the benefit to public health of its immediate availability to fulfil unmet medical needs, will be of key importance. The Commission will act immediately and swiftly after receipt of a positive scientific opinion by the CHMP.

Currently, three companies foresee reference to this procedure. Marketing authorisation holders are expected to submit an application for such a variation on the basis of data generated within the following timelines:

ESTIMATED DATA AVAILABILITY FOR THREE MOCK-UP MAS *via* VARIATION



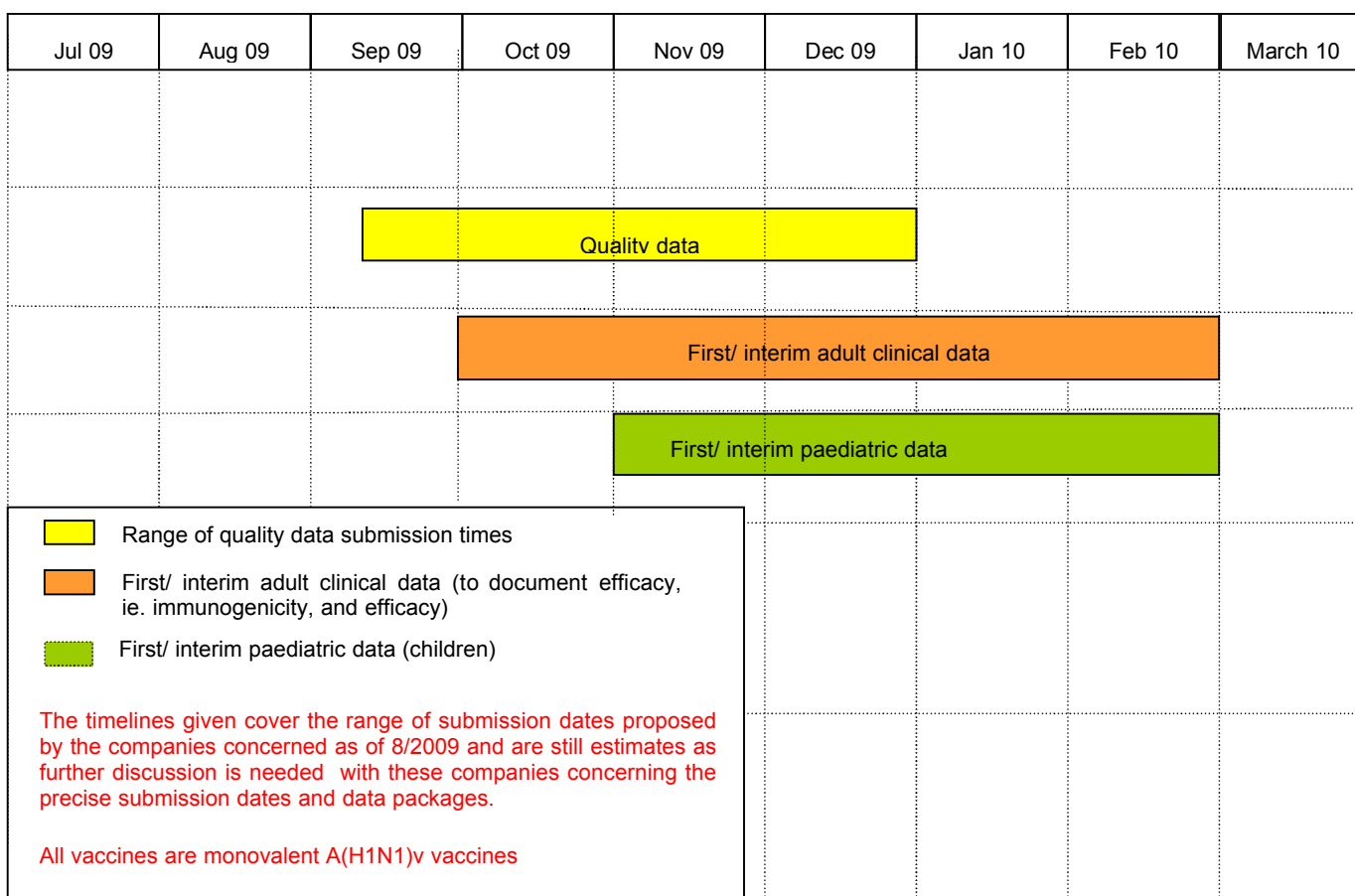
The extent of safety and efficacy data should correlate to the evolution of the influenza and pandemic situation, which will have to be taken into account throughout the process.

Currently, it is expected that the majority of quality data considered key by the CHMP for preparing a scientific opinion will be available from September 2009 onwards.⁴⁰ During the phase of data development the company exchanges scientific data with the EMEA to allow a "rolling review". Following this procedure, both EMEA and Commission – pending unforeseeable situations - strive to expedite their scientific and regulatory review processes compared to normal procedures: the EMEA estimates an accelerated formal variation review process of approximately 5 working days. This procedure will be followed by the formal process of authorisation through Commission Decision, for which the Commission estimates an expedited period of 10- 20 working days which is intended to be further reduced to a bare minimum.

(2) Central conditional marketing authorisation in emergency situations

This procedure will require a new marketing authorisation and therefore more data compared to the above mentioned variation procedure within the mock-up concept, thereby necessitating a more extensive scientific assessment. Currently, two companies foresee reference to this procedure. Marketing authorisation holders are expected to submit an application on the basis of data generated within the following timelines:

ESTIMATED DATA AVAILABILITY FOR TWO NEW CONDITIONAL MAAS



MAA: Market Authorisation Application

⁴⁰ <http://www.emea.europa.eu/pdfs/human/press/pr/46856809en.pdf>

The extent of clinical data required will correlate to the evolution of the influenza and the pandemic situation, which will have to be taken into account throughout the process. During the phase of data development the company exchanges scientific data with the EMEA to allow a "rolling review". Following this procedure, both EMEA and Commission - pending unforeseeable situations - strive to expedite their scientific and regulatory review processes compared to normal procedures: the EMEA estimates an accelerated formal review process of approximately one month. This procedure will be followed by the formal process of authorisation through Commission Decision. For this process, which involves application of the Comitology procedure and an adoption by the Standing Committee⁴¹, the Commission estimates an expedited period of 25- 40 working days followed by an additional review by the European Parliament of one month pending further arrangements after recent elections.⁴² This period is intended to be further reduced to a bare minimum. Use of this procedure will ensure the authorisation of marketing of vaccines in 27 Member States, which will also be recognised by the Members of the European Economic Area. Considering the need to adjust to any evolving situation these timelines are indicative.

(3) National authorisation of new vaccines

An application for such an authorisation is combined with the full data requirement for quality, safety and efficacy of the vaccine stipulating longer development and assessment times as compared to the other options. The legal timeline for the assessment follows the regular scheme of 210 days and may be reduced further upon the initiative of the national competent authority. Some companies have decided to submit a national application. It is at the discretion of the Member States to decide on any procedure to accelerate the assessment and authorisation process.

⁴¹ Articles 10, 35 of Regulation 726/2004, Decision 1999/468/EC

⁴² See footnote No. 21

ANNEX 4: DETAILED REQUIREMENTS FOR PHARMACOVIGILANCE

In detail, **Community legislation** includes specific pharmacovigilance obligations for marketing authorisation holders⁴³:

- to appoint a **qualified person** responsible for pharmacovigilance;
- to introduce and maintain a **pharmacovigilance plan** as part of the **risk management system**, which will be assessed as part of the evaluation of the application for a marketing authorisation and which could include specific obligations for pharmacovigilance reporting after application of Influenza A (H1N1) vaccines;
- to maintain **detailed records** of all suspected adverse reactions occurring either in the Community or in a third country;
- to promptly **report suspected serious adverse reactions**⁴⁴, to the competent authority or European Medicines Agency (EMA) (but no later than 15 days following the receipt of the information);
- to prepare and submit, to the competent authority or EMA **periodic safety update report (PSUR)**, documenting reports of all adverse reactions and including a scientific evaluation of the risk-benefit balance of the medicinal product, immediately upon request or at least every six months during the first two years following the initial placing on the market. Competent authorities will be allowed to request a PSUR any time when deemed necessary from a public health perspective. The timing of submission of the PSUR will be specified as a condition of the marketing authorisation or variation. Following EMA guidance for pandemic vaccines, the first report should be submitted on day 45 after approval and monthly thereafter for at least the first 6 months.
- to submit **complete clinical safety and efficacy (including immunogenicity) data**, including for the paediatric population, in the case of exceptional and temporary authorisation of a variation of a vaccine (in particular in the case of conditional marketing authorisations and varied mock-up pandemic influenza vaccines) on the basis of quality and limited clinical or safety data.⁴⁵ Clinical safety and efficacy are of the foremost importance in the case of the Influenza A (H1N1) vaccines, including information regarding population subgroups such as pregnant women and children.

for competent authorities⁴⁶:

- to ensure, by means of **repeated inspections**, compliance with the legal requirements;

⁴³ Title IX of Directive 2001/83/EC, Chapter 3 of Regulation 724/2006

⁴⁴ Serious adverse reaction: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/ birth defect.

⁴⁵ Regulation 1084/2003 and 1085/2003

⁴⁶ Title IX, Article 111 of Directive 2001/83/EC, Chapter 3 of Regulation 724/2006

- to make available through a **data-processing network** the reports of suspected serious adverse reactions to the agency and the Member States at the latest within 15 days after their notification;
- to assess the adverse reaction reports and PSURs and take appropriate measures;
- to exchange information and cooperate through the working groups of the EMEA on pharmacovigilance;
- to **suspend, revoke, withdraw or vary a marketing authorisation** and or to **prohibit the supply** of a medicinal product if the view is taken that the product is harmful or the risk-benefit balance is not positive under normal conditions of use or in the case of a lack of therapeutic efficacy; in such a case Member States are expected to inform each other, the EMEA and the Commission and to ensure appropriate coordination between Member States.

The **scientific Committee for Medicinal Products for Human Use (CHMP)**⁴⁷ of the EMEA has defined specific commitments, which should be systematically required in the marketing authorisation as part of the risk management plan for a pandemic influenza vaccine. These include, inter alia, the following:

- specific recommendations and formats for **reporting of adverse events by health care professionals** to the marketing authorisation holder;
- requirement of a submission of a **simplified PSUR** on Day 45 after shipment of the first batch of vaccine and thereafter monthly at least for the first 6 months, in the format defined by the CHMP;
- obligation for marketing authorisation holders, as part of their approved risk management plan, to launch prospective epidemiological **cohort studies** for each authorised vaccine with a focus on safety and involving a minimum sample of 9000 subjects involving all age groups (from 2 months up);
- Specific consideration should be given to document the safety of vaccines in **pregnant women and immunocompromised subjects**;
- For rare events such as **Guillain-Barré syndrome**, marketing authorisation holders should investigate the possibility of collecting data through the participation of specialist centres or clinics.

⁴⁷ CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009); <http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/35938109en.pdf>