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THE EURASIAN ECONOMIC COMMISSION
COUNCIL

DECISION

June 14, 2018 **No. 55** Moscow

on amendment of the Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016

In accordance with Article 7 of the Agreement on Common Principles and Rules for Circulation of Medicinal Products within the Eurasian Economic Union dated December 23, 2014 and paragraph 84 of Annex 1 to the Regulations of the Eurasian Economic Commission, approved by Decision of the Supreme Eurasian Economic Council No. 98 dated December 23, 2014, the Council of the Eurasian Economic Commission **decided to:**

1. Amend the Rules of authorisation and Assessment of Medicinal Products for Human Use, approved by the Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016 in accordance with the Annex.

2. This Decision shall come into effect 6 months after its official publication.

Members of the Eurasian Economic Commission's Council:

For the Republic of Armenia	**For the Republic of Belarus**	**For the Republic of Kazakhstan**	**For the Kyrgyz Republic**	**For the Russian Federation**
Seal: *EURASIAN ECONOMIC COMMISSION * FOR DOCUMENTS*	Seal: *EURASIAN ECONOMIC COMMISSION * FOR DOCUMENTS*	Seal: *EURASIAN ECONOMIC COMMISSION * FOR DOCUMENTS*	Seal: *EURASIAN ECONOMIC COMMISSION * FOR DOCUMENTS*	Seal: *EURASIAN ECONOMIC COMMISSION * FOR DOCUMENTS*
M. Grigoryan	**V. Matyushevsky**	**A. Mamin**	**Zh. Razakov**	**A. Siluanov**

ANNEX

to the Decision of the Council
of the Eurasian Economic Commission
No. 55 dated June 14, 2018

AMENDMENTS
made to the Rules of authorisation and Assessment of Medicinal Products for Human Use

1. In the second item of paragraph 29 and the first item of paragraph 30, the words "December 31, 2018" should be replaced with words "December 31, 2020".

2. Paragraph 188 shall be added as follows:

"188. Amendments to the marketing authorisation application of vaccines when the strain composition of vaccines for the prevention of influenza is changed, as well as authorisation of pandemic and prepandemic vaccines for the prevention of influenza, and amendment of their marketing authorisation application shall be made in accordance with Annex 24 hereto.".

3. Annex 24 shall be added as follows:

"ANNEX 24

to the Rules of authorisation and
Assessment of Medicinal Products for
Human Use

REQUIREMENTS
to the procedure of amendment of the marketing authorisation application of seasonal, pandemic, and prepandemic (zoonotic) vaccines when the strain composition of influenza vaccines is changed, as well as to the authorisation of seasonal, pandemic, and prepandemic (zoonotic) vaccines for influenza prevention

I. General provisions

These Requirements shall apply to the procedures for authorisation of influenza vaccines and define a single procedure of amending the marketing authorisation application of seasonal, pandemic, and prepandemic (zoonotic) vaccines when the strain composition of influenza vaccines is changed (updated) under the accelerated procedure, as well as authorisation of seasonal, pandemic, and prepandemic (zoonotic) vaccines for influenza prevention in the customs territory of the Eurasian Economic Union (hereinafter – the Union).

These Requirements are inseparably related to the Rules for conducting studies of biological medicinal products of the Eurasian Economic Union, approved by Resolution of the Council of the Eurasian Economic Commission No. 89 dated November 3, 2016.

These Requirements shall not apply to amendments that are not related to changes (updates) in the strain composition of seasonal, pandemic, and prepandemic (zoonotic) influenza vaccines.

II. Definitions

For the purposes hereof, the concepts having the following meanings shall be used:

"pandemic preparedness vaccine" means a candidate vaccine (or vaccine preparation technology) for the prevention of influenza, developed for the purpose of immunizing the population in the event of influenza caused by pandemic strains of the influenza virus;

"pandemic vaccine" means a vaccine for the prevention of influenza, designed to immunize the population in the event of influenza caused by pandemic strains of the influenza virus;

"prepandemic (zoonotic) vaccine" means a vaccine for the prevention of influenza, designed to immunize the population in the event of influenza

outbreaks caused by zoonotic strains of the influenza virus;

"seasonal vaccine" means a vaccine for the prevention of influenza caused by epidemic strains of the influenza virus, intended for annual immunization of the population;

"authorised authority (expert organization) of the reference Member State or the Member State concerned" means the authorised authority of the Union Member State in the field for medicinal products circulation, including the one authorised to register, confirm the registration (re-registration), amend the marketing authorisation application and perform the other procedures related to the authorisation of medicinal products for human use, provided for by the Rules of authorisation and Assessment of Medicinal Products for Human Use, approved by Resolution of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016 (hereinafter – the Rules).

III. Regulatory and procedural requirements for vaccine authorisation and amendment of the strain composition of influenza prevention vaccines

1. Seasonal influenza prevention vaccines

1.1. Requirements for the application of an influenza prevention vaccine authorisation

The application for authorisation of a new seasonal influenza vaccine must be accompanied by a set of documents stipulated by Annex 1 to the Rules.

1.2. Requirements for an application of changing the strain composition of seasonal influenza vaccines

The applicant may apply for changes to the strain composition of a seasonal influenza prevention vaccine after the official notification of the authorised authority (by the expert organization) of the Union Member State (hereinafter – the Member State) on the beginning of reception of such

applications following the publication of annual recommendations by the World Health Organization (WHO) on vaccination against influenza until the deadline established by the authorised authority (the expert organization) of a reference Member State. When submitting an application, the provisions of Annexes 2, 19, and 20 to the Rules must be followed.

In the "Name changes" table in paragraph 2 "Amendments" of Form III of the application for amendment of the medicinal product marketing authorisation application (Annex 2 to the Rules), it is required to specify: "The annual update of the influenza prevention vaccine strain(s)". The application should be submitted according to the amendment II procedure of type B.1.a.5 (in accordance with Annex 19 to the Rules).

For the purpose of annual updating of the influenza prevention vaccine strain(s), as an exception to the provisions provided for in subsections 2.3 and 3.3 of Annex 19 to the Rules, the amendment examination procedure affecting the changes in the API as described below shall apply.

According to this procedure, the applicant is not allowed to make any changes, and the authorised bodies (expert organisations) of the reference Member State and the Member States concerned may not require any changes to the composition of the influenza prevention vaccine marketing authorisation application dossier, except for amendments due to changes in the strain composition. The amendments that are not caused by the appearance of new strains shall be made in accordance with Sections II and III of Annex 19 and Annex 20 to the Rules.

Before submitting an application to change the strain composition of the vaccine, the applicant shall be entitled to apply to the authorised authority (expert organization) of the reference Member State in advance with a request to conduct scientific and pre-authorisation consultations to plan the examination procedure for the amendments being made, including in the case

of possible deviations from the terms provided for by such procedure.

1.3. Selection of epidemiologically relevant influenza virus strains for use in seasonal influenza prevention vaccines

During the preparation for the upcoming epidemic season, it is allowed to make annual changes to the composition of authorised seasonal influenza prevention vaccines in order to replace the strain(s) based on WHO recommendations. When predicting the occurrence of influenza epidemic situations involving the circulation of influenza virus strains not recommended by the WHO, the Member State shall be entitled to decide on amendment of the influenza prevention vaccines marketing authorisation application based on the decision of the authorised authority of the Member State or the influenza commission of the Member State.

Twice a year (usually in February and March for the Northern hemisphere, and in September for the southern hemisphere), the WHO publishes recommendations on influenza A and B virus strains that should be used in the production of influenza prevention vaccines for the upcoming epidemic season.

1.4. Procedure description

1.4.1. The procedure of amending the influenza prevention vaccine marketing authorisation application (updating the seasonal strains composition) in the reference Member State

The authorised authority (expert organization) of the reference Member State shall, within a period not exceeding 5 business days from the date of filing an application for amendment of the influenza prevention vaccine marketing authorisation application dossier, assess the completeness, comprehensiveness, and correctness of the submitted documents of the influenza prevention vaccine marketing authorisation application and send the

application and influenza prevention vaccine marketing authorisation application (the dossier subject to amendment) to the expert organization of the reference Member State.

If the application and influenza prevention vaccine marketing authorisation application comply with Section 5 hereof, the authorised authority (expert organization) of the reference Member State shall initiate the procedure of amending the influenza prevention vaccine marketing authorisation application and notify the applicant respectively. The procedure duration shall not exceed 40 calendar days.

The expert organization of the reference Member State shall conduct an examination of the influenza prevention vaccine marketing authorisation application within a period not exceeding 25 calendar days from the date of a notice to the applicant about the initiation of the amendment procedure in respect of the influenza prevention vaccine marketing authorisation application dossier. Upon completion of the examination procedure, the expert organization of the reference Member State shall prepare an assessment report on the safety, efficacy, and quality of the influenza prevention vaccine (hereinafter – the assessment report).

Within 25 calendar days from the date of a notice to the applicant about the initiation of the amendment procedure in respect of the influenza prevention vaccine marketing authorisation application dossier, the expert organization of the reference Member State shall be entitled to request the applicant to submit additional data required for the examination completion.

If a request is received from an authorised authority (expert organization) of the reference Member State, the applicant must submit additional data to the same within 7 business days. The deadline of the applicant's response to the request shall not be included into the overall procedure duration specified in the second item of this subsection. After receiving the requested additional

data, the authorised authority (expert organization) of the reference Member State shall resume the examination procedure.

The expert organization of the reference Member State shall conduct an examination of the additional data submitted by the applicant within a period not exceeding 5 business days.

Within 1 business day from the date of the assessment report, the expert organization of the reference Member State shall send the same to the applicant.

The authorised authority of the reference Member State shall, within 2 business days, decide to approve or reject the amendments to the influenza prevention vaccine marketing authorisation application based on an assessment report prepared by an expert organization of the reference Member State.

1.4.2. The procedure of amending the influenza prevention vaccine marketing authorisation application (updating the seasonal strains composition) in the Member State concerned

The applicant shall simultaneously submit to the authorised bodies (expert organisations) of the Member States concerned a statement on changes in the composition of the influenza prevention vaccine marketing authorisation application in accordance with Annex 2 to the Rules on paper and (or) electronic media and the documents confirming the payment of a fee (toll) for amendment of the influenza prevention vaccine marketing authorisation application in cases and in the manner established in accordance with laws of the Member States concerned.

The authorised authority (expert organization) of the reference Member State shall, through the integrated information system of the Union (hereinafter – the integrated system), notify the authorised bodies (expert organisations) of the Member States concerned and the applicant about the beginning of the

amendment procedure in respect of the influenza prevention vaccine marketing authorisation application in the reference Member State or about the refusal to perform the said procedure.

The authorised authority (expert organization) of the reference Member State shall, within 2 business days after receipt of a notice on the beginning of the amendment procedure in respect of the influenza prevention vaccine marketing authorisation application by the authorised bodies (expert organisations) of the Member States concerned, provide access to the documents contained in the influenza prevention vaccine marketing authorisation application through the integrated system.

The authorised authority (expert organization) of the Member State concerned shall, within a period not exceeding 5 business days from the date of obtaining access to the documents contained in the influenza prevention vaccine marketing authorisation application dossier, assess the completeness, comprehensiveness, and correctness of the documents submitted in accordance with the legislation of its state and begin the amendment procedure in respect of the influenza prevention vaccine marketing authorisation application dossier. The duration of this procedure should not exceed 40 calendar days from the date of submitting an application for amendment of the influenza prevention vaccine marketing authorisation application dossier.

The authorised authority (expert organization) of the reference Member State shall, within 25 calendar days from the date of a notice to the applicant about the beginning of the procedure in the reference Member State, prepare a draft assessment report and provide the authorised bodies (expert organisations) of the Member States concerned with access to it through the integrated system.

The authorised authority (expert organization) of the Member State concerned shall, within 1 business day from the date of receiving access, send

the comments on the draft assessment report to the authorised authority (expert organization) of the reference Member State.

The authorised authority (expert organization) of the reference Member State shall amend the assessment report, taking into account the comments received from the authorised bodies (expert organisations) of the Member States concerned, and provide the access of the authorised authority (expert organization) of the Member State concerned to the amended assessment report through the integrated system.

The authorised authority (expert organization) of the reference Member State shall be entitled to request from the applicant additional data required for the examination completion, taking into account the comments received from the authorised bodies (expert organisations) of the Member States concerned, and inform the applicant and the authorised bodies (expert organisations) of the Member States concerned respectively through the integrated system or otherwise.

The applicant shall send a response to the request to the authorised authority (expert organization) of the reference Member State within 7 business days after receipt of a request from the authorised authority (expert organization) of the reference Member State. The deadline for the applicant to respond to this request shall not be included into the overall duration of the amendment procedure in respect of the influenza prevention vaccine marketing authorisation application dossier.

The authorised authority (expert organization) of the reference Member State shall notify the authorised bodies (expert organisations) of the Member States concerned about the resumption of the amendment procedure in respect of the influenza prevention vaccine marketing authorisation application and provide them with access to the requested data within 2 business days from the date of receipt of such data by the authorised authority (expert organization) of

the reference Member State.

The authorised authority (expert organization) of the reference Member State shall prepare a draft assessment report taking into account the additional data provided by the applicant and provide access thereto to the authorised bodies (expert organisations) of the Member States concerned through the integrated system within 5 business days after the examination renewal in the reference state.

The authorised authority (expert organization) of the Member State concerned shall decide on the amendment of the influenza prevention vaccine marketing authorisation application or reject the amendments within 2 business days after the date of providing the authorised bodies (expert organisations) of the Member States concerned with access to the expert opinion and notify the applicant and the authorised authority (expert organization) of the reference Member State about the decision through the integrated system or otherwise.

After the authorised bodies (expert organisations) of the reference Member State or the Member State concerned have made a decision to amend the influenza prevention vaccine marketing authorisation application and received a relevant notice, the applicant shall submit to the authorised bodies (expert organisations) of the reference Member State or the Member States concerned a translation of the summary of product characteristics, a package leaflet, and package layouts of the influenza prevention vaccine in the official languages of the reference Member State and the Member States concerned (if there is a corresponding requirement in the legislation of the reference Member State and the Member States concerned) within 7 business days from the notice receipt date.

The authorised authority (expert organization) of the reference Member State shall notify the applicant of the decision to amend the influenza prevention vaccine marketing authorisation application and issue new

registration documents to the applicant within a period not exceeding 40 calendar days from the date of the start of the amendment procedure with respect to the influenza prevention vaccine marketing authorisation application dossier, or within a period not exceeding 10 calendar days from the date of resumption of the specified procedure after the applicant submits a response to the request for additional data required to complete the examination of the influenza prevention vaccine marketing authorisation application dossier.

The authorised bodies (expert organisations) of the Member States concerned inform the applicant of the decision to amend the influenza prevention vaccine marketing authorisation application and issue new registration documents to the applicant within a period not exceeding 40 calendar days from the date of start of the amendment procedure in respect of the influenza prevention vaccine marketing authorisation application dossier, or within a period not exceeding 10 calendar days from the date of resumption of the specified procedure after the applicant submits a response to the request for additional data required to complete the examination of the influenza prevention vaccine marketing authorisation application (provided that the applicant submits the documents required to amend the influenza prevention vaccine marketing authorisation application dossier).

The authorised bodies (expert organisations) of the Member States concerned shall place information on the amendment of the influenza prevention vaccine marketing authorisation application and updated documents of the influenza prevention vaccine marketing authorisation application in the Common Register of the authorised Medicinal Products through the integrated system.

If an assessment report is prepared with a negative conclusion, on the basis of which the authorised authority (expert organization) of the reference Member State will decide to refuse to amend the influenza prevention

marketing authorisation application dossier, the specified authorised authority (expert organization) shall notify the applicant about the same in electronic and (or) written form within 10 business days from the date of such decision.

2. Prepandemic (zoonotic) influenza prevention vaccines

2.1. Requirements for the application of a pre-pandemic (zoonotic) influenza prevention vaccine authorisation

An application for authorisation of a pre-pandemic (zoonotic) influenza prevention vaccine shall be submitted to the authorised authority (expert organization) of the reference Member State in accordance with Section I and subsection 12.2 of Section III of Annex 1 to the Rules.

2.2. Requirements for the application of changing the strain composition of the pre-pandemic (zoonotic) influenza prevention vaccine

An application for change of the strain composition of a pre-pandemic (zoonotic) vaccine for the influenza prevention shall be submitted as an amendment to the marketing authorisation application dossier. The said amendment shall be classified as type II in accordance with subsection B.1.a.5 of Annex 19 to the Rules.

3. Pandemic influenza prevention vaccines and pandemic preparedness vaccines

3.1. Requirements for the application of a pandemic preparedness vaccine authorisation

In order to prepare for a pandemic, vaccine manufacturers submit an application for authorisation of a candidate pandemic vaccine containing a virus strain with pandemic potential (a pandemic preparedness vaccine).

Creation of this type of vaccine involves the use of a mock-up vaccine concept. According to this concept, a new registered pandemic preparedness

vaccine and a mock-up vaccine will have the following identical characteristics:

production parameters;

preparation technology;

vaccine composition, including the content of the antigen, excipients, adjuvant (if required) and other components (except for the strain(s));

specification indicators and quality control methods of the pandemic preparedness vaccine.

If a pandemic influenza situation is recognized by WHO or the competent authorities of the Member States, the applicant must submit to the authorised authority (expert organization) of the reference Member State an application for amendment of the pandemic preparedness vaccine marketing authorisation application (pandemic strain update) in accordance with paragraph 4.1.3 of Annex 19 to the Rules in order to include the pandemic strain into the pandemic preparedness vaccine (pandemic strain update).

3.2. Requirements for the pandemic preparedness vaccine marketing authorisation application in the event of a threat of evolution of a pandemic situation

In the event of a threat of evolution of a pandemic situation, the pandemic preparedness vaccine marketing authorisation application must contain data on the potential pandemic strain(s) (the data requirements are contained in Section 5 hereof). The applicant may submit a marketing authorisation application containing only the data on strain(s) entered into the vaccine based on the available data in order to establish the post-authorisation measures (authorisation based on the conditions of the pandemic preparedness vaccine), provided that in the event of a threat of the development of a pandemic situation and after declaration of pandemic by the WHO, the applicant shall guarantee the submission of the results of clinical trials to the authorised

authority (expert organization) of the reference Member State and compliance with the requirements in accordance with Section VII hereof. After the WHO has declared a pandemic threat, the applicant should initiate consultations with the competent authorities of the Member States as soon as possible.

3.3. Requirements to the application of changing the composition of pandemic influenza vaccines (change of the pandemic strain) during the pandemic

After the official recognition of a pandemic (declaration of a pandemic situation by the WHO in the prescribed manner or announcement of the epidemic provoked by a pandemic type of the influenza virus by relevant authorities of the Member States), the applicant may submit the statement of changes in composition of pandemic influenza vaccines (change of the pandemic strain) to the authorised authority (expert organization) of the reference Member State in order to include the declared pandemic strain update the pandemic vaccine (update the pandemic strain).

In the absence of certain preclinical or clinical data in relation to a declared pandemic strain, the applicant must submit the missing preclinical and clinical data to the authorised authority (expert organization) of the reference Member State within the period agreed between the applicant and the authorised authority (expert organization) of the reference Member State.

4. Vaccine authorisation during the pandemic

4.1. Urgent procedure

Once a pandemic situation has been declared by the WHO or an epidemic caused by a pandemic type of virus has been declared by the relevant competent authorities of the Member States, a new pandemic vaccine shall be authorised urgently.

In the absence of pandemic, the applicant may submit a marketing authorisation application containing incomplete data for the purpose of registration of a new pandemic vaccine to the authorised authority (expert organization) of the reference Member State, provided that after declaration of pandemic by the WHO it will be able to provide the authority (expert organization) of the reference Member State with the missing clinical data and to comply with the requirements for authorisation of vaccines subject to establishment of post-authorisation measures (authorisation based on the conditions) in accordance with Section VII hereof. The applicant must include in the marketing authorisation application an appropriate justification for the possibility of establishing post-authorisation measures, a description of the missing data, and attach a written undertaking to submit them to the authorised authority (expert organization) of the reference Member State by amending the influenza prevention vaccine marketing authorisation application dossier. The applicant should initiate consultations with the competent authorities of the Member States as soon as possible.

4.2. authorisation of a seasonal or pre-pandemic influenza prevention vaccine as a pandemic influenza prevention vaccine

Depending on the pandemic development conditions, the current epidemiological situation and (or) in the absence of a registered pandemic preparedness vaccine, it is allowed to change the strain composition of the corresponding seasonal or pre-pandemic vaccine in accordance with paragraph 4.1.3 of Annex 19 to the Rules, provided that such changes will ensure the preservation of the quality, safety, and efficacy of the influenza prevention vaccine and are scientifically feasible.

If it is required to register a seasonal or pre-pandemic influenza prevention vaccine as a pandemic influenza prevention vaccine, the applicant

should initiate consultations with the authorised bodies (expert organisations) of the Member States as soon as possible in order to agree on the content of the seasonal or pre-pandemic influenza prevention vaccine marketing authorisation application dossier.

5. The procedure of changing the strain composition of seasonal influenza prevention vaccines

5.1. General requirements for the procedure of changing the strain composition of seasonal influenza prevention vaccines

The application and marketing authorisation application for seasonal influenza prevention vaccines must comply with the requirements set out in Annex 1 to the Rules and be submitted in the format of a general technical document (hereinafter – GTD).

It is allowed to submit a marketing authorisation application of the seasonal influenza prevention vaccine, which includes only the GTD sections that correspond to the amendments made and the nature of which is determined by the change (update) of the strain composition. The absence of any GTD sections or incomplete submission of the GTD must be accompanied by an explanatory document (indicating the reasons for the absence of such sections and (or) incomplete document submission).

The requirements for the modules of the seasonal influenza prevention vaccine marketing authorisation application established by subsections 5.2–5.5 hereof are given with the indication of numbers of the GTD sections in accordance with the marketing authorisation application structure as stipulated by Annex 4 to the Rules.

5.2. Requirements for documents of the seasonal inactivated influenza prevention vaccine marketing authorisation application when making changes to the strain composition of the seasonal inactivated influenza prevention vaccines

The application for changes to the strain composition of the seasonal inactivated influenza prevention vaccines shall be submitted together with the marketing authorisation application dossier, which includes the sections listed below. Any deviation from the requirements (including the absence of required or additional data) must be justified in the relevant section of module 3 of the marketing authorisation application and the corresponding summary (review) of module 2 of the marketing authorisation application and agreed with the authorised bodies (expert organisations) of the reference Member State before the applicant submits an application to the authorised authority (expert organization) of the reference Member State.

Module 1. Administrative information

1. Cover letter (as in the case of electronic submission of documents in the GTD format (hereinafter – eGTD))

1.1. Content (not required when submitting the documents in eGTD format)

1.2. General documentation

1.2.1. Amendment application

1.2.2. Documents confirming the payment for expert work and (or) registration fee (duty) in accordance with the legislation of the Member State performing the authorisation

1.3. Summary of product characteristics, patient leaflet (package leaflet), labeling

1.3.1. Drafts of summary of product characteristics, patient leaflet (package leaflet) and labeling layouts prepared in accordance with the requirements for patient leaflet and summary of product characteristics for medicinal use, approved by Resolution of the Council of the Eurasian Economic Commission No. 88 dated November 3, 2016 (hereinafter – the

requirements for patient leaflet and summary of product characteristics for medicinal use)

The texts may be amended due exclusively to the strains used in the specified epidemic season.

1.7. Information about specialists

1.7.1. Information about the specialist who prepared the quality summary

Module 2. Summary of the general technical document

2.1. The content of Modules 2-5

The content of Modules 2-5 (not required when submitting documents in eGTD format).

2.2. Introduction to the GTD

Update or supplementation of the previous introduction (if applicable).

2.3. General summary on quality

Update or supplementation of the previous general quality summary.

Module 3. Quality

3.2.S. Active pharmaceutical ingredient (hereinafter – the API)

3.2.S.2. API manufacturing process

3.2.5.2.3. Control of raw materials

Must include:

seed material: history, receipt procedure (source, date, conditions of receipt), strain data sheet;

passaging history (number of passages, passage conditions, cultivation substrate);

determination of hemagglutinin and neuraminidase characteristics (data from serological studies and (or) moleculargenetic research methods);

test reports (including the seed material test results).

3.2.5.2.4. Control of critical stages and intermediate products

3.2.5.2.5. Production process validation and (or) evaluation

Validation of the production process for monovalent non-packaged products (semi-finished monovaccine) should include:

changes specific to the introduced strain production process;

validation of critical production stages due to strains being introduced into the production;

virus inactivation process;

virus cleavage efficiency (if applicable).

3.2.S.3. Description of API characteristics

Selection of studies to set the characteristics (particle size distribution, the presence of aggregates, etc.).

3.2.S.4. API (monovaccine) quality control

3.2.5.4.1. Specification

Copies of approved specifications in tabular format.

3.2.5.4.2. Analytical procedures

3.2.5.4.3. Analytical procedure validation

Validation of the single radial immunodiffusion procedure for the introduced strain(s), taking into account the corresponding reference standards.

3.2.5.4.4. Batch analysis (batch analysis results)

should include the following test results of the first three batches of monovalent bulk products (including the indicators of hemagglutinin and neuraminidase authenticity), provided that these products are obtained:

from each batch of the working seed material of the new main seed material of the introduced strain(s);

from each batch of the working seed material of the approved main seed material of the introduced strain(s) (if the procedure of preparing the working seed material differs from the procedure of preparing the working seed material as previously regulated).

3.2.S.7. Stability

API stability tests: it is required to submit the test results for monovalent bulk products if they have been used for more than 1 year.

3.2.P. Medicinal product

3.2.P.1. Medicinal product description and composition

The vaccine composition is given.

3.2.P.2. Pharmaceutical development

3.2.P.2.2.1. Dosage form development

The modified vaccine composition (strains of a new epidemic season) and, if a clinical trial has been requested to justify an annual update, a certificate of analysis of the batch used in the clinical trial as the said certificate is prepared.

3.2.P.3. Medicinal product manufacturing process

3.2.P.3.2. Batch composition (batch formula)

3.2.P.5. Medicinal product quality control

3.2.P.5.1. Specifications

Copies of approved specifications and procedures to determine the specification indicators in tabular format.

3.2.P.5.3. Analytical procedure validation

Validation of a single radial immunodiffusion procedure for (a) new strain(s) (using a trivalent bulk product or medicinal product).

3.2.P.8. Medicinal product stability: data on stability in the previous season;

undertaking to study the vaccine stability during the period of its use;

protocols of post-authorisation vaccine stability studies.

If the seed material is tested for the presence of extraneous agents using the polymerase chain reaction (hereinafter –the PCR) and if, after consultation with the expert organization of the reference Member State, it was agreed that additional PCR tests of the seed material should be performed, this data should

be included into the influenza prevention vaccine marketing authorisation application dossier.

5.3. Requirements for submission of additional data (after the request of the authorised authority of the Member State)

If additional data is requested (depending on the type of additional data being submitted), the relevant sections of the marketing authorisation application must be submitted for amendment in the GTD format.

Module 1. Administrative information

1. Cover letter (as in the GTD)

1.1. Content (not required when submitting the documents in eGTD format)

1.7. Information about specialists

1.7.1. Information (brief summary) about the specialist who prepared the quality summary

Module 2. Summary of the general technical document

2.1. The content of Modules 2-5 (not required when submitting documents in eGTD format)

2.2. Introduction to the GTD

Update or supplementation of the previous introduction (if applicable).

2.3. General summary on quality

Update or supplementation of the previous general quality summary (if applicable).

2.5. Clinical data review

Update or supplementation of the previous review (if applicable).

2.7. Clinical data summary

Update or supplementation of the previous clinical review (if applicable).

The information contained in Modules 3-5 shall be provided when

additional quality data, preclinical[1] and/or clinical[2] data are requested.

5.4. Requirements for the marketing authorisation application documents on changes in the strain composition of live attenuated influenza prevention vaccines

The application for changes in the strain composition of live attenuated influenza prevention vaccines must contain the following documentation. Deviation from the requirements (lack of required or additional data) must be justified in the relevant section of Module 3 and in the relevant summary (review), as well as approved by the authorised bodies of the Member States before submitting the application.

Module 1. Administrative information

1. Cover letter (as in the GTD)

1.1. Content (not required when submitting the documents in eGTD format)

1.2. General documentation

1.2.1. Amendment application

1.2.2. Documents confirming payment of the fee (duty) for confirmation of authorisation (re-authorisation) and examination in the case and in the manner established in accordance with the legislation of the reference Member State

1.3. Summary of product characteristics, patient leaflet (package leaflet), labeling

1.3.1. Drafts of summary of product characteristics, patient leaflet (package leaflet) and labeling layouts prepared in accordance with the requirements for patient leaflet

The texts may be amended due exclusively to the strains used in the specified epidemic season.

1.7. Information about specialists

1.7.1. Information (brief summary) about the specialist who prepared the quality summary

Module 2. Summary of the general technical document

2.1. The content of Modules 2-5 (not required when submitting documents in eGTD format)

2.2. Introduction to the GTD

Update or supplementation of the previous introduction to the GTD (if applicable).

2.3. General summary on quality

Update or supplementation of the previous general quality summary.

Module 3. Quality

3.2.S.2. API manufacturing process

3.2.5.2.3. Control of raw materials

Seed material batches (history of seed material preparation technology), including:

a description of the procedure of obtaining the seed material, starting with the main seed material of the attenuation donor and the WHO-recommended strain(s);

the history of obtaining a cold-adapted reassortant strain using a WHO-recommended strain (indicating the location of isolation and the history of passage) and the attenuation donor used;

study of the attenuated strain genotype. Attenuated strain sequencing results;

establishment of phenotypic characteristics:

temperature-sensitive (thermolabile) phenotype (ts) and cold-adapted phenotype (ca), including the phenotype based on the results of attenuation completeness tests;

genetic stability of the seed material, including the appropriate genotypic

and phenotypic markers (for example, full-genome sequencing);

analytical test reports (including the tests for the absence of extraneous agents and data on infectious activity)[3];

neurovirulence tests[4].

3.2.5.2.4. Control of critical stages and intermediate products

3.2.5.2.5. Production process validation and (or) evaluation

For the bulk monovalent product production process (for changes specific to the introduced strain production process).

3.2.S.4. API quality control

3.2.5.4.1. Specification

Copies of approved specifications in tabular format.

3.2.5.4.2. Analytical procedures

3.2.5.4.3. Analytical procedure validation

Validation of analytical procedures in connection with the introduction of (a) new strain(s) and the use of new reagents.

3.2.5.4.4. Batch analysis (batch analysis results)

Test results of the first three batches of monovalent bulk products.

3.2.S.7. Stability

API stability tests: the test results for monovalent bulk products if they have been used for more than 1 year.

3.2.P. Medicinal product

3.2.P.1. Medicinal product description and composition

Medicinal product composition

3.2.P.2. Pharmaceutical development

3.2.P.2.2.1. Dosage form development

The modified vaccine composition (strains of a new season) and, if a clinical vaccine trial has been requested to justify an annual update, a certificate of analysis of the batch used in the clinical trial as they are prepared.

3.2.P.3. Medicinal product manufacturing process

3.2.P.3.2. Batch composition (batch formula)

3.2.P.5. Medicinal product quality control

3.2.P.5.1. Specifications

Copies of approved specifications and procedures to determine the specification indicators in tabular format.

3.2.P.5. Medicinal product quality control

3.2.P.5.3. Analytical procedure validation

Validation of analytical procedures (using a trivalent bulk material or a ready-to-use form of the medicinal product).

3.2.P.5.4. Batch analysis results

3.2.P.6. Reference standards and materials

Reference standards and materials for the introduced strain(s).

3.2.P.8. Medicinal product stability: data on stability in the previous season; commitments to study the stability;

protocols of post-authorisation vaccine stability studies.

5.5. Requirements for submission of additional data at the request of authorised bodies (expert organisations) of the Member States

If additional data is requested, depending on the type of additional data being submitted, the relevant sections of the marketing authorisation application must be submitted for amendment in the GTD format.

Module 1. Administrative information

1. Cover letter (as in the GTD)

1.1. Content (not required when submitting the documents in eGTD format)

1.7. Information about specialists

1.7.1. Information (brief summary) about the specialist who prepared the

quality summary

Module 2. Summary of the general technical document

2.1. The content of Modules 2-5 (not required when submitting documents in eGTD format)

2.2. Introduction to the GTD

Update or supplementation of the previous introduction to the GTD (if applicable).

2.3. General summary on quality

Update or supplementation of the previous general quality summary (if applicable).

2.5. Clinical data review

Update or supplementation of the previous clinical review (if applicable).

The information contained in Modules 3-5 shall be provided when additional quality data, preclinical[1] and/or clinical[2] data are requested.

[1] There is usually no need to provide preclinical and/or clinical data when updating seasonal influenza vaccine strains.

[2] The reactogenicity and immunogenicity profile of the vaccine should be monitored by monitoring the vaccine safety and preventive efficacy.

[3] If the seed material is checked for the presence of extraneous agents using PCR and if, after consultation with an expert organization, it was agreed to conduct additional PCR tests of the seed material (main and/or working one), these data must be included into the marketing authorisation application dossier.

[4] A neurovirulence test is generally not required for annual strain updates (i.e., strains with antigen drift). A neurovirulence test will be required if a new HA subtype of influenza A type virus or a new type of influenza B type virus that differs from the currently circulating genetic lines is included in the vaccine or if there are particular concerns related to the vaccine safety profile.".

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