EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Annex I. variation application(s) content for live attenuated influenza vaccines

Draft Agreed by Biologics Working Party	November 2010
Release for public consultation	16 December 2010
End of consultation (deadline for comments)	31 March 2011
Agreed by Biologics Working Party	7 July 2011
Adoption by CHMP	21 July 2011
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Keywords	*Human influenza, live attenuated vaccine, variation procedure, community annual strain update, fast-track, season*

Note: this Annex contains the quality aspects of technical requirements for annual strain update. The nonclinical and clinical aspects are currently under preparation and will be published separately when completed.

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1. First step submission – "Quality" variation application

The MAH shall submit a Type II variation application containing the adequate **quality documentation** in accordance with Article 18 of Commission Regulation (EC) No 1234/2008, by the **Agency recommended target annual deadline**, which will be **published every year together with the EU Annual strain(s) recommendations**.

The current requirements for the content of the European application dossier are set out in Annex I to Directive 2001/83/EC, as amended.

The variation application should follow the EU recommendations of the Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) and should therefore include the following supporting documentation:

Module 1: Administrative information and prescribing information

1.0 Cover Letter

1.1 Comprehensive Table of Contents (not required if submitted in eCTD format)

1.2 Application Form (from European Variation Application Form as published in the NTA, Volume 2C).

1.3 Product Information

1.3.1 SPC, Labelling and Package Leaflet

Note: Only changes related to the new strains used may be introduced in these texts. The year of the season should not be part of the name of the medicinal product; it should be included in section 1 of SPC and corresponding sections of labelling. (At submission of the of variation application, the full set of annexes of the product information in all languages should be submitted to the Agency and MSs electronically in accordance with the CHMP members distribution list as published on the Agency website).

1.4 Information about the Quality Expert:

The relevant expert declaration(s) and signature must be provided, corresponding to the quality overall summary submitted in Module 2.

Module 2: Common technical document summaries

2.1 CTD Table of Contents (Module 2 – 3) (not required if submitted in eCTD format)

2.2 CTD Introduction

2.3 Quality Overall Summary (addendum to "previous" Quality Overall Summary)

Module 3: Chemical-pharmaceutical and biological information for chemical active substances and biological products

Please note that only relevant and adequate sections of the CTD variation application should be submitted. All sections not felt to be necessary should however be justified adequately in the Summary/Overview.

3.2.S.2 Manufacture

3.2.S.2.3 Control of Materials

- seed lots:

- Production history of the seed including:

- description of the derivation of the seed starting from master attenuated donor virus and WHO recommended strain(s);

- passage history;

- genetic sequence of the seed;

- phenotypic characterisation (including attenuation test and haemagglutinin and neuraminidase antigenicity);

- genetic stability for the seed lot including relevant genotypic and phenotypic markers (e.g. full genetic sequencing);

- analytical protocols (including extraneous agents safety test)*;

- neurovirulence test.**

3.2.S.2.4 Control of Critical Steps and Intermediates

3.2.S.4.1 Specification (copy of approved specifications in a tabular format)

3.2.S.4.2 Analytical procedures

3.2.S.4.3 Validation of analytical procedures. Relevant aspects of validation should be confirmed (e.g. specificity, repeatability of the assay linked to the use of new reagents) .

3.2.S.4.4 Batch analysis results of monovalent bulks:

- results of first three monovalent bulks from each new seed lot intended for commercial production.

3.2.S.2.5 Process validation and/or Evaluation (name, manufacturer)

monovalent bulks:

- manufacturing process strain specific changes

3.2.S.7 Drug Substance: Stability (Stability tests on the active substances: results from monovalent bulks where they are used for more than one year).

3.2.P.1 Composition

3.2.P.2.2.1 Pharmaceutical development: formulation development (actual formula (new season's strains) and Certificate of Analysis when available (either in quality or in clinical submission) of batch(es) used in clinical trial(s), where these are required.

3.2.P.3.2 Batch formula (actual formula)

3.2.P.5.1 Specifications (Copy of approved specifications and routine tests analytical methods in a tabular format)

3.2.P.5.3 Validation of analytical procedures; validation of potency test for new strains (either using trivalent bulk or drug product)

3.2.P.5.4 Batch analysis (name, dosage form)

Batch analysis results including thermal stability

3.2.P.8 Drug Product: Stability

- Stability data from previous season

- Stability commitment(s)

- Post-approval stability protocol for the final lot stability

* Note: Where the seed virus is tested for extraneous agents using PCR, and if in discussion with the Agency and Rapporteurs the need for additional PCR testing of the seed has been agreed, these data should be included in this application.

** Neurovirulence testing of annual updates (i.e. antigenically drifted strains) is normally not required. Neurovirulence testing will be required if a new HA subtype of influenza A virus (i.e. non-H1, non-H3 subtype) or a novel influenza B virus type differing from the currently circulating genetic lineages is included in the vaccine or in case specific safety concerns arise.