Reference 4

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON HARMONISATION OF REQUIREMENTS FOR INFLUENZA VACCINES

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HARMONISATION OF REQUIREMENTS FOR INFLUENZA VACCINES
(CPMP/BWP/214/96)

A. YEARLY CHOICE OF INFLUENZA VIRUS STRAINS FOR VACCINES

WHO has three international influenza centres (at the National Institute for Medical Research in Mill Hill UK; and at the Centers for Disease Control in Atlanta, USA and at CSL Ltd, Parkville, Australia), which are assisted by national laboratories, designated by WHO. The national laboratories isolate viruses and then refer them to an international centre for detailed antigenic analysis. Reports are regularly sent to WHO in Geneva.

Once a year, in mid-February, a meeting of WHO experts takes place in Geneva, leading to a recommendation on the influenza A and B virus variants which should be used for the production of vaccine for the coming season, but there remains very broad flexibility within this recommendation. The WHO recommendations are aimed worldwide and therefore need to be adapted to the epidemiological situation of the European Union (EU). The predominant influenza viruses are believed to be similar from one Member State of the EU to another, There is thus little scientific justification for different composition of vaccines throughout the EU.

As from 1992, a meeting of EU experts will have to be convened each year after the WHO meeting, as soon as practically possible, in order to take an EU wide decision regarding influenza virus strains for vaccine production for the next season, taking into consideration the epidemiology of influenza in the EU.

B. LABELLING

There should be clear information about influenza virus strains and season of use, since EU vaccines often contain virus strains which are related to, but not identical to those recommended by the WHO. This may cause confusion if some vaccine labels show the WHO strains and others show the actual vaccine strains.

Information on immediate package, outer packaging and package leaflet should comply with Council Directive 92/27/EEC and in addition the labelling and package leaflets should contain:

Immediate package	- season of use e.g. 1997/98 season
Outer packaging	- WHO/EU recommended strains e.g. A/Wuhan/359/95 (H3N2)-like strain - season of use
Package leaflet	- WHO/EU recommended strains followed by actual strains e.g. A/Wuhan/359/95 (H3N2)-like strain (A/Nanchang/933/95 RESVIR-9) - Statement that the vaccine complies with WHO recommendation (northern hemisphere) and EU decision for "x" season

The actual vaccine strains (ie those approved at the annual meeting of EU experts) will also be named in the dossier submitted for annual licensing and in the production and test protocols.

C. POTENCY OF INFLUENZA VACCINE

For influenza vaccines to be acceptable throughout the EU, they should comply with the European Pharmacopoeia (EP) requirements and contain 15 μg HA per strain and per dose. The lower 95% confidence limits of the potency assay should indicate a content of at least 12 μg HA per strain and per dose.

D. CONTROL AUTHORITY BATCH RELEASE OF INFLUENZA VACCINE

1. INTRODUCTION

1.1 Directive 89/342/EEC relating to immunological products (consisting of vaccines, toxins or serums and allergens) provides in article 4.3. that, where a Member State considers it necessary in the interests of public health, it may require that samples from each batch be submitted for examination by a State laboratory or a designated laboratory for the following medicinal products:

- live vaccines;
- immunological medicinal products used in the primary immunisation of infants or other groups at risk;
- immunological medicinal products used in public health immunisation programmes;
- new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorisation.

Harmonisation of such examination by EU national authorities must be achieved to permit effective batch release of vaccines within the EU.

The objective of this batch examination is the verification that the product is in conformity with the approved specifications. The testing has to be completed within 60 days of receipt of the samples.

1.2 Where a Member State has examined a batch of a product and declared it to be in conformity with the approved specifications, another Member State may not repeat this examination for the purpose of release.

The objective of this document is the harmonisation of control tests carried out in the framework of batch examination in order to achieve mutual recognition.

1.3 Batch release should be carried out by a control authority with recognised competence in batch release of influenza vaccines. A vaccine batch released by one Member State must be acceptable to other Member States. Batch release depends upon mutual confidence and effective exchange of information between the Member States. The batch release procedures

outlined below are phased to deal with vaccine submissions under normal circumstances (phase 1) and abnormal circumstances (phase 2). Phase 1 of batch release is necessary for all vaccine batches whereas phase 2 of batch release is introduced under the special circumstances described below. Test methods and results for phases 1 and 2 must comply with the European Pharmacopoeia monograph on influenza vaccines.

1.4 Manufacturers are responsible for presenting release certificates delivered by the competent authorities when required.

Records of batch release tests (phases 1 and 2) and the full documentation submitted by the manufacturer should be kept for at least 10 years by the control authority. They should be available to other EU control authorities upon request.

2. PHASE 1 OF BATCH RELEASE: PROTOCOL SUBMISSION AND BATCH RELEASE TESTS (BASIC EP TESTS)

2.1 Protocol submission

The manufacturer's detailed protocol of production and tests carried out according to the European Pharmacopoeia monograph on influenza vaccines shall be approved by the control authority for each vaccine batch. The protocol should be based upon the WHO summary protocol for influenza vaccine (inactivated) (WHO Technical Report Series 638, 1979) an example of which is illustrated in paragraph 5. Manufacturers should submit full details of test results; it is insufficient to indicate only "pass" or "fail".

2.2. Basic EP tests

Tests to be performed by the control authority in accordance with the EP monograph as a basis for batch release:

2.2.1 At least twenty doses of each vaccine batch (product supplied in final package) and 20 ml of bulk vaccine shall be submitted to the control authority. For purified subunit vaccines, an additional 10 ml of monovalent vaccine shall be submitted for the first 5 lots of vaccine produced from a new influenza strain;

2.2.2 Tests to be performed on each batch of vaccine prior to release:

a) haemagglutinin antigen concentration/identity test using reference materials supplied currently by the National Institute for Biological Standards and Control, UK;

b) endotoxin content;

2.2.3 Tests to be performed on each lot of blended bulk vaccine:

a) none;

2.2.4 Tests to be performed on the first 5 lots of monovalent purified subunit vaccine following the introduction of a new influenza strain:

a) test for purity;

3. PHASE 2 OF BATCH RELEASE: PROTOCOL SUBMISSION AND ADDITIONAL EP TESTS

Additional tests from the EP monograph on influenza vaccines may be necessary for batch release in special circumstances:

- a change in the vaccine production process has been approved;
- a change in the site of manufacture has been approved;
- evidence of unexpected adverse clinical reactions or quality defects from previous batches of a given vaccine;
- evidence of marked inconsistencies in the vaccine production process;
- a critical report from the inspector from the competent authority;
- changes in the manufacturer's testing procedures;
- identification of unexpected variability of the manufacturer's test results.

Phase 2 batch release procedures:

3.1 The number of additional doses of each vaccine batch (product supplied in final package) or the volume of trivalent or monovalent bulk vaccine to be submitted for testing to the control authority will depend on the nature of the additional tests.

3.2 The nature of the additional batch release tests to be performed will depend on the circumstances for introduction of phase 2 tests.

3.3 Information concerning failed batches may be required as part of phase 2 batch release procedures.

4. RELEASE CERTIFICATE

A release certificate for each vaccine batch shall be presented to the manufacturer after approval when the results of testing are satisfactory. The release certificate must give details of:

4.1. Name and address of manufacturer

4.2. Trade name and proper name of product

4.3. Marketing Authorisation Number (Country)

4.4. Batch number

4.5. Number of containers

4.6. Number of doses per container

4.7. Type of container

4.8. Date of release and reference number

4.9. Date of expiry

4.10 Statement of compliance

4.11 Name and function of signatory

5. SUMMARY PROTOCOL FOR INACTIVATED INFLUENZA VACCINES

The following summary protocol is an example of the type of information required for batch release. The data submitted should be in accordance with the current EP monograph on influenza vaccines.

Name of product:.....

Marketing authorisation:.....

Name and address of manufacturer:.....

Batch number: :.....

Filling lot number: :.....

Date of manufacture: :.....

Date of expiry:.....

Type of container:.....

Number of doses:.....

Dose volume:.....

Composition:.....

e.g. strain 1	15 µg HA/0.5 ml
strain 2	15 µg HA/0.5 ml
strain 3	15 µg HA/0.5 ml

Statement of quality:

.....

.....

e.g. I certify that lot number.....of this product satisfies the requirements of the European monograph on influenza vaccines.

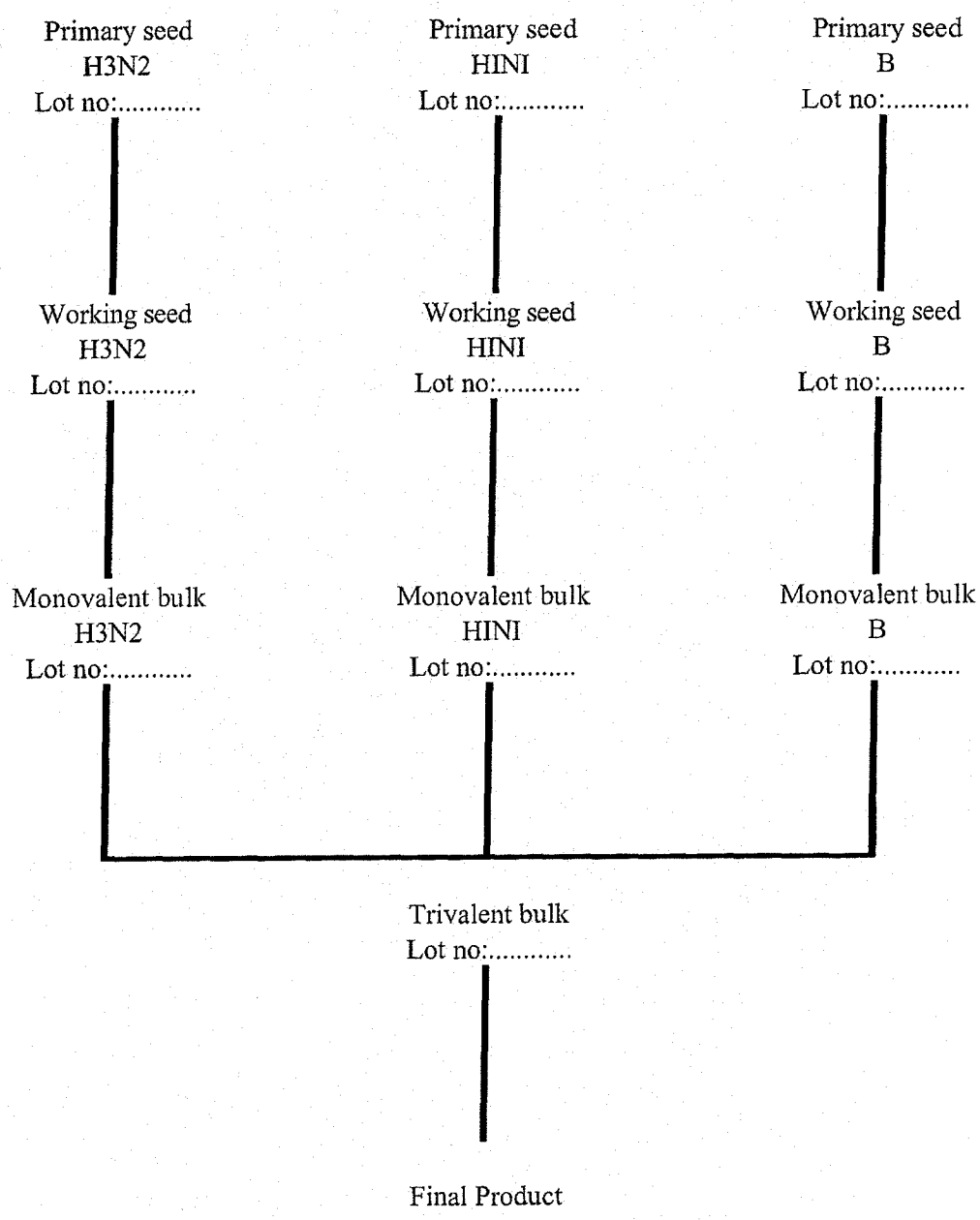
Signature:

.....

Name (typed):

.....

PRODUCTION FLOW SHEET



Filling Lot no:.....

SEED VIRUS

1. Information on manufacture

1.1 Virus strain:.....

1.2 Source and lot No of primary seed:.....

1.3 Date of receipt:.....

1.4 Passage history on receipt (dates, temperatures):.....

1.5 Comments:.....

1.6 Storage conditions:.....

1.7 Working seed lot No:.....

1.8 Passage history of seed lot(s) (dates, temperatures):.....

1.9 Added antibiotics:.....

1.10 Storage conditions of working seed lot(s):

2. Tests on working seed virus

2.1 Sterility

Method:.....

Date of test:.....

Volume tested:.....

Test results:.....

2.2 Test for mycoplasma

Method:.....

Date of test:.....

Volume tested:.....

Test results:.....

2.3 Identity

(a) Haemagglutinin

Date of test:.....

Test results:.....

e.g.

Antigen	HI titre Antiserum			
	Shang/11/87	Sich/2/87	Taiw/l/86	B/Yam/16/88
A/Shang/11/87 (H3N2) Ref				
A/Sich/2/87 (H3N2) Ref				
A/Taiw/l/86 (HINI) Ref				
A/Shang/11/87 Working seed lot no:				

(b) Neuraminidase

Date of test:.....

Test results:.....

e.g.

Antigen	HI titre Antiserum		
	anti-N2NA	anti-NlNA	anti-BNA
A/Shang/11/87 (H3N2) Ref			
A/Sich/2/87 (H3N2) Ref			
A/Taiw/l/86 (HINI) Ref			
B/Yam/16/88 Ref			

A/Shang/11/87
Working seed
lot No .....

2.4. Infectivity titre:.....

Date of tests:.....

Test results:.....

MONOVALENT VIRUS POOL

1. Information on manufacture

Name and address of manufacturer:.....

1.1 Virus strain:.....

1.2 Lot number(s):.....

1.3 Working seed lots used:.....

1.4 Date of inoculation:.....

1.5 Date of harvesting:.....

1.6 Method of inactivation:.....

1.7 Date of inactivation:.....

1.8 Method of disruption (if any):.....

1.9 Date of disruption (if any):.....

1.10. Concentration/purification procedure:.....

1.11 Added antibiotics:.....

1.12 Filtration details (if any):.....

2. Tests on monovalent virus pool

2.1 Test for inactivation

Date of test:.....

Test results:.....

2.2 Test for haemagglutinin antigen content

Method:.....

Date of test:.....

Test results:.....

2.3 Identity of haemagglutinin

Method:.....

Date of test:.....

Test results:.....

2.4 Purity (for surface antigen vaccines only)

Method:.....

(e.g. type of PAGE system, reducing/non reducing conditions)

Date of test:.....

Test results:.....

(e.g. HA, M and NP bands must be identified. Comparison between whole virus and surface antigen preparation must be made)

BULK VACCINE

Date of test:.....

Test results:.....

1. Information on manufacture

Name and address of manufacturer:.....

1.1 Lot number:.....

1.2 Lot number and volume of monovalent pools used to prepare bulk:.....

.....

1.3 Other substances added and volumes:.....

.....

1.4 Date of blending:.....

2. Tests on bulk vaccine

Analytical tests

Method(s):.....

Test results:.....

(include test for mercury, if appropriate)

FINISHED PRODUCT

1. Information on manufacture

Name and address of manufacturer:.....

1.1 Lot number:.....

1.2 Date of filling:.....

1.3 Type of container:.....

1.4 Volume in container:.....

1.5 Number of doses filled:.....

2. Tests on finished product

2.1 Identity for haemagglutinin

Method:.....

Date of test:.....

Test results:.....

2.2 Sterility

Method:.....

Date of test:.....

Test results:.....

2.3 Haemagglutinin antigen content

Method:.....

Date of test:.....

Test results:.....

2.4 Total protein (this test may be performed on bulk vaccine)

Method:.....

Date of test:.....

Test results:.....

2.5 Abnormal toxicity

Method:.....

Date of test:.....

Test results:.....

2.6 Ovalbumin (this test may be performed on bulk vaccine)

Method:.....

Date of test:.....

Test results:.....

2.7 Endotoxin

Method: .....

(e.g. type of limulus kit)

Date of test:.....

Test results:.....

2.8 pH

Date of test:.....

Test results:.....

2.9 Preservative content

Method:.....

Date of test:.....

Test results:.....

2.10 Appearance:.....

E. CLINICAL TRIALS RELATED TO YEARLY LICENSING OF INFLUENZA VACCINE

1. INTRODUCTION

When a new application for marketing authorisation for an influenza vaccine is made, full clinical trial data should be submitted with the application. Such clinical trials are outside the scope of this note for guidance. However, the strain composition of influenza vaccines is modified periodically to take account of the changes in the prevalent viruses causing influenza and manufacturers should apply for yearly licensing to accommodate strain changes.

Vaccine manufacturers are required to be involved in ongoing clinical trials of influenza vaccines and to present the results to the competent authorities. Guidance for performing these clinical trials is given in this section.

The purpose of such trials is to verify:

- the tolerance or incidence of adverse reactions;
- the immunogenicity of the hemagglutinin of the vaccine strains, i.e. the titre and frequency of anti-HA antibody responses;

Whenever the characteristics of a new strain incorporated into the vaccine or the susceptibility of the population to the new strain requires adjustment of the doses, manufacturers may be advised to test various doses of antigens to confirm the adequacy of 15 μg HA per strain and per dose.

The yearly clinical trials on influenza vaccine shall be carried out in accordance with Good Clinical Practice for Trials on Medicinal Products in the European Community.

This information will be submitted at the time of yearly licensing and should include satisfactory evidence of immunogenicity and safety before a licence is granted.

2. GENERAL REQUIREMENTS

2.1 Vaccine used in the trial

The composition of the vaccine used in the trial shall be such as to fulfill the requirements of the yearly EEC recommendation with regard to vaccine strains. The batches of vaccine used shall be representative of the product placed on the market.

2.2 Trial population

The tolerance and efficacy of the vaccine shall be evaluated separately in two groups of healthy volunteers, aged between 18 and 60 and over 60; for the latter group, it is important that the previous vaccination status of each subject be known and recorded. Volunteers receiving influenza vaccine within the previous 6 months should be excluded because they may compromise assessment of vaccine immunogenicity.

Groups of at least 50 individuals shall be constituted.

2.3 Trial procedure

a) Just prior to vaccination, a 10 ml venous blood sample shall be taken from each trial subject, for base-line titration of circulating anti-HA antibodies;

b) Immediately thereafter, each subject shall receive 1 dose of vaccine (0.5 ml) by intramuscular or subcutaneous injection into the upper arm. The injection shall be given into the opposite arm from which blood was drawn;

c) approximately 3 weeks after vaccination, a 10 ml blood sample shall be taken from each subject. Sera shall be separated and stored at -20°C; samples shall be kept at the disposal of the control laboratories for epidemiological studies and possible further antibody titration;

d) in the event of intercurrent infection, nasal and/or pharyngeal swabs shall be collected, in order to allow diagnosis of either influenza or another viral respiratory infection.

2.4 Monitoring of adverse reactions

a) Trial subjects shall receive, at the time of vaccination, a standardised form to complete and give to the investigator when they come for the post-vaccination blood sampling;

b) the form shall allow for collection of the following information:

- initials of the subject, with date or year of birth;
- previous anti-influenza vaccinations and previous adverse reactions, if any;
- previous influenza infections, with date, description of symptoms and virological confirmation, if any;
- adverse reactions for the 3 days following vaccination, either local (induration, erythema, ecchymosis, pain) or general (fever, shivering, malaise, other side-effects);
- other adverse reactions lasting 2 days beyond vaccination should be noted.

2.5 Antibody titration

All sera shall be assayed for anti-hemagglutinin antibody against the prototype strains by HI (Palmer et al., 1975) or SRH (Schild et al., 1975, Aymard et al., 1980) tests.

Positive and negative sera as well as reference preparations may be obtained from a reference laboratory.

2.6 Interpretation of results and statistics

Antibody titrations shall be done in duplicate; pre- and post-vaccination sera shall be titrated simultaneously.

The titre assigned to each sample shall be the geometric mean of two independent determinations:

a) for the purposes of calculation, any HI result < 10 (= undetectable) shall be expressed as 5 and any negative SRH result shall be expressed as 4 mm^2(*);

b) in HI tests, seroconversion corresponds to:

- negative prevaccination serum / postvaccination serum ≥, 40;
- a significant increase in antibody titre, i.e. at least a fourfold increase in titre;

c) in SRH tests, seroconversion corresponds to: (*)

- negative prevaccination serum / postvaccination serum: area ≥, 25 mm^2;
- a significant increase in antibody titre, i.e. at least a 50% increase in area;

d) statistical parameters to be determined:

- geometric mean of prevaccination serum anti-HA antibody titres;
- increase in the geometric mean of antibody titre;
- number of seroconversions;
- proportion of subjects with a titre of antibodies before vaccination;
- proportion of subjects with a titre of antibodies after vaccination;

e) clinical tolerance: frequency, mean time of appearance and duration of all local and general side-effects shall be calculated.

Interpretation of results should take into account the route of administration and any recent history of influenza immunisation or infection.

3. CRITERIA FOR ASSESSMENT OF VACCINES

3.1. Serological data

a) the following serological assessments should be considered for each strain in adult subjects, aged between 18 and 60, and at least one of the assessments should meet the indicated requirements :

- number of seroconversions or significant increase in antihaemagglutinin antibody titre > 40%;
- mean geometric increase > 2.5;
- the proportion of subjects achieving an HI titre ≥40 or SRH titre >25 mm^2 (*) should be > 70%.

b) the following serological assessments should be considered for each strain in adult subjects aged over 60, and at least one of the assessments should meet the indicated

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* In most SRH test systems, a zone area of 25 mm^2 is approximately equivalent to an HI titre of 1:40 (Wood et al, 1994). However, this relationship can be affected by experimental conditions and should be reexamined in each laboratory so as to calibrate the test system adequately.

requirements:

- number of seroconversions or significant increase in antihaemagglutinin antibody titre > 30%;
- mean geometric increase > 2.0;
- the proportion of subjects achieving an HI titre ≥40 or SRH titre ≥25 mm^2 (*) should be > 60%.

3.2. Clinical data

The frequency of the following symptoms should be assessed:

a) local reactions:

- indurations larger than 50 mm diameter and persisting for more than 3 days;
- ecchymosis;

b) general symptoms:

- temperature above 38^0C for 24 hours or more;
- malaise;
- shivering.

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