HARMONISATION OF REQUIREMENTS FOR INFLUENZA VACCINES

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HARMONISATION OF REQUIREMENTS FOR INFLUENZA VACCINES

A. YEARLY CHOICE OF INFLUENZA VIRUS STRAINS FOR VACCINES

WHO has two international influenza centres (at the National Institute for Medical Research in Mill Hill and at the Centre for Disease Control in Atlanta), 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 Community (EC). The predominant influenza viruses are believed to be similar from one Member State of the EC to another. There is thus little scientific justification for different composition of vaccines throughout the EC.

Since 1992, an annual meeting of EC experts is convened after the WHO meeting, as soon as practically possible, in order to take an EC wide decision regarding influenza virus strains for vaccine production for the next season, taking into consideration the epidemiology of influenza in the EC.

B. POTENCY OF INFLUENZA VACCINE

The potency of influenza vaccines used in the Member States is generally between 10 and 15 μg HA per strain and per dose. There is concern at accepting antigen content below 15 μg HA, especially because of poor antibody response in the elderly, who are one of the target populations.

Thus for influenza vaccines to be acceptable throughout the EEC, they should 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 13.5 μg HA per strain and per dose.
C 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 EC national authorities must be achieved to permit effective batch release of vaccines within the EC.

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 EC 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 Batch number
4.4 Number of containers
4.5 Number of doses per container
4.6 Type of container
4.7 Date of release and reference number
4.8 Date of expiry

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

Primary seed
H3N2
Lot n°: ............

Primary seed
H1N1
Lot n°: ............

Primary seed
B
Lot n°: ............

Working seed
H3N2
Lot n°: ............

Working seed
H1N1
Lot n°: ............

Working seed
B
Lot n°: ............

Monovalent bulk
H3N2
Lot n°: ............

Monovalent bulk
H1N1
Lot n°: ............

Monovalent bulk
B
Lot n°: ............

Trivalent bulk
Lot n°: ............

Final product

Filling lot N°: ............
Seed Virus

1. Information on manufacture
   1.1 Virus strain:
   1.2 Source and lot No of primary seed:
   1.3 Passage history of receipt:
   1.4 Date of receipt:
   1.5 Comments:
   1.6 Storage conditions:
   1.7 Working seed lot No:
   1.8 Passage history of seed lot(s):
   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:
### b) Neuraminidase

<table>
<thead>
<tr>
<th>Antigen</th>
<th>NT Titre</th>
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<tbody>
<tr>
<td>anti-N2NA</td>
<td>Antiserum</td>
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- A/Shang/11/87 (H3N2) Ref.
- A/Sich/2/87 (H3N2) Ref.
- A/Taiw/1/86 (HIN1) Ref.
- B/Yam/16/88 Ref.
- A/Sang/11/87

Working seed lot n° ...

### 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 Concentration/purification procedure:
1.9 Added antibiotics:
1.10 Filtration details (if any):

2. Tests on monovalent virus pool
2.1 Test for inactivation
   Date of test:
   Test result:

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:
D. CLINICAL TRIAL 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. The results of the trials are not part of the yearly licensing procedure. 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 haemagglutinin 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, various doses of antigens need to be tested 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 the note for guidance on Good Clinical Practice.

The clinical trials are carried out by the manufacturers, who will forward the results, as soon as they have been obtained, to the competent authorities and in any event before the next influenza season.

2. GENERAL REQUIREMENTS

2.1 Vaccine used in the trial

The composition of the vaccine used in the trial shall be such as to fulfil the requirements of the yearly EC 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.

Groups of at least 50 individuals shall be constituted.
2.3 Exclusion criteria

The following subjects shall not be entered into a trial:
- subjects known to be allergic to chicken protein;
- subjects with fever or presenting an infectious episode;
- pregnant women.

2.4 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.

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

2.6 Antibody titration

All sera shall be assayed for anti-haemagglutinin 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.
2.7 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 mm²;

b) in HI tests, seroconversion corresponds to:
   - negative prevaccination serum/postvaccination serum 2 40;
   - a significant increase in antibody titre, i.e. at least a fourfold increase in titre;

c) in SHR tests, seroconversion corresponds to: (*)
   - negative prevaccination serum/postvaccination serum: area 2 25 mm²;
   - 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.

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:
   - number of seroconversions or significant increase in antihaemagglutinin antibody titre >40%;
   - mean geometric increase >2.5;
   - the proportion of subjects achieving an HI titre 2 40 or SRH titre 2 25 mm² (*) should be >70%.

* In most SRH test systems, a zone area of 25 mm² is approximately equivalent to an HI titre of 1:40. However, this relationship can be affected by experimental conditions and should be re-examined in each laboratory so as to calibrate the test system adequately.
b) The following serological assessments should be considered for each strain in the group of subjects aged over 60:
   - number of seroconversions or significant increase in antihaemagglutinin antibody titre > 30%;
   - mean geometric increase > 2;
   - the proportion of subjects achieving an HI titre 2 40 or SRH titre 2 25 mm² 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 °C for 24 hours or more;
   - malaise;
   - shivering.

References


* In most SRH test systems, a zone area of 25 mm² is approximately equivalent to an HI titre of 1:40. However, this relationship can be affected by experimental conditions and should be re-examined in each laboratory so as to calibrate the test system adequately.