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VACCINES FOR HUMAN USE

Vaccina ad usum humanum

For a combined vaccine, where there is no monograph to cover a particular combination, the vaccine complies with the monograph for each individual component, with any necessary modifications approved by the competent authority.

DEFINITION

Vaccines for human use are preparations containing substances capable of inducing a specific and active immunity in man against an infecting agent or the toxin or the antigen elaborated by it. They shall have been shown to have acceptable immunogenic activity in man with the intended vaccination schedule. They may contain an adjuvant.

Vaccines for human use may contain: organisms inactivated by chemical or physical means that maintain adequate immunogenic properties; living organisms that are naturally avirulent or that have been treated to attenuate their virulence whilst retaining adequate immunogenic properties; antigens extracted from the organisms or secreted by them or produced by genetic engineering; the antigens may be used in their native state or may be detoxified by chemical or physical means and may be aggregated, polymerised or conjugated to a carrier to increase their immunogenicity.

Terminology used in monographs on vaccines for human use is defined in chapter 5.2.1.

Bacterial vaccines are suspensions of various degrees of opacity in colourless or almost colourless liquids, or may be freeze-dried. The concentration of living or inactivated bacteria is expressed in terms of International Units of opacity or, where appropriate, is determined by direct cell count or, for living bacteria, by viable count.

Bacterial toxoids are prepared from toxins by diminishing their toxicity to a non-detectable level or by completely eliminating it by physical or chemical procedures whilst retaining adequate immunogenic properties. The toxins are obtained from selected strains of micro-organisms. The method of production is such that the toxoid does not revert to toxin. Toxoids may be liquid or freeze-dried. They may be purified and adsorbed. Adsorbed toxoids are suspensions of white or grey particles dispersed in colourless or pale yellow liquids and may form a sediment at the bottom of the container.

Viral vaccines are prepared from viruses grown in animals, in fertilised eggs, in suitable cell cultures or in suitable tissues or by culture of genetically engineered cells. They are liquids that vary in opacity according to the type of preparation or may be freeze-dried. Liquid preparations and freeze-dried preparations after reconstitution may be coloured if a pH indicator such as phenol red has been used in the culture medium.

PRODUCTION

General provisions. The production method for a given product must have been shown to yield consistently batches comparable with the batch of proven clinical efficacy and safety in man. Requirements for production including in-process testing are included in individual monographs. Where justified and authorised, certain tests may be omitted

where it can be demonstrated, for example by validation studies, that the production process consistently ensures compliance with the test.

Unless otherwise justified and authorised, vaccines are produced using a seed-lot system. The methods of preparation are designed to maintain adequate immunogenic properties, to render the preparation harmless and to prevent contamination with extraneous agents.

Unless otherwise justified and authorised, in the production of a final lot of vaccine, the number of passages of a virus, or the number of subcultures of a bacterium, from the master seed lot shall not exceed that used for production of the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy.

Vaccines are as far as possible free from ingredients known to cause toxic, allergic or other undesirable reactions in man. Suitable additives, including stabilisers and adjuvants may be incorporated. Penicillin and streptomycin are not used at any stage of production nor added to the final product; however, master seed lots prepared with media containing penicillin or streptomycin may, where justified and authorised, be used for production.

Consistency of production is an important feature of vaccine production. Monographs on vaccines for human use give limits for various tests carried out during production and on the final lot. These limits may be in the form of maximum values, minimum values or minimum and maximum tolerances around a given value. While compliance with these limits is required, it is not necessarily sufficient to ensure consistency of production for a given vaccine. For relevant tests, the manufacturer must therefore define for each product a suitable release limit or limits to be applied in view of the results found for batches tested clinically and those used to demonstrate consistency of production. These limits may be subsequently refined on a statistical basis in the light of production data.

Substrates for propagation. Substrates for propagation comply with the relevant requirements of the Pharmacopoeia (5.2.2, 5.2.3) or in the absence of such requirements with those of the competent authority. Processing of cell banks and subsequent cell cultures is done under aseptic conditions in an area where no other cells are being handled. Serum and trypsin used in the preparation of cell suspensions shall be shown to be free from extraneous agents.

Seed lots. The strain of bacterium or virus used in a master seed lot is identified by historical records that include information on the origin of the strain and its subsequent manipulation. Suitable measures are taken to ensure that no micro-organism other than the seed strain is present in a seed lot.

Culture media. Culture media are as far as possible free from ingredients known to cause toxic, allergic or other undesirable reactions in man; if inclusion of such ingredients is necessary, it shall be demonstrated that the amount present in the final lot is reduced to such a level as to render the product safe. Approved animal (but not human) serum may be used in the growth medium for cell cultures but the medium used for maintaining cell growth during virus multiplication shall not contain serum, unless otherwise stated. Cell culture media may contain a pH indicator such as phenol red and approved antibiotics at the lowest effective concentration although it is preferable to have a medium free from antibiotics during production.

Propagation and harvest. The seed cultures are propagated and harvested under defined conditions. The purity of the harvest is verified by suitable tests as defined in the monograph.

Control cells. For vaccines produced in cell cultures, control cells are maintained and tested as prescribed. In order to provide a valid control, these cells must be maintained in conditions that are rigorously identical with those used for the production cell cultures, including use of the same batches of media and media changes.

Control eggs. For live vaccines produced in eggs, control eggs are incubated and tested as prescribed in the monograph.

Purification. Where applicable, validated purification procedures may be applied.

Inactivation. Inactivated vaccines are produced using a validated inactivation process whose effectiveness and consistency have been demonstrated. Where there are recognised potential contaminants of a harvest, for example in vaccines produced in eggs from healthy, non-SPF flocks, the inactivation process is also validated with respect to the potential contaminants. A test for effectiveness of the inactivation process is carried out as soon as possible after the inactivation process, unless otherwise justified and authorised.

Stability of intermediates. During production of vaccines, intermediates are obtained at various stages and are stored, sometimes for long periods. Such intermediates include:

- seed lots,
- live or inactivated harvests from bacterial or viral cultures,
- purified harvests that may consist of toxins or toxoids, polysaccharides, bacterial or viral suspensions,
- purified antigens,
- adsorbed antigens,
- conjugated polysaccharides,
- final bulk vaccine,
- vaccine in the final closed container stored at a temperature lower than that used for stability studies and intended for release without re-assay.

Except where they are used within a short period of time, stability studies are carried out on the intermediates in the intended storage conditions to establish the expected extent of degradation. For final bulk vaccine, stability studies may be carried out on representative samples in conditions equivalent to those intended to be used for storage. For each intermediate (except for seed lots), a period of validity applicable for the intended storage conditions is established, where appropriate in the light of stability studies.

Final bulk. The final bulk is prepared by aseptically blending the ingredients of the vaccine.

Adsorbents. Vaccines may be adsorbed on aluminium hydroxide, aluminium phosphate, calcium phosphate or other suitable adsorbent; the adsorbents are prepared in special conditions which confer the appropriate physical form and adsorptive properties.

Antimicrobial preservatives. Antimicrobial preservatives are used to prevent spoilage or adverse effects caused by microbial contamination occurring during the use of a vaccine. Antimicrobial preservatives are not included in freeze-dried products. For single-dose liquid preparations, inclusion of antimicrobial preservatives is not normally acceptable. For multidose liquid preparations, the need for effective antimicrobial preservation is evaluated taking into account likely contamination during use and the maximum recommended period of use after broaching of the container. If an antimicrobial preservative is used, it shall be shown that it does not impair the safety or efficacy of the vaccine. Addition of antibiotics as antimicrobial preservatives is not normally acceptable.

During development studies, the effectiveness of the antimicrobial preservative throughout the period of validity shall be demonstrated to the satisfaction of the competent authority.

The efficacy of the antimicrobial preservative is evaluated as described in chapter 5.1.3. If neither the A criteria nor the B criteria can be met, then in justified cases the following criteria are applied to vaccines for human use: bacteria, no increase at 24 h and 7 days, 3 log reduction at 14 days, no increase at 28 days; fungi, no increase at 14 days and 28 days.

Final lot. For vaccines for parenteral administration, the final lot is prepared by aseptically distributing the final bulk into sterile tamper-proof containers which, after freeze-drying where applicable, are closed so as to exclude contamination. For vaccines for administration by a non-parenteral route, the final lot is prepared by distributing the final bulk under suitable conditions into sterile, tamper-proof containers.

Appearance. Each container (vial, syringe or ampoule) in each final lot is inspected visually or mechanically for acceptable appearance.

Degree of adsorption. During development of an adsorbed vaccine, the degree of adsorption is evaluated as part of the consistency testing. A release specification for the degree of adsorption is established in the light of results found for batches used in clinical testing. From the stability data generated for the vaccine it must be shown that at the end of the period of validity the degree of adsorption will not be less than for batches used in clinical testing.

Stability. During development studies, maintenance of potency of the final lot throughout the period of validity shall be demonstrated; the loss of potency in the recommended storage conditions is assessed and excessive loss even within the limits of acceptable potency may indicate that the vaccine is unacceptable.

Expiry date. Unless otherwise stated, the expiry date is calculated from the beginning of the assay or from the beginning of the first assay for a combined vaccine. For vaccines stored at a temperature lower than that used for stability studies and intended for release without re-assay, the expiry date is calculated from the date of removal from cold storage. If, for a given vaccine, an assay is not carried out, the expiry date for the final lot is calculated from the date of an approved stability-indicating test or failing this from the date of freeze-drying or the date of filling into the final containers. For a combined vaccine where components are presented in separate containers, the expiry date is that of the component which expires first.

The expiry date applies to vaccines stored in the prescribed conditions.

Animal tests. In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests must be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. The criteria for judging tests in monographs must be applied in the light of this. For example, if it is indicated that an animal is considered to show positive, infected etc. when typical clinical signs or death occur then as soon as sufficient indication of a positive result is obtained the animal in question shall be either humanely destroyed or given suitable treatment to prevent unnecessary suffering. In accordance with the General Notices, alternative test methods may be used to demonstrate compliance with the monograph and the use of such tests is particularly encouraged when this leads to replacement or reduction of animal use or reduction of suffering.

TESTS

Vaccines comply with the tests prescribed in individual monographs including, where applicable, the following:

pH (2.2.3). Liquid vaccines, after reconstitution where applicable, comply with the limits for pH approved for the particular preparation.

Adjuvant. If the vaccine contains an adjuvant, the amount is determined and shown to be within acceptable limits with respect to the expected amount (see also the tests for aluminium and calcium below).

Aluminium (2.5.13): maximum 1.25 mg of aluminium (Al) per single human dose where an aluminium adsorbent has been used in the vaccine, unless otherwise stated.

Calcium (2.5.14): maximum 1.3 mg of calcium (Ca) per single human dose where a calcium adsorbent has been used in the vaccine, unless otherwise stated.

Free formaldehyde (2.4.18): maximum 0.2 g/l of free formaldehyde is present in the final product where formaldehyde has been used in the preparation of the vaccine, unless otherwise stated.

Phenol (2.5.15): maximum 2.5 g/l is present in the final product where phenol has been used in the preparation of the vaccine, unless otherwise stated.

Water (2.5.12): maximum 3.0 per cent *m/m* for freeze-dried vaccines, unless otherwise stated.

Extractable volume (2.9.17). Unless otherwise justified and authorised, it complies with the requirement for extractable volume.

STORAGE

Store protected from light. Unless otherwise stated, the storage temperature is 5 ± 3 °C; liquid adsorbed vaccines must not be allowed to freeze.

LABELLING

The label states:

- the name of the preparation,
- a reference identifying the final lot,
- the recommended human dose and route of administration,
- the storage conditions,
- the expiry date,
- the name and amount of any antimicrobial preservative,
- the name of any antibiotic, adjuvant, flavour or stabiliser present in the vaccine,
- the name of any constituent that may cause adverse reactions and any contra-indications to the use of the vaccine,
- for freeze-dried vaccines:
 - the name or composition and the volume of the reconstituting liquid to be added,
 - the time within which the vaccine is to be used after reconstitution.