ANNEX 2

MANUFACTURE OF BIOLOGICAL MEDICINAL PRODUCTS FOR HUMAN USE

Scope

The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products prepared by the following methods of manufacture will fall under the scope of this annex (1). Biological medicinal products manufactured by these methods include: vaccines, immunosera, antigens, hormones, cytokines, enzymes and other products of fermentation (including monoclonal antibodies and products derived from r-DNA).

a) Microbial cultures, excluding those resulting from r-DNA techniques;

b) Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques;

c) Extraction from biological tissues

d) Propagation of live agents in embryos or animals

(Not all of the aspects of this annex may necessarily apply to products in category a).

Note

In drawing up this guidance, due consideration has been given to the general requirements for manufacturing establishments and control laboratories proposed by the WHO.

The present guidance does not lay down detailed requirements for specific classes of biological products, and attention is therefore directed to other guidelines issued by the Committee for Proprietary Medicinal Products (CPMP), for example the note for guidance on monoclonal antibodies and the note for guidance on products of recombinant DNA technology ("The rules governing medicinal product in the European Community", Volume 3).

Principle

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The way in which biological medicinal products are produced, controlled and administered make some particular precautions necessary.

Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the production of biological medicinal products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products are variable. Moreover, the materials used in these cultivation processes provide good substrates for growth of microbial contaminants.

Control of biological medicinal products usually involves biological analytical techniques which have a greater variability than physico-chemical determinations. In-process controls therefore take on a great importance in the manufacture of biological medicinal products.

(1) Biological medicinal products manufactured by these methods include: vaccines, immunosera, antigens, hormones, cytokines, enzymes and other products of fermentation (including monoclonal antibodies and products derived from r-DNA).

Personnel

1. All personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured should receive additional training specific to the products manufactured and to their work. Personnel should be given relevant information and training in hygiene and microbiology.

2. Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology and veterinary medicine, together with sufficient practical experience to enable them to exercise their management function for the process concerned.

3. The immunological status of personnel may have to be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated where necessary with appropriate specific vaccines and have regular health checks. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with infectious agents. Visitors should generally be excluded from production areas.

4. Any changes in the immunological status of personnel which could adversely affect the quality of the product should preclude work in the production area. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status or chest X-ray.

5. In the course of a working day, personnel should not pass from areas where exposure to live organisms or animals is possible to areas where other products or different organisms are handled. If such passage is unavoidable, clearly defined decontamination measures, including change of clothing and shoes and, where necessary, showering should be followed by staff involved in any such production.

Premises and equipment

6. The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step, bearing in mind the level of contamination of the starting materials and the risk to the finished product.

7. The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis and the use of closed systems. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.

8. In principle, dedicated facilities should be used for the production of BCG vaccine and for the handling of live organisms used in production of tuberculin products.

9. Dedicated facilities should be used for the handling of Bacillus anthracis, of Clostridium botulinum and of Clostridium tetani until the inactivation process is accomplished.

10. Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.

11. Simultaneous production in the same area using closed systems of biofermenters may be acceptable for products such as monoclonal antibodies and products prepared by DNA techniques.

12. Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross contamination. For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.

13. Positive pressure areas should be used to process sterile products but negative pressure in specific areas at point of exposure of pathogens is acceptable for containment reasons.

    Where negative pressure areas or safety cabinets are used for aseptic processing of pathogens, they should be surrounded by a positive pressure sterile zone.

14. Air filtration units should be specific to the processing area concerned and recirculation of air should not occur from areas handling live pathogenic organisms.

15. The layout and design of production areas and equipment should permit effective cleaning and decontamination (e.g. by fumigation). The adequacy of cleaning and decontamination procedures should be validated.

16. Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.

17. Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilisation. The use of 'clean in place' and 'sterilise in place' systems should be encouraged. Valves on fermentation vessels should be completely steam sterilisable. Air vent filters should be hydrophobic and validated for their scheduled life span.

18. Primary containment should be designed and tested to demonstrate freedom from leakage risk.

19. Effluents which may contain pathogenic micro-organisms should be effectively decontaminated.

20. Due to the variability of biological products or processes, some additives or ingredients have to be measured or weighed during the production process (e.g. buffers). In these cases, small stocks of these substances may be kept in the production area.

Animal quarters and care

21. Animals are used for the manufacture of a number of biological products, for example polio vaccine (monkeys), snake antivenoms (horses and goats), rabies vaccine (rabbits, mice and hamsters) and serum gonadotropin (horses). In addition, animals may also be used in the quality control of most sera and vaccines, e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).

22. General requirements for animal quarters, care and quarantine are laid down in Directive 86/609/EEC[2]. Quarters for animals used in production and control of biological products should be separated from production and control areas. The health status of animals from which some starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in such areas must be provided with special clothing and changing facilities. Where monkeys are used for the production or quality control of biological medicinal products, special consideration is required as laid down in the current WHO Requirements for Biological Substances n° 7.

Documentation

23. Specifications for biological starting materials may need additional documentation on the source, origin, method of manufacture and controls applied, particularly microbiological controls.

24. Specifications are routinely required for intermediate and bulk biological medicinal products.

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[2] Directive 2003/65/EC of the European Parliament and of the Council of 22 July 2003 amending Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (OJ L 230, 16.09.2003, p. 32- 33)

Production

Starting materials

25. The source, origin and suitability of starting materials should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests.

26. Where sterilisation of starting materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation).

Seed lot and cell bank system

27. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.

28. The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the marketing authorisation dossier. Scaling up of the process should not change this fundamental relationship.

29. Seed lots and cell banks should be adequately characterised and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Seed lots and cell banks should be established, stored and used in such a way as to minimise the risks of contamination or alteration.

30. Establishment of the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.

31. Evidence of the stability and recovery of the seeds and banks should be documented. Storage containers should be hermetically sealed, clearly labelled and kept at an appropriate temperature. An inventory should be meticulously kept. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken should be recorded.

32. Only authorised personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimise the risks of total loss.

33. All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned to the stock.

Operating principles

34. The growth promoting properties of culture media should be demonstrated.

35. Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling take place.

36. Centrifugation and blending of products can lead to aerosol formation, and containment of such activities to prevent transfer of live micro-organisms is necessary.

37. If possible, media should be sterilised in situ. In-line sterilising filters for routine addition of gases, media, acids or alkalis, defoaming agents etc. to fermenters should be used where possible.

38. Careful consideration should be given to the validation of any necessary virus removal or inactivation undertaken (see CPMP notes for guidance).

39. In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.

40. A wide variety of equipment is used for chromatography, and in general such equipment should be dedicated to the purification of one product and should be sterilised or sanitised between batches. The use of the same equipment at different stages of processing should be discouraged. Acceptance criteria, life span and sanitation or sterilisation method of columns should be defined.

Quality control

41. In-process controls play a specially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for quality (e.g. virus removal) but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.

42. It may be necessary to retain samples of intermediate products in sufficient quantities and under appropriate storage conditions to allow the repetition or confirmation of a batch control.

43. Continuous monitoring of certain production processes is necessary, for example fermentation. Such data should form part of the batch record.

44. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.