Report on the prevention of microbial contamination of medicinal products.

Department of Health and Social Security
Medicines Commission

Report on the Prevention of Microbial Contamination of Medicinal Products

Chairman: The Lord Rosenheim KBE MD FRCP FRS

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Dear Secretary of State

On 16 March 1972 you asked the Medicines Commission "in pursuance of their functions under the Medicines Act 1968, to arrange for an immediate review of measures which should be taken in the course of production, distribution, storage and use of medicinal products to prevent them becoming vehicles of infection".

At their meeting on 29 March 1972 the Commission appointed a Committee under the Chairmanship of Lord Rosenheim to undertake this review and to report to them. The Committee produced an interim report on heat sterilized fluids for parenteral administration which was accepted by the Commission on 20 July 1972 and subsequently presented to you.

The Committee have now produced a final report covering the remainder of their remit. It draws attention to potential sources of contamination of medicinal products and makes a number of recommendations.

Following Lord Rosenheim's untimely death, Dr Frank Hartley chaired the Committee through its final stages.

The Medicines Commission accepted the report at their meeting on 8 February 1973, and I now have much pleasure in submitting it to you.

Yours sincerely
ANDREW WILSON
Acting Chairman, Medicines Commission

Dear Professor Wilson

I am writing to thank you for the final report of the Medicines Commission on the prevention of microbial contamination of medicinal products, which I have read with great interest. I am arranging for its early publication and will ensure that its recommendations are brought to the attention of those concerned.

Please convey my thanks to all involved with the preparation of this and the interim report for the time and trouble they have taken.

Yours sincerely
KEITH JOSPEH

In December 1972, when the major part of the Committee's work had been accomplished, members learned with deep regret of the death of Lord Rosenheim.

Dr F. Hartley accepted the members' nomination to take the Chair for the remaining meetings.

CONTENTS

I. Introduction

1. BACKGROUND TO THE FINAL REPORT

1.1 On 16 March 1972, the Secretary of State for Social Services announced in Parliament that he had invited the Medicines Commission, "in pursuance of their functions under the Medicines Act 1968, to arrange for an immediate review of measures which should be taken in the course of production, distribution, storage and use of medicinal products to prevent them becoming vehicles of infection".

At their meeting on 29 March 1972 the Commission appointed a Committee with the following membership:

The Lord Rosenheim KBE MD FRCP FRS (Chairman)
Dr F. Hartley CBE BSc PhD FPS FRIC
Dr G. E. Paget MD
Professor E. F. Scowen DS McD FRCP FRCS FRCPE FRCPath
Professor R. E. O. Williams BSc MD FRCP FRCPath
Professor A. Wilson CBE PhD MD FRCP FPS

to consider the remit from the Secretary of State and to report to them. The Commission directed that, as a first priority, consideration should be given by the Committee to measures relating to sterile products.

1.2 The Committee produced an interim report on the manufacture of heat sterilized infusion fluids for parenteral administration which was accepted by the Medicines Commission on 20 July 1972. Thereafter the interim report was submitted to the Secretary of State who accepted it and published it on 14 August 1972.

1.3 The Committee have been pleased to learn that the United Kingdom Health Departments took immediate steps to bring the interim report to the attention of those concerned with the manufacture of heat sterilized infusion fluids, both in industry and the hospital service.

1.4 The remainder of the Committee's remit involved consideration of the following topics:

Chapter II:	Sterilization by methods other than the use of steam.
Chapter III:	The manufacture of sterile products other than infusion fluids; contamination hazards in non-sterilized products.
Chapter IV:	Additions to intravenous infusion fluids.
Chapter V:	Indicators and tests in the sterilization process.
Chapter VI:	Points arising from the report of the Committee set up under Mr C. M. Clothier QC to inquire into the circumstances which led to the use of contaminated infusion fluids at Devonport Hospital, Plymouth, in March 1972.

1.5 The Committee decided that problems relating to the sterilization of devices, equipment and appliances lay outside their remit. Although many of the Committee's recommendations apply to the manufacture of blood

products, they have not concerned themselves with the technical problems peculiar to these products.

1.6 The Committee wish to repeat and amplify their view, expressed in the interim report, that their recommendations relate to industry, to hospital manufacturing units and to all other places where the manufacture of medicinal products takes place. The same standards of production and control should apply to all.

1.7 The Committee noted that the controls over certain sterile medicinal products at present exercised under the Therapeutic Substances Act 1956 will continue to be operated under the Medicines Act 1968 when the earlier Act has been repealed.

1.8 The Committee understand that the Health and Agriculture Departments are currently undertaking the revision of the Guide to Good Pharmaceutical Manufacturing Practice in the light of experience and the recommendations contained in the Commission's interim report. Further recommendations relevant to the content of the Guide are made in this report, and the Committee hope that the Departments will take these into account in the revision and arrange publication of the revised Guide at the earliest practicable date.

II. Sterilization by Methods Other than the Use of Steam

2. In their interim report the Committee considered sterilization by autoclaving. Of other methods of sterilization in use, the Committee have considered the following.

3. DRY HEAT STERILIZATION

3.1 Sterilization by dry heat is appropriate for equipment, particularly glassware, and medicinal products which will withstand the process. Ovens used for this process should comply with British Standard 3421.

3.2 The Committee consider that the sterilization of medicinal products by means of dry heat should be carried out in accordance with the procedures given in the British Pharmacopoeia.

4. RADIOSTERILIZATION

4.1 Radiosterilization is used mainly for the sterilization of plastics; it is also used to a small extent for the sterilization of medicinal products including some controlled by the Therapeutic Substances Act.

4.2 Some materials are seriously degraded by exposure to irradiation, resulting in lowering of potency or the creation of toxic degradation products, and this should be borne in mind by manufacturers when considering the suitability of the process for a particular product.

4.3 The Committee consider that there is a need for guidance to manufacturers on the application of this method of sterilization to medicinal products; they recommend that an appendix on the subject should be included in the new edition of the Guide to Good Pharmaceutical Manufacturing Practice.

5. STERILIZATION BY ETHYLENE OXIDE

5.1 Ethylene oxide is used for sterilizing some heat-labile materials. The process does not lend itself to physical methods of measurement, and consequently stringent microbiological controls and test procedures must be applied.

5.2 The Committee accept the value of ethylene oxide as a sterilizing agent for some containers, medical equipment and the few medicinal products for which only surface sterilization is needed. Its application to medicinal products should have regard to the risks of chemical incompatibility and of the production of toxic residues and to its inefficacy against organisms occluded in crystals or otherwise protected from the gas.

III. Manufacture of Sterile Products

6. In its interim report the Committee examined the problems of manufacture of large volume infusion fluids, terminally sterilized by autoclaving. The Committee have now examined the problems of contamination associated with the manufacture of sterile products generally.

7. MANUFACTURING PROCESSES

7.1 Sterile medicinal products may be made as solids, liquids, pastes or sprays. Some of these forms cannot be sterilized in the final containers; instead they need to be prepared in bulk in a sterile condition and filled aseptically. Aseptic filling is dealt with in the succeeding section of this report. So far as manufacture is concerned, problems of contamination arise for all sterile medicinal products, whether terminally sterilized or not. There are dangers of contamination from the manufacturing environment, including operatives, or from the starting materials, including containers. Terminal sterilization should not be allowed to mask contamination arising from bad manufacturing practice.

7.2 The Committee recommend that manufacturers should only use equipment which can be satisfactorily cleaned, and that this equipment should be regularly cleaned and maintained under competent supervision in accordance with written programmes.

7.3 All starting materials, particularly those of natural origin, can introduce contamination into a product. Containers and ingredients used in small quantities may not always be recognized as sources of contamination. The Committee recommend that manufacturers apply appropriate microbiological controls to all starting materials.

8. ASEPTIC FILLING OPERATIONS

The Committee have also considered current practice in the filling of products unsuitable for sterilization in their final containers. Three matters are of particular importance:

(i) whichever method of air cleansing is used for the filling room as a whole, particular attention should be paid to the local environment at points where the product is at maximum risk;

(ii) there is a need for appropriate and repeated training of all personnel employed in the filling process and for the adoption of a written training scheme;

(iii) the incursion into the filling area by untrained personnel is clearly hazardous.

9. CONTAINERS AND CLOSURES

9.1 The Committee now make the following recommendations with regard to containers, in addition to those made in the interim report:

(i) multi-dose containers are prone to contamination in use and their use should be avoided whenever practicable;

(ii) cardboard or cork liners are unsuitable as part of a closure for sterile products and should not be used;
(iii) all containers for sterile products should be so designed that any interference with them is evident;

9.2 The container is an integral part of the finished product and its design and specification should be considered in this light. The Committee recommend that the licensing authority established under the Medicines Act 1968 should ensure that due consideration is given to containers as part of the processing of applications for product licences.

10. PRESERVATIVES

The Committee have considered the use of antimicrobial preservatives in pharmaceutical preparations. They regard three points as being of particular importance:

(i) preservatives should not be used to mask unsatisfactory manufacturing practice;
(ii) care must be taken to select a preservative appropriate to the product;
(iii) there is a need for more reliable preservatives and for the definition of an acceptable preservative.

11. STERILE RADIOPHARMACEUTICALS

The Committee have discussed the preparation of radiopharmaceuticals. They consider that the normal precautions for the preparation of sterile medicinal products should always be observed. They appreciate that sterility and pyrogen tests cannot be meaningfully applied to short-life isotopes before release, but such tests carried out in retrospect can be valuable in assessing the techniques used. Collaboration between pharmacists and physicists is necessary to ensure all aspects of the safety of these products.

12. OTHER PRODUCTS AS VEHICLES OF INFECTION

12.1 The British Pharmacopoeia Commission has received the report of its ad hoc Committee on Microbial Contamination which recommends the imposition of bacteriological controls on particular starting materials and products where the possibility of contamination by pathogens exists. The Committee are of the opinion that the recommendations of this report should be further publicised; they should be observed by all manufacturers concerned with such starting materials and products.

12.2 The Committee have noted that certain eye preparations and solutions for internal irrigation are not currently required to be sterile, except when they are manufactured for compliance with the requirements of the official compendia. The Committee are of the opinion that all products in these categories should be required to be sterile.

12.3 For some products in the following groups the recommended use may require the products to be free from contamination:

(i) dusting powders;
(ii) eardrops;
(iii) nasal drops.

12.4 The Committee recommend that the licensing authority should impose a sterility requirement as a condition of product licences for all eye preparations and solutions for internal irrigation and that in the case of dusting powders, eardrops and nasal drops it should consider the need for such a requirement whenever appropriate.

IV. Additions to Intravenous Infusion Fluids

13.1 Medicinal products are frequently added to intravenous infusions after manufacture either before or during administration. The Committee recognise the need for such additions, but they draw attention to two possible hazards:

(i) contamination of the infusion fluid by micro-organisms during the addition process;

(ii) incompatibility between the additive and the fluid.

13.2 Hospital nursing staff are commonly instructed to make such additions either to the container or through the giving set. It appears that they may not always have received adequate tuition for this purpose during their standard training.

13.3 The question of such training does not lie within the terms of reference of the Committee, but they consider that it needs attention and have therefore suggested to the Department of Health and Social Security that it be considered by the Standing Medical, Nursing and Pharmaceutical Advisory Committees.

V. Indicators and Tests in the Sterilization Process

14. The Committee have considered the value of chemical and biological indicators which are available for use in sterilization processes.

15. **CHEMICAL INDICATORS**

The chemical indicators at present available undergo a change of colour or form when exposed to the sterilizing agent. By their nature they can do no more than establish that a particular container, or group of containers, has been exposed to the sterilizing environment. They cannot provide evidence that the container has been exposed for a time sufficient to guarantee sterility, and consequently they are of value only in the negative sense of revealing failure to sterilize the product.

16. **BIOLOGICAL INDICATORS**

Biological indicators contain selected bacterial spores which are sensitive to the sterilizing agent. Although the use of such indicators may appear to be a logical method of control, in practice it is difficult to obtain spore preparations of consistent and appropriate resistance.

17. **OTHER CONTROLS OF THE STERILIZATION PROCESS**

The Committee have concluded that chemical and biological indicators are of doubtful reliability and hence of secondary importance. They consider that the correct way to control a sterilization process for which the physical requirements are known is to ensure that these requirements are met by the use of a sound method of physical measurement.

18. **STERILITY TESTING**

18.1 The Committee have considered the value of sterility testing in manufacture.

18.2 Compliance of a sample with the requirements of a sterility test is no guarantee of sterility throughout the batch. A low level or uneven distribution of contamination may not be detected by conventional methods of sampling and testing. This obtains for either aseptically processed or terminally sterilized products. Nevertheless, sterility testing of a batch is a valuable safeguard capable of detecting contaminated samples; when used over a large series of batches, such testing provides a good indication of the quality of manufacture. For this reason, the Committee support the reasoned application of the test as part of the control procedure.

18.3 Sterility testing as such is no safeguard against bad manufacturing practice, nor is it a substitute for care and vigilance in the sterilization process itself. Meticulous attention to the details of the manufacturing processes and accurate recording are essential.

VI. Problems Referred to the Medicines Commission by the Clothier Committee of Inquiry

19. The Clothier Committee of Inquiry called attention to a number of problems relating to sterile medicinal products, and these were, as suggested, referred to the Medicines Commission. Some of them have already been the subject of recommendations in the Commission's interim report, and the following paragraphs deal with the outstanding matters.

20. DELAYED STERILITY TESTING

A report by the then Ministry of Health into an incident of contamination in 1966 recommended the manufacturer to consider the use of delayed sterility testing. After re-examing the value of such testing, the Committee have concluded that the newer methods of membrane filtration or concentrated broth injection are more satisfactory, and have the advantage of being immediately applicable. The Committee recommend the adoption of one of these newer methods by manufacturers.

21. SPOT CHECKS ON PRODUCTS AFTER MANUFACTURE

21.1 The Committee are informed that the Medicines Division of the Department of Health and Social Security has commenced a planned programme of sampling and analysis of medicinal products, both sterile and non-sterile, and covering those manufactured both in industry and in the hospital service. The programme provides for spot checks after distribution.

21.2 It is the opinion of the Committee that spot checks, as part of the planned programme of sampling, will continue to play a useful and necessary part in the maintenance of satisfactory standards.

22. BATCH NUMBERS IN A RECALL PROCEDURE

22.1 The Committee have considered the value of a system by which the distribution of individual batches of medicinal products would be recorded on invoices by wholesale dealers for use in an emergency recall procedure.

22.2 The purpose of such a system would be to facilitate the rapid recall of faulty batches. The Committee heard the views of the pharmaceutical trade associations and understood that some manufacturers and wholesale dealers operate other simpler systems. These involve the recording by manufacturers of the period during which a particular batch is sold and of the customers supplied during that period.

22.3 The Committee note that in several instances manufacturers using these simple systems have operated them successfully, and the Committee regard them as satisfactory provided that they are capable of rapid implementation. The Committee accept that the recording of batch numbers on invoices by wholesale dealers would create much additional work and

consider that they would not be justified in recommending adoption of the practice.

22.4 All recall systems depend on the maintenance of appropriate records, and the Committee note that the recall arrangements of manufacturers and wholesale dealers are now examined by the Medicines Inspectorate of the Department of Health and Social Security as part of the licensing procedure. The Committee recommend that these arrangements should be subject to periodic review by the Inspectorate.

22.5 In general, less elaborate arrangements than those of industry are necessary for the recall of hospital manufactured products. However, any arrangements made should provide for the rapid retrieval of faulty products. All products should bear a batch number on the label.

VIII. Conclusions

23. SUMMARY OF RECOMMENDATIONS

The principal recommendations and conclusions of the Committee are as follows:

(i) Starting materials, containers, equipment and operatives should always be recognized as potential sources of contamination, and appropriate controls and cleansing procedures should be applied (paragraphs 7, 12).

(ii) Particular attention must be given to the working environment for the filling of products unsuitable for sterilization in their final containers (paragraph 8).

(iii) Care should be taken to apply a method of sterilization which is appropriate to the product to be treated (paragraphs 3–5).

(iv) A reliable method of physical measurement should be used to control the sterilization process; chemical and biological indicators are of secondary importance (paragraphs 15–17).

(v) Sterility testing of batches can be a valuable safeguard capable of detecting contaminated samples, but it is no substitute for care and vigilance in the sterilization process itself (paragraph 18).

(vi) Broth injection or membrane filtration should be used in sterility testing of batches of infusion fluids (paragraph 20).

(vii) All eye preparations and solutions for internal irrigation should in future be required to be sterile (paragraph 12).

(viii) The licensing authority should review the sterility requirements for certain categories of products according to their use (paragraph 12.4).

(ix) The licensing authority should take into account the container when assessing or reviewing applications for product licences (paragraph 9).

(x) The batch recall arrangements of manufacturers should be periodically reviewed by the licensing authority (paragraph 22).

(xi) The training of staff involved in additions to intravenous infusion fluids should be reviewed (paragraph 13).

(xii) The same standards of production and control should apply to both commercial manufacturers and to hospital manufacturing units (paragraph 1.6).

(xiii) Where appropriate, recommendations on the topics covered by the report should be included in the revision of the Guide to Good Pharmaceutical Manufacturing Practice (paragraph 1.8).

24. GENERAL CONCLUSION

The safety of the patient is directly related to the understanding of essential procedures by all those involved in the handling of medicinal products. The Committee consider that there is no short cut to the implementation of measures for the prevention of contamination and that controls imposed through licensing and inspection cannot replace the intelligent, vigilant and constant application of well-defined and established techniques.

Appendix

ACKNOWLEDGEMENTS

The Committee would like to place on record their gratitude to the professional and technical staff of the Department of Health and Social Security for valuable help and information concerning the topics covered by this report. They wish to acknowledge particularly the considerable help in the preparation of the report they have received from the Secretaries, Mr K. G. Reeve and Mr R. P. Cleasby, to whom they are greatly indebted.

The Committee are very grateful to the Association of the British Pharmaceutical Industry, the National Association of Pharmaceutical Distributors and the Proprietary Association of Great Britain for submitting valuable information on batch recall procedures.

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