Interim report on heat sterilized fluids for parental administration / Medicines Commission.

Department of Health and Social Security

Medicines Commission

Interim Report on Heat Sterilized Fluids for Parenteral Administration

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, of which I was made Chairman, to undertake this review and to report to them. They directed that, as a first priority, consideration should be given by the Committee to measures relating to sterile products.

My Committee decided, in the first instance, to concentrate upon the manufacture of heat sterilized infusion fluids for parenteral administration. Certain points of importance concerning present practice in the manufacture of these fluids have been brought to our attention and we thought that they should be considered as a matter of urgency. We have therefore thought it proper to comment briefly on these and make certain recommendations immediately in this interim report which was accepted by the Medicines Commission on 20 July 1972.

This interim report is enclosed. The Commission will now study the remainder of their remit and will report further in due course.

Yours sincerely,

ROSENHEIM

Dear Lord Rosenheim,

I have read with keen interest the Medicines Commission's interim report on heat sterilized infusion fluids for parenteral administration and would like to thank you and the members of your Committee for the time and trouble which you have devoted to producing a report on this important subject in such a short time. Steps will be taken at once to publish the report and its recommendations will be brought to the attention of those concerned.

Yours sincerely,

KEITH JOSEPH

1. INTRODUCTION

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
Dr F Hartley CBE BSc PhD FPS FRIC
Dr G E Paget MD
Professor E F Scowen DSc MD FRCP FRCS FRCPE FRCPath
Professor A Wilson CBE PhD MD FRCP FPS
Professor R E O Williams BSc MD FRCP FRCPath

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.

The Committee in the first instance decided to concentrate upon the manufacture of heat sterilized infusion fluids for parenteral administration.

1.2 The Committee have received evidence from manufacturers of autoclaves and from manufacturers of infusion fluids. They have also received evidence about the manufacture of infusion fluids in hospitals and about the implementation of the Medicines Act and its enforcement. A list of those who have given evidence is given in Appendix 1.

1.3 Many millions of bottles of infusion fluids for parenteral use have been manufactured by both hospitals and the pharmaceutical industry and used without ill-effect but certain points of importance concerning present practice in their manufacture have been brought to the attention of the Committee and they have therefore felt it proper to comment briefly on these and make certain recommendations immediately in an interim report. Other matters within their remit will be dealt with later and after they have given full consideration to

the Report of the Committee set up under the Chairmanship of Mr C M Clothier QC to enquire into the Devonport incident.

1.4 When considering the scope of the present interim report the Committee did not have before them the recommendations of the Clothier Committee, but their views are in general in accord with those expressed in the report of that Committee which was published on 12 July 1972.

1.5 The total usage of intravenous fluids in one year is 10 million containers nearly half of which the hospitals manufacture.

In view of this, the Committee wish to make it clear that their recommendations about the manufacture of infusion fluids relate equally to hospitals and to the pharmaceutical industry. The same production standards should be applied to both although it should be borne in mind that products manufactured in hospitals are generally used more quickly and travel less far after manufacture than those made by commercial firms.

2. MANAGEMENT CONTROL

2.1 The Committee have heard evidence that the staff engaged in sterilization procedures are not always adequately trained and supervised.

The Committee regard the following points as of major importance in the management of manufacture in this field:

(i) a clearly established chain of command and responsibility

(ii) adequate training and supervision of all personnel involved in production

(iii) written job instructions.

(iv) maintenance and study of full records.

2.2 The Committee recommend that these points should be brought to the attention of manufacturers both in industry and hospitals and that any suspected defect in a process or product should be reported immediately up the chain of command so that appropriate action can be taken.

3. GENERAL CONCLUSION

The Committee's overall conclusion is that if accepted good practice in the manufacture of sterile products were followed

with intelligence at every point, the chances of microbial contamination would be minimal. They wish to stress that all stages in preparing a sterile product are of equal importance and that too much reliance should not be placed on the detection of contamination by sampling and testing procedures which can never take the place of adequate in-process control or be a guarantee of the sterility of the total output.

4. PROCESSING INCLUDING COOLING

4.1 Sterilization of infusion fluids is carried out in autoclaves; vessels in which closed containers of fluids are heated by exposure to steam under pressure. The British Pharmacopoeia indicates that for sterilization to be achieved, the fluid must be maintained at a temperature of 115° C to 116° C for 30 minutes. Other combinations of time and temperature can achieve the required result.

4.2

(i) The Committee heard evidence that there are some autoclaves in current use which have only rudimentary instrumentation. They recommend that sterilizers should be so equipped that the conditions in the load can be readily checked.

(ii) Some autoclaves show evidence of poor maintenance and inadequate control, and a programme of preventive maintenance is less usual than attention forced by failure. The Committee consider that autoclaves should have at least one year's maintenance guaranteed by their maker, and that regular preventive maintenance is essential.

4.3 The Committee consider that management should understand the possible failures associated with the operation of steam sterilizing equipment. The commonly held view that autoclaving is a foolproof process is false. Uncritical reliance on the equipment, however modern in design, will lead to hazard. There is no alternative to competent and informed surveillance of the process.

4.4

(i) All equipment should be regularly and frequently maintained, instruments calibrated and correct functioning checked. Full records, including those of all maintenance performed, must be kept and studied.

(ii) The temperature within the load must be known and the contents of the vessels in the load must be held at the sterilizing temperature for the requisite time.

(iii) Details of the sterilizing conditions for each batch must be recorded for examination as part of the quality control procedure and filed.

(iv) The Committee offer no comment at the present time about chemical or biological indicators.

4.5 The Committee heard that only limited use is made in industry of spray cooling. The purpose of spray cooling is to shorten the time of the process and to reduce the hazard to the operator from premature opening of the sterilizer door whilst the contents of the load are still under pressure.

The Committee were convinced that spray cooling presents a potential source of contamination unless close attention is given to the design of bottle closures. If bottle closure is adequate, the method of cooling is immaterial from the point of view of contamination and the sterilization of water used for cooling is irrelevant.

5. GLASS BOTTLES AND THEIR CLOSURES

5.1 Where glass bottles are used, the Committee recommend that they should conform to the British Standard for bottles and plug closures. They see no reason why glass bottles should not be used more than once provided that after adequate examination, bottles showing chips, cracks and other imperfections are rejected. Examination of new bottles and of all closure components is likewise essential.

5.2 The Committee heard evidence that only certain kinds of closures were satisfactory and that even with these, individual closures did not always meet their specification. The accepted type of seal for bottles of parenteral infusion fluids is a flanged rubber plug held in place by an aluminium screw cap or spun-on aluminium retaining ring. Some form of overseal of aluminium or other material is also generally used to provide additional protection from adventitious contamination.

5.3 Overseals do not necessarily protect against microbial contamination and may in fact provide additional hazard.

(i) If a plug closure is ill-fitting or if the neck bore of the bottle is misshapen micro-organisms may penetrate the seal between bottle and closure. Any subsequent disturbance of the closure during storage, transport or use may result in microbial contamination of the contents. This hazard is increased with bottles filled under vacuum.

(ii) Where an overseal is used moisture may collect on top of the rubber closure and become contaminated. When the closure is pierced the contents may become contaminated.

5.4 The Committee therefore recommend that:

(i) Glass bottles should be sealed with tightly fitting rubber plug closures held firmly and securely in place by an aluminium screw cap or retaining ring.

(ii) The sterilization procedure should ensure that on removal from the autoclave the top surface of the rubber closure is dry and therefore less liable to support the growth of bacteria.

6. PLASTIC CONTAINERS

6.1 The Committee considered whether plastic containers had any advantage over glass containers and were likely to replace them in the future.

6.2 **The advantages of plastics**

(i) Plastic containers are collapsible and do not require an airway, hence there is less risk of contamination.

(ii) There is no problem from flaking of glass or leaching of particulate matter from rubber closures as there is with glass containers.

(iii) They are less fragile.

(iv) They suffer less from closure faults and are not subject to hairline cracks as are glass bottles (see 6.2[vii] and 6.2 [viii] below).

(v) Disinfection of the closure is unnecessary in some cases because of the use of sterile administration ports protected by removable caps.

(vi) They are lighter in weight, cheaper and easier to transport and less liable to incur damage in transit.

(vii) They are generally overwrapped in a plastic envelope which provides both protection and a ready means of detecting leaks.

The disadvantages of plastics

(viii) They are liable to 'seam failure' and pin-holing.

(ix) Some types contain plasticisers and other additives which may be toxic and liable to leach on storage. Care must be given to the choice of formulation of the plastic used which should be compatible with the contained fluids.

(x) The storage life of the product is reduced because of the higher moisture transmission of the plastics.

(xi) Difficulties have been experienced in attaching some giving sets to packs. The need to cut the outlet port with sterile scissors is inconvenient and a potential contamination hazard.

6.3 The Committee were asked to consider whether plastic containers should be accepted as being suitable for intravenous infusion fluids in view of the difficulty of examination through a more or less opaque material. They find that two types of plastic containers are in general use; one in clear transparent plastic and the other translucent, and it is only the latter type in which examination of the contents may be difficult.

The Committee consider that visual examination of the filled containers cannot give a positive indication of sterility or of contamination and the lack of transparency is not therefore in itself a hazard.

6.4 The Committee understand that the use of plastic containers is likely to continue to increase and consider that the advantages over glass outweigh the known disadvantages. They recommend that development work to improve the quality and design of plastic containers should be encouraged.

7. ADMINISTRATION OF PARENTERAL INFUSION FLUIDS

The Committee consider that the dangers associated with the administration of parenteral infusion fluids are outside their remit. They were nevertheless, interested to see the preliminary report of a clinical trial of administration sets with terminal

membrane filter units, and recommend that further trials be undertaken with a view to establishing the usefulness of such filters.

8. SAMPLING AND TESTING

8.1 Sampling for a sterility test

(i) It is important that a batch be defined and that sampling should have regard to the fact that any contaminated containers are unlikely to be distributed uniformly throughout the load sterilized as a group. For products sterilized by autoclaving a batch should comprise not more than one autoclave load, this practice being in line with the Pharmacopoeial definition.

(ii) Because there may be variations in temperature within an autoclave, it is necessary to establish the number and location of containers to be tested to increase the chances of detecting unsatisfactory procedures. Some guidance on the proportion of containers to be taken is given in the Pharmacopoeia but such guidance cannot replace the responsibility of those in charge of a process to ensure that their sampling system is adequate for their particular circumstances.

(iii) Similar considerations apply to the volume of the sample to be used for the test. Guidance is given in the Pharmacopoeia, but it may be both feasible and desirable to test volumes larger than the recommended minimum.

(iv) From their enquiries into current practice, the Committee gained the impression that adequate attention is not always paid to the design of sampling systems and that the quality control personnel are not always personally involved in sampling.

8.2 Testing for sterility

(i) The Committee recommend that greater use should be made of new methods of testing particularly suited to large-volume injections, such as the membrane filter techniques and where suitable, the addition of concentrated nutrient medium to the contents of a container with subsequent incubation of the whole.

(ii) There appears to be inadequate follow-up when tests prove positive. The number and nature of contaminating organisms should be established and attempts made to investigate their source.

8.3 **Pharmacopoeial standards, methods and guidance**

(i) It is not always realised that Pharmacopoeial standards are intended to apply to a product at the time of administration and that appropriate allowances for deterioration during storage should therefore be made when designing standards for the release of manufactured batches.

(ii) Pharmacopoeial methods are written as a guide for trained personnel capable of using judgement. In the view of the Committee this approach is desirable and should be maintained. If the tests were described in greater detail, they would be more likely to be applied in an unreasoning way and control might in fact be less effective. Such directions as are given by the Pharmacopoeia should be free from ambiguity and the current directive on the use of positive controls in the sterility test is open to some criticism on this score.

8.4 A sterility test giving negative results is not in itself a guarantee of uniform good quality in a batch and this should be constantly in mind. The Committee consider, however, that suitably designed sterility tests have a proper place in the quality control of infusion fluids as a final check on the adequacy of earlier procedures.

The Committee recommend that:

(i) Careful attention should be paid to the design of sampling systems in order to fit the particular circumstances of the product being manufactured.

(ii) Methods of sterility testing should be reviewed critically by each manufacturer. There should always be adequate follow-up of positive results.

9. HOSPITAL MANUFACTURE OF INFUSION FLUIDS

9.1 The Committee received evidence that the facilities and methods used for the production of parenteral infusion fluids vary greatly from hospital to hospital, and consider that such facilities should eventually be limited to selected large units.

9.2 In the Committee's view control of hospital manufacture should be no less rigorous than that which applies to pharmaceutical firms who are required to be licensed under the Medicines Act, where standard provisions with which licensees must comply are laid down by Statutory Instrument and where inspection both precedes the issue of a licence and is to be repeated at intervals during its currency; the Act also provides that the licence may be withdrawn in stated circumstances which relate inter alia to the safety of the product. Even though the Medicines Act does not bind the Crown, equivalent standards should be applied to hospital manufacture as are applied to commercial operators under the Act.

9.3 Hospital pharmaceutical services are to be reorganised on a regional basis following the recommendations of the Noel Hall Report and this provides an excellent opportunity for concentrating the production of infusion fluids in centres with adequate facilities. Inspection of facilities should be undertaken by the Department but Regional Pharmacists should be given responsbility for management. They should know what is happening in their regions and have authority to close down hospital manufacture.

9.4 The Committee recognise that conditions of manufacture in some hospitals cannot be sufficiently improved without substantial expenditure on accommodation, equipment and personnel. This reinforces the Committee's view that the hospital manufacture of infusion fluids should be concentrated in a few large centres. The Committee regard this reorganisation as a matter of considerable urgency.

10. MEDICINES ACT – LICENSING AND ENFORCEMENT

10.1 Under the Medicines Act 1968, all manufacturers' premises in the UK in which infusion fluids are manufactured have been inspected within the past few months. In future manufacturer's licences should not be granted until the installations have been inspected and found capable of satisfactory operation. Any new manufacturers will be unable to start manufacturing until a licence has been granted.

10.2 Regulations have been made under the Act laying down standard provisions with which the holders of licences must comply and further regulations of this type are in course of

drafting and will eventually become the subject of statutory consultation process under the Medicines Act.

10.3 The Guide to Good Pharmaceutical Manufacturing Practice prepared by the Health and Agriculture Departments in co-operation with industry sets out agreed good practice for the guidance of all manufacturers. The Committee understand that it is the intention of the Department to revise the Guide in the light of experience. They have suggested certain matters which the Department should incorporate in the Guide (see paras 2,4,5 and 8).

11. ADDENDUM

The Committee entirely concur with the conclusion of the Clothier Committee that nothing can replace the constant and vigilant application of skill and intelligence to the task of producing parenteral fluids which, by their nature, can so easily become the vehicles of infection.

APPENDIX I

Acknowledgements

The Committee have been deeply impressed by the extensive knowledge of the staff of the Department of Health and Social Security concerning the procedures and processes of sterilization and are greatly indebted to them for valuable information. They would also like to place on record their gratitude to Mr Keith Reeve and Miss Alice Perkins who have most efficiently served as Secretaries.

The Committee are particularly grateful to Dr Peter Main (Director of Research, The Boots Company Ltd) for preparing a paper on polythene containers for infusion fluids and to those listed below who gave either written or oral evidence or who answered a questionnaire.

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Association of British Sterilizer Manufacturers.
Department of Health and Social Security.
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