# The Quality Control of Non-Sterile Products

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*This is based on the author's B.Pharm. thesis entitled "THE QUALITY CONTROL OF NON-STERILE PRODUCTS PREPARED AT ST. LUKE'S HOSPITAL DISPENSARY".*

## Introduction

Quality of pharmaceutical products is the sum of all the factors which contribute directly or indirectly to the safety, effecetiveness and acceptability of the product.

Quality to the patient is **fitness for use.** Confidence is important not only for the patient himself but also for all the members of the health profession.

Quality affects also the manufacturer's costs. If there were no defects in the product, quality costs would disappear. However since we are human beings defects do unfortunately exist and costs include:-

a) the preparation and conduction of programs for reaching and improving good quality,
b) selection and control of ingredients and final product including packing and labelling,
c) maintenance of equipment,
d) consumption of products in the destructive tests,
e) testing of products in field storage or in stock to evaluate degradation,
f) keeping detailed records of all stages of manufacture.

## Quality factors

Quality is built in the product. Factors to be considered are therefore:—

a) **Personnel** whose background of education, training and experience in manufacturing and control of manufacturing has to be assessed. Employees should know

1) what is supposed to be done,
2) what is being done,
3) knowledge for regulating what is done in a way which will predictably eliminate any non-conformance.

Work must be broken down to well-defined operations and written instructions for every stage be made available. (Fig. 1)

b) **Motivation of personnel.** While training employees particular attention should be given to quality. Communications to employees may be effected by journals or manuals. Complaint letters should be posted with the defect display. Cartoons can be used to get the message across effectively but to a relaxed audience.

c) **Building.** In a hospital especially, demand is unpredictable and if a particular product becomes suddenly very popular and the only possible action is to stretch the resources to the utmost, production sometimes continues under hazardous conditions. Required are the following:-

1) good standards of air filtration, heating and cooling,
2) improvement of room finishes,
3) enclosing of pipework,
4) removal of old woodwork,
5) Proper spacing of machinery and equipment for good, safe operation and cleaning,
6) storage space for batches.

d) **Containers and closures.** Quality, strength, capacity suitability and compliance with standard specifications of closures and container materials must be established. The container, holds and protects the product against physical and adverse environmental conditions like moisture, crushing and light. It presents the product in a convenient quantity and form. Decoration of container informs patient about the identity and purpose of its contents.

Glass is the best standard container material. It is relatively unreactive, strong, easily cleaned, but fragile and heavy. Plastics which are flexible may be preferred for example, in dispensing nasal drops.

However for plastics when used in direct contact with a medicament, the length of time of contact may determine whether problems such as discolouration, leaching and absorption or adsorption of a constituent of the product may arise. Storage conditions, pH, temperature and/or time, surface treatment of plastic container configuration, type of polymer used, method of package preparation and light transmission are also to be considered. The special properties of various available materials must be recognised:- eg. PVC for ointments is resistant to oils but is plasticised by esters like methyl salicylate. Same can be said for polystyrene containers.

Metals are employed in collapsible tubes for semi-solid dermatological preparations. To avoid interaction, internal linings are employed.

Fig. 1

**EXAMPLE OF AN EXTEMPORANEOUS PRODUCT WORKSHEET**

| | |
|---|---|
| Type of product:<br>Nose drops | Product Name<br>Ephedrine Nasal drops 1% B.P.C. |
| Use: to reduce swelling turninate bodies in hay fever, and catarrhal infections | CODE:..... B/N..... |

**METHOD OF PREPARATION**

1. Tare an amber glass bottle at the 100ml volume —
2. Weigh 0.5g **chlorbutol** —
3. Heat about 60ml purified water to 60°C in a conical flask that can be closed later with a glass or polypropylene stopper —
4. Add (2) and insert the stopper —
5. Shake vigorously until solution is complete —
6. Weigh **1g ephedrine hydrochloride** —
7. Weigh **0.5g sodium chloride** —
8. Dissolve (6) and (7) in (5) —
9. Cool, filter if necessary and make to 100mls through the filter —
10. Divide into unit containers —

| | |
|---|---|
| Preparaed by:<br>Date: | No. of containers filled:<br>Qty. in each:<br>Filled by: Date: |

SAMPLE OF LABEL

Labelled by: .....
.....
Date:

PRODUCT CHECKED BY: DATE:

Further notes:
Nasal drops should be supplied in coloured fluted glass bottles fitted with a plastic screw cap incorporating a glass dropper tube fitted with a rubber teat or in a plastic squeeze f bottle fitted with a plastic cap incorporating a dropper device.

Closures give further protection. They should be easily removed and replaced, and should not react with container contents. Any imperfection enhances absorption of water vapour by hygroscopic products. Simplest type is the screw-cap. Also available are press-in and slip-over closures.

e) **Labelling.** Labels should be neatly written to give the patient clear and complete instructions on the use of the preparation and storage conditions. Red printing is used for external preparations. Labels are never attached to closures and should not overlap. They should state clearly the name, amount and strength of the prescribed preparation, directions for use, any relevant warnings, including recommended storage conditions. For small bottles one label should state name, amount and strength of preparation and prescription number. Further important information is stuck at the back.

Only one product is labelled at a time and the exact number of labels are issued to avoid mislabelling of products especially when of different strength.

f) **Equipment.** It is important to have personnel experienced in the techniques necessary for the maintenance of pharmaceutical manufacturing equipment. It should always be cleaned after use. Balances should be calibrated every six months, however daily monitoring against secondary standards is effective.

g) **Specifications for control to guide production.** Manufacture of pharmaceutical products is controlled by the U.S.P., N.F., B.P., B.P.C., which have achieved legal status. They give officially accepted methods of establishing identity, purity and composition of substances in chemical products. They give minimum standards eg. tolerance on percentage active ingredient, minimal sampling plans and standards governing the conduct of an operation. They give also recommendations on containers for dispensing.

h) **Sampling procedures and practices.** These aim at obtaining specimens representative of the constitution and condition of the batch. It could be done in-process and on the product. It gives the opportunity to inspect the materials, containers and labels.

i) **Documentation.** A file is opened for every ingredient to include the certificate of supplier, result of lab analysis, result of test mix which verifies suitability of ingredient in production process. A batch document is also created to include input materials and batch numbers, references to ingredient files, product assays, including initials of every individual associated with every production step from weighing through the release of product by Quality Controller.

## Chemical and physical aspect of Quality Control

Chemical, physical and physico-chemical methods of analysis check that the formulated preparations are quantitatively correct and of satisfactory purity at the time of dispensing.

Lately attention has been diverted to a more precise study of the identity and toxicity of likely impurities which influence the safety and stability of the finished product. The procedure then depends on the nature and level of contamination, nature of drug and equipment, istrumentation and time available. Such control implies a large volume of work and it may be preferable to supplement it by inspection of manufacturer's premises and in-process control.

Sources of chemical and mechanical contamination may include:

a) accidental inclusion of dirt, glass, porcelain, metallic and plastic fragments from sieves, equipment and containers, water.
b) incomplete solution of a solute.
c) uneven distribution of suspended matter.
d) insufficient attention to chemical stability of pharmaceutical chemicals and additives under manufacturing conditions.
e) cross-contamination.
f) release of chemicals from product container which influence stability, therapeutic efficacy and safety of product.

Factors affecting quantity of product ingredients are:

a) weighing on dispensing balances,
b) measurement of liquids.

## Instrumental Analysis

Analytical information by instrumental analysis gives quick and detailed results besides saving money because the result is expressed faster.

Techniques used extensively in the purity and quantitative determination of a drug are UV-visible spectrophotometry, colourimetry, IR spectroscopy, 'H' nuclear magnetic resonance, acid-base titration, polarography, gas chromatography and HPLC.

The assays given in official guides to chemical analysis are rarely specific. However they are regarded as sufficiently specific when taken

in conjunction with other requirements of the monograph.

**Microbiological aspect**

An item certified non-sterile is most probably contaminated by microbes. Intensive research in UK has shown that:-

1) Contamination was more common in preparations made or repacked in the hospital pharmaceutical department than in pre-packed commercial products.
2) The heaviest contamination was in distilled, demineralised and peppermint water, other aromatic waters and alkaline suspensions such as mixtures containing magnesium hydroxide or magnesium trisilicate.
3) Aqueous topical creams, peppermint water and alkaline mixtures containing peppermint flavouring were most prone to contamination with **Pseudomonas aeruginosa.**
4) Generally products having a consistently low microbial count are those with a low pH; high sucrose content and a low pH; a low pH and containing benzoic acid; a moderate concentration of chloroform or a high alcohol content.

**SOURCES OF MICROBIAL CONTAMINATION**

1) RAW MATERIALS
2) PHARMACEUTICAL EQUIPMENT
3) PRODUCTION PROCESS
4) AIR & ENVIRONMENT
5) PERSONNEL
6) CONTAINERS AND CLOSURES FOR PACKING
7) FORMULATION

Raw materials are to be obtained from reliable sources and tested before use. The containers should be opened prior to manufacturing process and checked. Most important is water. Distilled water if not properly collected and stored may harbour bacteria. During storage **P. aeruginosa** can grow in water produced in hospital. Rubber and plastic connections in a still may be sources of infection necessating either frequent sterilisation of the system or the introduction of all-glass equipment. Boiling distilled water immediately before use kills at least organisms like pseudomonas and may be used safely in preparing medicaments at S.L.H.

Consider now pharmaceutical equipment. Production batches remaining in the orifices can form foci for the infection of subsequent batches. Therefore all equipment should be thoroughly cleaned with hot water and detergent immediately after use. It should also be protected from dust during storage.

The production process is also important. Weak points in a production process that may enhance microbial proliferation are: temperature of certain steps and water condensation on the surfaces of ointment or solutions if not allowed to cool before applying closures of final containers.

Walls, floors and ceilings should be smooth and as free as possible from cracks and crevices. Dry sweeping and dusting has to be avoided and replaced by daily swabbing with disinfectant solution. Air supply should be treated to remove most micro-organisms.

The personnel should be trained in hygiene thinking. They should acquire at least elementary knowledge of conditions supporting the growth and dispersal of micro-organisms. They are to wear clean overalls and caps and should be subjected to the same health requirements as are food workers. They should not be employed when suffering from respiratory and skin infections.

If a contaminated formulation is found the assumption is that the contaminent has the ability to adapt or grow in the preservation system. Protection has to be both during and after its preparation. Therefore the efficacy of the preservative has to be evaluated because for example, chloroform can bind itself to powder surfaces in preparations which contain insoluble solids. Such preparations have therefore decreased content of preservative but at the binding site the preservative activity is enhanced.

**Conclusion**

A manufacturer is responsible for the quality of a product. However, it is very difficult for him to ensure quality when the product is in the hands of the patient.

The importance of training and educating the patient must not be underestimated. Products should be used for their intended purpose as instructed and should be stored for a defined period of time, under appropriate conditions. Such information shoud be clearly given on the label of the preparation.

It is the duty of community and hospital pharmacists to educate the patients and explain the potential hazards of using contaminated products.

**Reference:**

Bonanno, M.A., *The quality control of non-sterile products prepared at St. Luke's Hospital dispensary*, B.Pharm. Thesis 1986, Pharmacy Department, University of Malta.