Additional standards are as follows:

- Gowning. There are guidelines that describe the requirements for respective areas and the type of gowning recommended.
- Grade d. Hair and, where relevant, beard should be covered. A protective suit with either shoes or overshoes is recommended.
- Grade c. All conditions mentioned in grade d plus a single or two-piece trouser suit closing at neck and wrist. The fabric chosen to prepare these gowns is expected not to shed fibers or particulate matter (lint-free cloth).
- Grades a and b. All requirements mentioned in d and c plus headgear, a face mask, along with foot covers, gloves, and covering of eyes with spectacles. The garments used in classes a and b areas must be sterilized, and it is advisable not to make repeated use of them.

Pharmaceutical water. Water is a major component solvent used in all manufacturing processes; as a part of the final product its characteristics are critical. In the pharmaceutical industry, water is defined according to its quality as in Figure 1.

Normally, water received from metropolitan supplies may contain residual chlorine, although it is potable. Thus it is chemically impure. It is first deionized and subsequently ultrafiltered, or passed through the reverse osmosis system, to yield highly purified water. This water is also used as the feed water for generating distilled water and, finally, water for injection (WFI), which is kept continuously flowing through the distribution loop at a temperature around 80°C. Since this water needs to comply with very high standards of purity and microbiological content, an elaborate water-testing system is needed. Equipment such as total organic carbon analyzers, which can be fitted on line in the circulation loop, allow monitoring of the WFI quality.

Pure steam, which is generated using WFI or highly purified water, must be used for sterilizing all product contact parts. After condensation, it should comply with all the tests performed on WFI.

System-related elements.

Deviation control system Any change in a sop, which is an unplanned activity, must be reported to quality assurance immediately as a deviation, where its impact on product quality and safety is evaluated.

Change control system A planned deviation is categorized by an expert committee as critical or noncritical (type 1 or type 2). This committee also reviews the impact of such a change on safety and efficacy of product.

Corrective action preventive action Issues related to the points observed in internal audits or external audits in the manufacturing and testing areas need to be addressed in a timely manner so that they do not recur. The corrective action preventive action (CAPA) system follows up these actions.

Other system-related issues include audits (internal/external), training, and sop writing.

Equipment

Equipment used in production should be installed, operated, and maintained as per cGMP guidelines. Where appropriate, Installation/Operational/Performance Qualification (IQ/OQ/PQ) protocols, calibration, and validation studies need to be designed and executed. All equipment should be maintained on current calibration and preventive maintenance schedules performed as recommended by their manufacturers.

Documentation

All operations in GMP manufacturing, whether dealing with facility, equipment, material usage, manufacturing, or product release must be performed as outlined in the SOPS. This ensures that the manufacture is performed in strict accordance with established manufacturing, regulatory, and safety procedures. Any deviation from sops has to be reported, and its effect on the clinical product documented. Each sop is uniquely identified, usually stored in both electronic and paper formats, and maintained by the document control department.

Production or batch records are used to document all manufacturing operations that are performed in the production of human vaccines. These records are established in accordance with appropriate sops, and are distributed and controlled by the document control department. Any deviations from manufacturing operations outlined in the sops are documented in the appropriate batch records. Batch records are especially important when it becomes necessary to revisit the manufacturing operations, if some inconsistency or deficiency is discovered in the clinical product.

Validation protocols must be maintained on file as part of the documented record of a production process. Process and quality control validation are becoming more important to confirm the robustness of the methods employed.

SPECIAL CIRCUMSTANCES IN VACCINE MANUFACTURING

Although manufacturing processes and practices have advanced with the development and application of new technology, certain critical vaccines are still manufactured by traditional methods because of lack of suitable substitute technology, or lack of incentive for developing improved technology. An example is the smallpox vaccine, which was manufactured by methods originally developed in the late 18th century, until the increased concern of bioterrorism in the aftermath of the anthrax bioterror events that followed the September 11, 2001, airliner hijackings in the United States led to a new demand for this vaccine. After a 30-year hiatus in efforts to develop an improved process, government solicitation of bids from manufacturers willing to produce a new version of the vaccine resulted in the awarding of the supply contract to a company committed to providing vaccine produced by a new in vitro tissue culture manufacturing process, which substantially improved purity and speed to market.

Source of water (raw water) ⇒ Potable water ⇒ De-ionized water ⇒ purified water ⇒ distilled water ⇒ Water for Injection

Figure 1 Schematic indication of water quality.