**Seminar Class # 6**

**WATER IN PHARMACEUTICALS PRODUCTION**

Water is, overall, by far the biggest single usage item in pharmaceutical manufacturing. It is used:

As an ingredient (many liquid products consist mainly of water)

As an in-process material used at some stage in manufacture, but which does not appear in the ﬁnal product. (An example is the water that is used in granulating and coating solutions in tablet manufacture. Little of it remains in the end-product — except, of course, any non-volatile impurities, or even microorganisms it may have contained)

For drinking

For washing (people, ﬂoors, walls, equipment, containers)

For rinsing

For cooling

As a source of steam

Basic considerations, all of which have signiﬁcant product-quality implications, are:

The quality of the feed water to the plant

The uses to which the water will be put

The standards to which the waters used for different purposes must comply

The water treatment methods that must be applied to ensure that water used for various purposes complies with the appropriate standard

The design and installation of water treatment systems

The control and monitoring of the quality of the output water

Put simply, and rather obviously, the nature and extent of the water treatment will depend on the quality of what is available as source water and on what is needed as the output from the treatment process. Water may be originally obtained from a number of sources. Water from wells or bore-holes, given suitable treatment, has been used to manufacture pharmaceuticals. In many countries, the most usual source is normal mains, or town, water of potable (drinkable) quality. For pharmaceutical purposes, it may be considered that there are three basic grades of water:

Potable Water

Puriﬁed Water

Water for Injections

As noted earlier, a recent EC Guidance note (2001), following the lead of the European Pharmacopoeia, distinguishes a fourth grade of water — Highly Puriﬁed Water. (See also Santora and Mani.1)

**Potable Water**

Potable water, quite simply, is water that is ﬁt and safe to drink — that is, it is the stuff that comes from the mains and out of the faucets (or taps). As far as it is possible to ascertain, no detailed monograph on potable water appears in any pharmacopoeia. Some pharmacopoeias make reference to it in terms such as “suitable water freshly drawn from the public supply” and “palatable and safe to drink,” but no monograph. An international standard was published by the World Health Organization (WHO) in 1971 and an EC Guideline (1978) set standards for appearance, pH, limits for toxic substances and microbial contamination, and so on, but the precise deﬁnition of quality standards for water tends to vary with location. To produce potable water, the primary source material (from rivers, lakes, wells, etc.) needs some form of treatment (ﬂocculation, settling, ﬁltration, chlorination, etc.). Potable water can contain a range of dissolved organic and inorganic substances, suspended colloidal matter, and relatively low levels of microorganisms. Although it has been suggested that potable water can be used as an ingredient in the manufacture of some nonsterile pharmaceutical products (creams, ointments, and tablet granulations for example), informed opinion holds that potable water should only be used for drinking, personal washing, and also for the initial washing and rinsing of equipment and containers, provided (in the case of surfaces in contact with product) this is followed by rinsing with either puriﬁed water or water for injections, as appropriate and relevant. Although it may seem strange that water that is ﬁt to drink is not considered ﬁt to be used as an ingredient of pharmaceutical products, this is indeed generally considered to be so. “Mains water” (or “city water”) usually (dependent on location and original source) contains small, but not insigniﬁcant, quantities of dissolved, and possibly suspended, impurities. Some of these, although harmless to normal ﬁt people when swallowed, can cause harm to those who are ill and weak or when administered by other routes than by mouth. They can also adversely affect formulations, for example by causing precipitation, or through ionic solutes disturbing the delicate balance of some emulsions. Potable water will also contain at least some level of (ever-increasing) microorganisms. These can cause infection in patients and break down some formulations (e.g., emulsions). Particular care is necessary when potable water (and indeed any water) is held in a storage tank, where microbial growth could be proliﬁc.

**Puriﬁed Water**

Puriﬁed water is potable water that has been treated so as to conform with deﬁned ofﬁcial standards. That is, for example, the monographs that appear in the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), and the British Pharmacopoeia (BP). These monographs set down tests and limits for chemical purity, based on speciﬁc limit tests, and more general techniques such as electrical conductivity and residue on evaporation, but do not specify allowable microbial levels.

It is usual, however, for manufacturers to deﬁne their own in-house limits, with a limit of not more than 100 organisms per ml being common. Commonly adopted “warning limits” vary from 10 to 50 organisms per ml. Often, the complete absence of particular types, or groups, of organisms (e.g., coliforms, pseudomonads) is speciﬁed. Puriﬁed water is produced from potable water by distillation, ion exchange, reverse osmosis or other suitable means. It is used for “general” manufacturing purposes (that is, generally as an ingredient of nonsterile and certainly not of injectable products) and as a ﬁnal rinse for washing of containers and other primary packaging components, and in ﬁnal rinses when cleaning equipment (in both cases when these are intended to be used only for nonsterile products).

**Water for Injections**

Here it is necessary to draw an important distinction — between water for injections, which is in bulk (e.g., in a bulk holding tank or circulating in a ringmain distribution system) and water for injections that has been sterilized and is in fact sterile. Various pharmacopoeias make this distinction in different ways. The EP/BP deﬁnes water for injections as, in effect, water that complies with the requirements for puriﬁed water, with the additional requirement of not more than 0.25 IU of bacterial endotoxin. The EP/BP further distinguishes two subgrades of water for injection: “water for injections in bulk” (in effect, the water that is used in the preparation of bulk solutions intended ultimately for injection, and which will be sterilized at a later stage in the process) and “sterilized water for injections.” Sterilized water for injections is deﬁned as water for injections that has been ﬁlled and sealed into “suitable containers” and then “sterilized by heat in conditions which ensure that the product still complies with the test for bacterial endotoxins.” Thus, this deﬁnition is speciﬁcally directed at the water in sealed ampoules or vials, which is used to dissolve or suspend sterile powders immediately prior to injection. Note that the EP/BP requires that water for injections should be produced by distillation. Some other countries permit the use of reverse osmosis. The USP also distinguishes between “water for injection,” “sterile water for injection,” “sterile water for irrigation” and “bacteriostatic water for irrigation.” Water for injections (not necessarily sterilized if the product is later to be sterilized, but most certainly sterilized, and sterile, if it is not) is used for the manufacture of injections, ophthalmic products, and other sterile products intended for critical clinical applications. Here we encounter a matter of fundamental importance, and although it will be encountered again when we turn later to consider sterile production in more detail, it is so important that it is well worth stressing now: Although “water for injections in bulk” is not required to be sterile, this does not mean that it may contain an abundance of organisms, and it is usual for manufacturers to set their own in-house limits. Opinions tend to vary on what these should be, but not more than 500 cfu (colony forming units) per liter, with not more than 100 cfu per liter as a “warning limit” and a complete absence of speciﬁed organisms (e.g., coliforms), is commonly suggested.

**Other Waters**

Other waters include water used for cooling and as boiler feed for the production of steam. Cooling water used for cooling equipment does not have any deﬁned standard — nor does it need any, provided that it is retained within a sealed system and does not come into contact with product or the production environment. It has been suggested that it is prudent to add chemicals to such water in order to minimize microbial growth. However, in the accidental event of contact with product or environment, it would need to be recognized that, while the microbial risk may have been reduced, the chemical contamination risk has been increased. The water used following the sterilization cycle in some types of autoclaves to cool the sterilized load is a different matter altogether. It should be sterilized water for injections quality to protect against the potentially hazardous consequences of water (or residues from it) remaining on the load or, say, entering a vial or ampoule through a faulty seal or a crack. The quality of water used to feed boilers is, from a pharmaceutical point of view, of no importance — provided there will be no contact (direct or indirect) between the steam produced by the boiler and the products manufactured, or with the contact surfaces of the equipment used to manufacture them. Where the steam will come into contact with products, containers, or the contact surfaces of manufacturing equipment, the water used to produce it should not contain volatile additives like amines or hydrazines. If the steam is intended to be used for sterilization (e.g., in autoclaving, “live-steaming,” or sterilize in place [SIP]) then it must be “clean steam“ (or “pure steam”), produced from deionized (or reverse-osmosis water) water by a well-designed clean steam generator, which will yield a condensate that complies with the requirements for water for injections.

**Water Treatment and Supply Systems**

The EC GMP Guide Annex 1 on sterile products (and the statement is relevant to water used for other purposes) states (paragraph 35):

Water treatment and distribution plants should be designed, constructed and maintained so as to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injection should be produced, stored, and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C .

(Many would argue that the temperature at which water should be held and circulated should be not less than 80°C.) In the treatment of water to produce the required quality grade(s), it is not merely a question of the correct selection, installation, and maintenance of the major items of equipment (e.g., stills, de-ionizers). It is a matter of viewing the whole water production, supply, and distribution process as an integrated system, and controlling it and monitoring it to ensure the consistent supply of water of the required quality. This requires consideration of the source-water arriving at the plant, its nature and quality, and what sort of settling, coarse ﬁltration, scavenging, or other pretreatment it may require; through to the deionization equipment, its installation, monitoring, maintenance and regeneration; on to the still itself, its installation, control and monitoring, via any holding vessel (with provision for elevated temperature storage, and with vent valves protected by hydrophobic bacteria-retentive ﬁlters) and the recirculation system; to ﬁnal delivery to production areas. The overall concept should be what has been termed a “sanitary design” — a system that aims at minimizing microbial growth, at minimizing chemical and particulate contamination arising from the system itself, and that permits cleaning and sterilization “in place.” Except in the very smallest systems, where water is taken direct from the still as required, water should be distributed to the required production outlets via holding tank(s) and a recirculating loop, in all of which the water (at 80°C) is maintained in constant turbulent motion. Tanks and pipework should be constructed of 316 stainless steel, with internal surfaces (including all welds) highly polished to prevent minipockets of stagnant water where organisms can ﬂourish. The following sources of contamination should be avoided or kept to a minimum:

Excessive length pipe runs

Too many valves

Nonsanitary valves and joints

Threaded joints

Dead-legs

Undrainable loops and bends

Unprotected vents

Pumps

Tanks

It is pointless to install a system that works well just for the ﬁrst week or so. It needs to be monitored and maintained to ensure that it continues to work well. Here there is a vital need for close cooperation between microbiological quality control which will perform the microbiological monitoring, and the engineers who will need to service and maintain the system to ensure it remains capable of supplying the quality of water required. Care needs to be taken to ensure that in the very act of sampling for microbiological and chemical testing, the system itself is not contaminated. The following, extracted from EC Guidance Note on the Quality of Water for Pharmaceutical Use (2001) will serve as a summary of the various grades of water and their usage:

4. Requirements of the European Pharmacopoeia

The European Pharmacopoeia provides standards for the following grades of water:

Water for Injections Puriﬁed Water Highly Puriﬁed Water

4.1 Potable Water is not covered by a pharmacopoeial monograph but must comply with the regulations on water laid down by the competent authority. Testing should be carried out at the manufacturing site to conﬁrm the quality of the water. Potable water may be used in chemical synthesis and in the early stages of cleaning pharmaceutical manufacturing equipment unless there are speciﬁc technical or quality requirements for higher grades of water. It is the prescribed source feed water for the production of pharmacopoeial grade waters. 4.2 Water for Injections (WFI) is water for the preparation of medicines for parenteral administration when water is used as a vehicle (water for injections in bulk) and for dissolving or diluting substances or preparations for parenteral administration before use (sterilised water for injections).

Production Control of the chemical purity of WFI presents few major problems. The critical issue is that of ensuring consistent microbiological quality with respect to removal of bacteria and bacterial endotoxins. Distillation has a long history of reliable performance and can be validated as a unit operation, hence it currently remains the only ofﬁcial method for WFI.

WFI in bulk is obtained from water that complies with the regulation on water intended for human consumption laid down by the competent authority, or from puriﬁed water, by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or suitable metal and which is ﬁtted with an effective device to prevent the entrainment of droplets. The correct maintenance of the apparatus is essential. During production and storage, appropriate measures are taken to ensure that the total viable aerobic count is adequately controlled and monitored.

WFI complies with the tests for Puriﬁed Water with additional requirements for bacterial endotoxins (not more than 0.25 IU of endotoxin per ml), conductivity and Total Organic Carbon

4.3 Puriﬁed Water is water for the preparation of medicinal products other than those that require the use of water which is sterile and/or apyrogenic. Puriﬁed Water which satisﬁes the test for endotoxins may be used in the manufacture of dialysis solutions.

Production Puriﬁed Water is prepared by distillation, by ion exchange or by any other suitable method, from water that complies with the regulations on water intended for human consumption laid down by the competent authority.

4.4 Highly Puriﬁed Water is intended for use in the preparation of products where water of high biological quality is needed, except where Water for Injections is required.

Production Highly Puriﬁed Water is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority. Current production methods include, for example, double-pass reverse osmosis coupled with other suitable techniques such as ultraﬁltration and deionisation. Highly Puriﬁed Water meets the same quality standards as WFI, but the production methods are considered less reliable than distillation and thus it is considered unacceptable for use as WFI.”

Steam Possible uses of steam include:

General factory heating

Production process heating (steam-jacketed vessels, heating coils)

Steam cleaning

Sterilization (autoclaving, “live-steaming” of vessels and pipes, sterilization in place [SIP])

Where steam is not associated with product manufacture, and does not come into contact with product or manufacturing materials (or with surfaces that will contact product or materials), then, pharmaceutically speaking, the quality of that steam is not particularly relevant. Where there is any such contact, then the steam should be of such a quality that, when condensed, the water thus produced would comply with the requirements for puriﬁed water. When used as the sterilizing medium (e.g., in autoclaves, SIP systems) the steam should be clean steam. That is, steam that, when condensed, will form water for injections quality water.