Supplementary Training Modules on Good Manufacturing Practice

Water for Pharmaceutical Use

Part 1: Introduction and treatment

WHO Technical Report Series No 970, 2012. Annex 2

World Health Organization

Water for Pharmaceutical Use

Objective

- General principles, water system requirements and uses
- Water quality specifications
- Application of specific types of water to processes and dosage forms
- Water purification systems, storage and distribution
- Operational considerations
- Inspection of water systems

Water for Pharmaceutical Use

Introduction

- Look at information on specifications of Water for Pharmaceutical Use (WPU)
- Which Quality of water to be used in production and control
  - APIs, finished products, etc.
- GMP for design, installation, operation of systems
- Supplementary to general GMP guidelines
- See also other guidelines, pharmacopoeia, etc.

1.1.1 – 1.1.2

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Additional guidelines

- WHO Guideline for Drinking water quality (WHO)
- Water and steam systems (ISPE)
- Bioprocessing Equipment Standard (ASME – BPE 2000)
- European Pharmacopoeia, United States Pharmacopeia, International Pharmacopoeia
- Inspection of Utilities (PIC/S)

1.1.3

Water for Pharmaceutical Use

Principles

- Like any starting material, production of water should conform to Good Manufacturing Practice (GMP) norms
- Potential for microbial growth
- Systems must be properly validated / qualified
- Water for parenteral use should not be contaminated with pyrogens or endotoxins
- Specifications and periodic sampling and testing required

Water for Pharmaceutical Use

Why purify raw water?

- Although reasonably pure, it is always variable due to seasonal variations, regional variation in water quality
- Must remove impurities and control microbes to avoid contaminating products
- Treatment depends on water's chemistry and contaminants, influenced by, e.g. rainfall, erosion, pollution, dissolution, sedimentation, decomposition

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Contaminants of water (1)

- There is no pure water in nature, as it can contain up to 90 possible unacceptable contaminants
- Contaminant groups:
  - *Inorganic compounds*
  - *Organic compounds*
  - *Solids*
  - *Gases*
  - *Microorganisms*

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Contaminants of water (2)

Problem minerals

- Calcium, magnesium, copper, aluminium, heavy metals, arsenic, lead, cadmium, nitrates
- Iron, manganese, silicates, carbon dioxide
- Hydrogen sulfide
- Phosphates

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Contaminants of water (3)

Microorganisms – Biofilm formation

- Protozoa
  - *Cryptosporidium*
  - *Giardia*
- Bacteria
  - *Pseudomonas*
  - *Gram negative, non-fermenting bacteria*
  - *Escherichia coli and coliforms*

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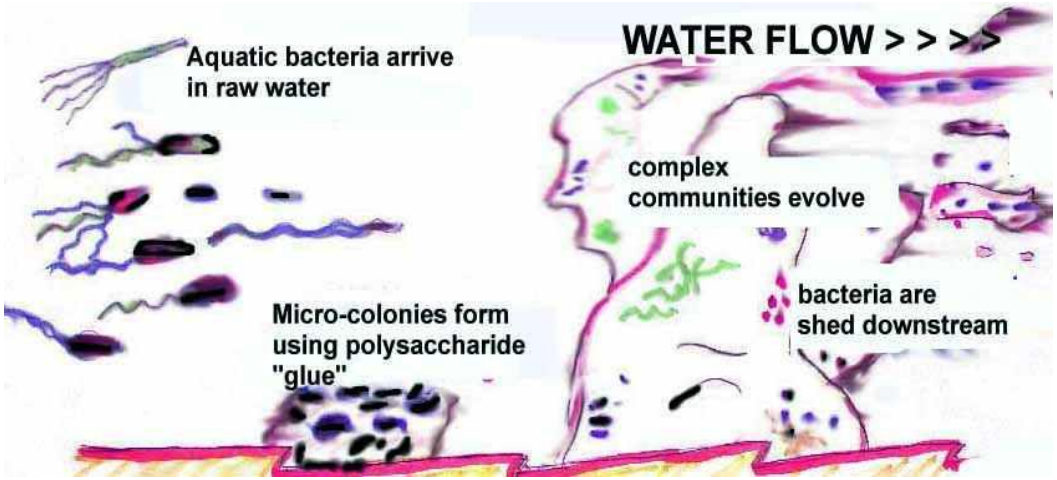
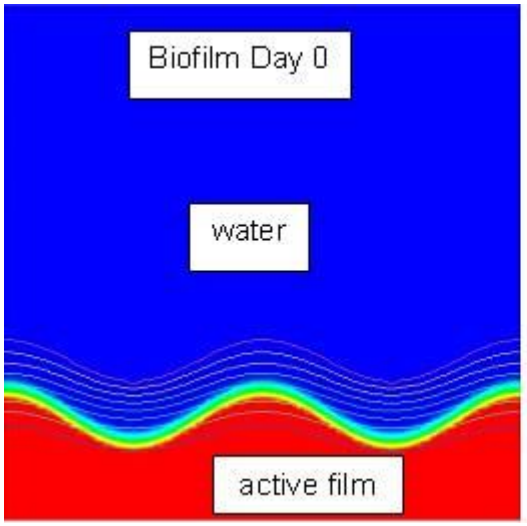
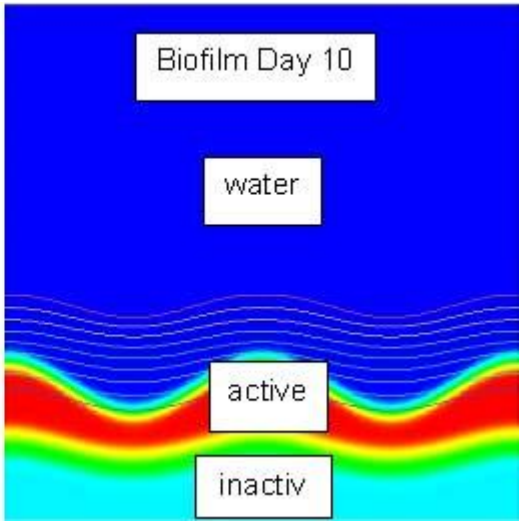
Biofilm formation

1. Free-swimming aquatic bacteria use *polymucosaccharides* to colonize surfaces

2. Complex communities evolve which shed microcolonies and bacteria







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Water for Pharmaceutical Use

Background to water requirements and use

- Water is the most widely used substance / raw material
- Used in production, processing, formulation, cleaning, quality control
- Unique chemical properties
  - *Able to dissolve, absorb, adsorb, suspend compounds and contaminants*
- Different grades of water quality available
- See also EMEA "Note for guidance on the quality of water for pharmaceutical use"

1.2.1

Water for Pharmaceutical Use

Background to water requirements and use (2)

- Control quality of water during *production, storage and distribution*
- Contaminants, microbial and chemical quality
- Microbial contamination risk and concern
- Water is used on demand
  - *not like other materials where sampled and tested, and THEN used. Thus no batch or lot release before use. It has to meet the specification "on demand" when used*
  - *Micro test results require incubation periods therefore results later after already used*

1.2.2

Water for Pharmaceutical Use

Background to water requirements and use (2)

- Microbial control is a high priority
- Microbes may proliferate (production, storage and distribution)
- System design, periodic sanitization and other measures
- Different grades of water quality (dependent on its use)

1.2.3. – 1.2.4.

Water for Pharmaceutical Use

General Principles of water systems

- Design, installation, commissioning, qualification / validation, operation, performance and maintenance to ensure reliable, consistent production of water of required quality
- Prevent unacceptable microbial, chemical and physical contamination during production, storage and distribution
- Operate within design capacity
- Quality Assurance involved in approval of use after installation and maintenance work, or changes

2.1. – 2.3.

Water for Pharmaceutical Use

Water system requirements (2)

Regular monitoring of:

- Water quality
  - *Chemical and microbiological*
  - *Endotoxin level where relevant*
- System performance, storage and distribution systems
- Records of results, trends and action taken
- Validated sanitization procedure followed on a routine basis

2.4. – 2.5.

Water for Pharmaceutical Use

Water quality specifications

Presentation of water processed, stored and distributed *in bulk. (Not applicable for patient administration)*

Specifications in pharmacopoeia include different types of water

- Drinking water / potable water
- Bulk Purified water (BPW)
- Bulk Highly Purified Water (BHPW)
- Bulk Water for Injection (BWFI)

3.

Water for Pharmaceutical Use

Drinking water / potable water

- Must comply with specification (WHO, ISO and national or regional agencies) – regular testing needed
- Supplied under continuous positive pressure
- Defect free plumbing system to prevent contamination
- Could be from public water supply system or natural sources
- Source water quality influences the treatment required

3.2.1., 3.2.3., 3.2.6.

Water for Pharmaceutical Use

Drinking water:

Natural sources could include **springs, wells, rivers and lakes**

Treatment includes **desalinization, softening, removal of specific ions, particle reduction and antimicrobial treatment.**

3.2.2

Water for Pharmaceutical Use

Bulk Purified Water (BPW)

- Prepared from potable water (as minimum quality feed)
- Meet pharmacopoeia specification - chemical and microbial purity
- Alert and action limits (determined)
- Protected from recontamination
- Protected from microbial proliferation
- RO/EDI

3.3.1.

Water for Pharmaceutical Use

Bulk Highly Purified Water (BHPW)

- Prepared from potable water (as minimum feed)
- Specification only in the European Pharmacopoeia
- Same quality standard as WFI (microbiological and limit for endotoxins)
- Prepared by combination of methods including double reverse osmosis (RO) plus ultrafiltration (UF) and deionization (DI)
- Protect from recontamination and microbial proliferation

3.4.1. – 3.4.3.

Water for Pharmaceutical Use

Bulk Water for Injections (BWFI)

- Prepared from potable water source treated further, or PW
- WFI is not sterile and is not a final dosage form
- WFI is an intermediate bulk product
- According to *The International and European Pharmacopoeias* – final purification step should be distillation
- To meet pharmacopoeia specification for chemical and microbial purity (including endotoxin)
- Alert and action limits

3.5.1 – 3.5.4.

Water for Pharmaceutical Use

Application of specific types of water to processes and dosage forms

- Water used for different stages of:
  - *Washing, preparation, synthesis, manufacturing, formulation*
- Which grade of water is suitable for a particular stage?
  - As required by national authority
  - Consider nature and intended use of intermediate or finished product
  - Stage in process where water is used
- Let's look at types of water and indicate their use

4.1. – 4.2.

Water for Pharmaceutical Use

Application of specific types of water to processes and dosage forms

- BHPW
  - preparation of products when water of high quality (i.e. very low in microorganisms and endotoxins) is needed
- BWFI
  - manufacture of injectable products for dissolving or diluting substances or preparations during the manufacturing of parenterals
  - manufacture of sterile water for preparation of injections
  - final rinse after cleaning of equipment and components
  - preparation of steam

4.3. – 4.5.

Water for Pharmaceutical Use

Complete the table

Use	***Which type of water?***
Preparation of injectable products	?
Final rinse of equipment after cleaning	?
Final rinse of equipment and components that come into contact with injectable products	?
?	HPW
?	Potable water

Water for Pharmaceutical Use

Water purification systems: So far:

- Principles for pharmaceutical water systems
- Water quality specifications
  - Drinking-water, Bulk purified water, Bulk highly purified water, Bulk water for injections
- Specific types of water for processes and dosage forms
- General considerations for water purification systems
- Next slides focus on water purification, storage and distribution systems