Practice 001:

Table 1: Water Use Requirements for Active Pharmaceutical Ingredients (APIs)

Water Types Permitted for APIs:[1]	Potable	Reduced Ion	Deionized (DI)	Low Microbial DI	Low Endotoxin DI	PW	HPW	WFI
Early & Intermediate Steps[2]	X	X	X	X	X	X	X	X
Final Steps[3] (Non-Sterile API):								
Type of Drug Product for which API will be used:								
• Non-Sterile Drug Product		X	X	X	X	X	X	X
• Non-Sterile Inhalation Drug Product				X	X		X	X
• Sterile, Non-Parenteral Drug Product				X	X		X	X
• Parenteral Drug Product					X		X	X
Final Steps (Sterile API):								
• Sterile, Non-Parenteral Drug Product						X[4]	X[4]	X[4]
• Parenteral								X[4]
Water Used for Cleaning/Rinsing of Equipment, Containers, Closures (Non-Sterile API):								
• Initial Rinse	X	X	X	X	X	X	X	X
• Final Rinse[5]	Same water quality as used in manufacturing of next product to contact equipment, containers, and/or closures.							
Water Used for Cleaning/Rinsing of Equipment, Containers, Closures (Sterile API):								
• Initial Rinse					X		X	X
• Final Rinse								X

Footnotes:

1. Water for production must be demonstrated to be suitable for its intended use.
2. Examples of water usage in early and intermediate API manufacturing steps:
   - Water is used to wash organic extracts;
   - Water or aqueous solution is used to quench a reaction upstream;
   - There are recrystallizations from the organic phase after the use of water;
   - There are chemical reactions after the use of water; and
   - Water functions as a **Solvent*** for strong base or acid.

(Table 1 footnotes continued on next page.)

(Footnotes Table 1: Continued from previous page)

3. Water used in final steps of API processes is defined as water that comes in direct contact with the isolated final API or the final solution prior to isolation of the API, or where the water is used as a final rinse on product-contact equipment, containers, or closures used for the final isolated API. Examples of water usage in final API manufacturing steps:
   - Later stages of API process for an API used in injectable or inhalation dosage forms;
   - If water is the last liquid to touch the API prior to drying (e.g., cake washing, precipitation, crystallization, or humidification for drying); and
   - API is precipitated or crystallized from solution by addition of water to an organic solution, with no subsequent dissolution of the solid, after isolation of the solid, even with organic cake wash.
4. Where no further sterilization steps are employed, the water must be rendered sterile.
5. If the water or solvent used for final rising during cleaning is lower quality than the quality required for the next process, the equipment must be rinsed with water or solvent at least as high quality as the water or solvent used for subsequent process prior to using the equipment.

Table 2: Water Use Requirements for Drug Products

Water Types Permitted for Drug Products:	**Potable**	**PW**	**HPW**	**WFI**
Manufacture of:				
• Non-Sterile Drug Product		X	X	X
• Non-Sterile Inhalation Drug Product		X[1]	X	X
• Sterile, Non-Parenteral Drug Product		X[2]	X[2]	X[2]
• Parenteral				X[2]
Water Used for Cleaning/Rinsing of Equipment, Containers, Closures:				
Initial Rinse				
• Non-Sterile Drug Product	X	X	X	X
• Non-Sterile Inhalation Drug Product	X	X	X	X
• Sterile, Non-Parenteral Drug Product		X	X	X
• Parenteral		X	X	X
Final Rinse				
• Non-Sterile Drug Product		X	X	X
• Non-Sterile Inhalation Drug Product		X	X	X
• Sterile, Non-Parenteral Drug Product		X	X	X
• Parenteral				X

Footnotes:

1. Lower microbial action levels may be needed for water used in inhalation drug products.
2. Where no further sterilization steps are employed, the water must be rendered sterile. If the sterile, non-parenteral drug product has endotoxin requirements, WFI must be used.

Air Classification:

EU Grade	ISO Classification		US Designation	
	At Rest*	In Operation*	At Rest	In Operation
A	4.8	4.8	100	100
B	5	7	100	10,000
C	7	8	10,000	100,000
D	8	Undefined	100,000	Undefined

Table 1. Air Handling Systems Performance Criteria

Operating Conditions	Performance Criteria
Minimum airflow velocity within 6 inches of the filter face for Grade A	72 feet per minute (0.36 m/s) across the filter face.
Maximum airflow velocity within 6 inches of the filter face for Grade A	Not to exceed manufacturer's specified limit.
Airflow velocity at a defined distance proximal to the work surface (e.g., 6 to 12 inches above work surface) for Grade A	Airflow velocity must be within alert/action levels and demonstrate an airflow pattern that sweeps particulate matter away from the critical zone.
Airflow velocity at filter face for all Classifications	Airflow velocity must fall within the manufacturer's specified ranges.
Room Differential Pressures & Balance	Maintain a positive pressure differential of at least 10 pascals of water (0.04 inches WG) between adjacent rooms of different air classifications. Where required, maintain validated pressure differential between adjacent rooms of the same air classifications Maintain a positive pressure differential of at least 12.5 pascals (0.05 inches of water) between the aseptic processing room and any adjacent unclassified room(s).
Room Classification Total Airborne Particulate levels	