

Guidance Number: 078

Table 1: Minimum Water Quality Requirements

Water Type	Microbial Alert Level	Microbial Action Level	Chemical Quality Requirements
Potable	> 300 cfu/mL	<ul style="list-style-type: none"> - 2 consecutive samples at > 300 cfu/mL, - Positive for objectionable microorganisms, or - A single result > 500 cfu/mL. 	<p><u>Alert & Action Levels:</u> not required.</p> <p><u>Specifications:</u> must meet WHO potable drinking water & applicable National Drinking Water Regulations.</p>
Reduced Ion	Based on system performance and product requirements, but not to exceed 100 cfu/ml	<ul style="list-style-type: none"> - Alert level exceeded on 2 consecutive samples at a given sampling location, - Positive for objectionable microorganisms, or - A single result, based on system performance and product requirements, but not to exceed 300cfu/ml. 	<p><u>Alert & Action Levels:</u> established based on process and product requirements. Conductivity action level not to exceed 50µS/cm at 20 C.</p> <p><u>Specifications:</u> not required unless registered.</p>
Deionized	> 50 cfu/mL	<ul style="list-style-type: none"> - Alert level exceeded on 2 consecutive samples at a given sampling location, - Positive for objectionable microorganisms, or - A single result >100 cfu/mL. 	<p><u>Alert Level:</u> result above applicable compendial conductivity or TOC test limits for PW at any sampling location.</p> <p><u>Action Level:</u> alert level exceeded at 2 or more sampling locations or on 2 consecutive samples at a given sampling location.</p> <p><u>Specifications:</u> not required unless registered.</p>

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Water Type	Microbial Alert Level	Microbial Action Level	Chemical Quality Requirements
Low Microbial Deionized	Based on system performance.	<ul style="list-style-type: none">- Alert level exceeded on 2 consecutive samples at a given sampling location,- Positive for objectionable microorganisms, or- A single result >10 cfu/mL¹.	<p><u>Alert Level:</u> result above applicable compendial conductivity or TOC test limits for PW at any sampling location.</p> <p><u>Action Level:</u> alert level exceeded at 2 or more sampling locations or on 2 consecutive samples at a given sampling location.</p> <p><u>Specifications:</u> not required unless registered.</p>
Low Endotoxin Deionized	BET Alert Level based on product requirements and system performance, but not to exceed 0.125 EU/ml. Microbial Alert Level based on system performance.	<ul style="list-style-type: none">- Positive for objectionable microorganisms,- A single result >10 cfu/mL¹,- Any 2 consecutive BET alerts, or- Any single result ≥0.25EU/mL.	<p><u>Alert Level:</u> above compendial conductivity or TOC test limits for PW at sampling location.</p> <p><u>Action Level:</u> alert level exceeded at 2 or more sampling locations or on 2 consecutive samples at a given sampling location.</p> <p><u>Specifications:</u> not required unless registered.</p>

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Water Type	Microbial Alert Level	Microbial Action Level	Chemical Quality Requirements
PW	> 50 cfu/mL	<ul style="list-style-type: none">- Alert level exceeded on 2 consecutive samples at a given sampling location,- Positive for objectionable microorganisms, or- A single result >100 cfu/mL.	<p><u>Alert & Action Levels:</u> not required.</p> <p><u>Specifications:</u> must meet compendial PW requirements for conductivity and TOC and any additional applicable compendial requirements.</p>
HPW or WFI	>1 cfu/100 mL, or BET Alert Level based on product requirements and system performance, but not to exceed 0.125 EU/ml.	<ul style="list-style-type: none">- Alert level exceeded on 2 consecutive samples at a given sampling location,- Positive for objectionable microorganisms,- A single result >10 cfu/100mL,- Any 2 consecutive BET alerts, or- Any single result ≥ 0.25EU/mL.	<p><u>Alert & Action Levels:</u> not required.</p> <p><u>Specifications:</u> must meet compendial PW requirements for conductivity and TOC and any additional applicable compendial requirements.</p>

Footnotes:

1. The default action level is >10cfu/ml, unless alternate levels are justified as suitable for intended use for the final API, and by the impact of bioburden on the drug product, and by the performance of the water system. In no case shall the action limit be greater than 50 cfu/ml.

Table 2: Minimum Water Sampling Frequencies

Water Type	Minimum Sampling Frequency ¹
Water Used in Early & Intermediate API Steps	Weekly - rotating sampling locations so that all locations are sampled at least semiannually.
Water Used in Final Steps of API Process ²	Weekly - rotating sampling locations so that all Critical Use Points (CUP) are sampled at least every two weeks.
PW, HPW, or WFI ^{3,4}	<ul style="list-style-type: none"> • Sample the generator three times a week with at least one day between samplings; • Sample three different CUPs weekly with at least one day between samplings; • Sample all CUPs at least every two weeks; and • Sample all use points at least monthly.

Footnotes:

1. All samples shall be tested for microorganism counts (TVO). Low Endotoxin Deionized Water, HPW, and WFI samples shall also be tested for BET. Where on-line conductivity and total organic carbon probes are used with established alert and action levels, chemical testing frequency may be less frequent and is based on validated intervals.
2. Where the type of water used at a sampling location changes with the manufacturing step, the frequency of testing may be varied to match the water use.
3. In the event the PW, HPW, or WFI Distribution System is monitored continuously by validated in-line controls, sampling and testing for bacterial endotoxins and microorganisms (as applicable) may be suspended for intervals (such as weekends) of up to 3 days, provided that the water is not used for production, is continuously recirculating through the distribution system, and all normal operating ranges (NOR) are maintained.
4. Following a water system shutdown that exceeds a validated time interval, action must be taken to ensure adequate water quality. Selected samples representative of the water quality, including the worst case system location at a minimum, shall be collected and tested. All test results shall be reviewed and approved before any products manufactured using the water are released.