

# Comparison of *EP* “Heavy Metals” Test with *USP* “Conductivity” Test

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The *US Pharmacopeia* “Conductivity” and the *European Pharmacopeia* “Heavy Metals” tests were compared to demonstrate that the *USP* method can determine the presence or absence of heavy metals in process water samples.

The *European Pharmacopeia* (*EP*) specifies a limit for heavy metals in purified water and water for injection (WFI) of 1.0 parts per million (ppm) when the sample has been concentrated 10-fold by evaporation (*i.e.*, limit of 0.1 ppm in the original sample) (1). *EP* 2.4.8 “Method A, Heavy Metals Test” uses a subjective comparison of the test sample’s color with that of a prepared 1.0-ppm lead standard exhibiting a “slight brown colour” when compared with a negative control. Any brown color in the sample must be “not more intense” than that of the 1.0-ppm standard. The *US Pharmacopeia* (*USP*) requirements for purified water and WFI include “Total Organic Carbon” <643> and “Conductivity” <645> tests, but do not have specific tests for heavy metals (2).

Because heavy metals in an aqueous solution exist in an ionic state, their detection should be possible using the “Conductivity” test. This test would eliminate the need for sample concentration and reagents maintenance—which are required for the heavy metals chemistry test—and the subjectivity of a pass–fail decision.

A standard of 1.0-ppm lead was prepared, as specified in *EP* 2.4.8. A 0.1-ppm lead sample prepared from the standard was used as the test sample. This solution was tested by

the *USP* <645> “Conductivity” and the *EP* “Heavy Metals” tests to demonstrate that the quantitative conductivity measurement can be used in place of the qualitative chemistry test with equal or better sensitivity. A prepared 0.01-ppm lead standard also was tested to determine the limit of the tests’ sensitivities.

## Materials and methods.

**Materials.** The following materials were used, per *EP* 2.4.8: 1.0-ppm lead standard, reagents, and WFI or sterile WFI (sWFI).

**Methods.** Comparison of *USP* “Conductivity” and *EP* “Heavy Metals” tests.

- Prepare a 0.1-ppm lead standard by diluting the 1.0-ppm lead standard 10:1 with WFI or sWFI.
- Prepare a 0.01-ppm lead standard by diluting the 1.0-ppm lead standard 100:1 or by diluting the 0.1-ppm lead standard 10:1 with WFI or sWFI.

Table I: Comparison of the *USP* “Conductivity” and *EP* “Heavy Metals” tests on unconcentrated samples.

Lead (ppm)	USP stage 1			USP stage 2			USP stage 3			EP test
	Result (μS/cm)	Spec. (μS/cm)	Note	Result (μS/cm)	Spec. (μS/cm)	Note	Result (μS/cm)	Spec. (μS/cm)	Note	
0.1	6.82	≤1.1	Fail	7.90	≤2.1	Fail	7.9	≤4.7	Fail	Pass
0.1	7.08	≤1.1	Fail	7.78	≤2.1	Fail	4.9	NA**	Fail	Pass
0.1	5.10	≤1.1	Fail	7.00	≤2.1	Fail	4.9	NA**	Fail	Pass
0.01	1.63	≤1.1	Fail	1.82	≤2.1	Pass	NA	NA	NA	Pass
0.01	1.63	≤1.1	Fail	1.81	≤2.1	Pass	NA	NA	NA	Pass
0.01	1.51	≤1.1	Fail	1.59	≤2.1	Pass	NA	NA	NA	Pass
0*	1.04	≤1.1	Pass	NA	NA	NA	NA	NA	NA	Pass
0*	1.08	≤1.1	Pass	NA	NA	NA	NA	NA	NA	Pass
0*	0.97	≤1.1	Pass	NA	NA	NA	NA	NA	NA	Pass

\* water for injection. \*\* pH of sample exceeds allowable range. Spec. denotes specification. NA denotes not applicable.

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Table II: Evaluation of the requirement for concentration before testing.

Lead* (ppm)	10×** (ppm)	USP stage 1			USP stage 2			USP stage 3			EP test
		Result (μS/cm)	Spec. (μS/cm)	Note	Result (μS/cm)	Spec. (μS/cm)	Note	Result (μS/cm)	Spec. (μS/cm)	Note	
0.1	1.0	78.3	≤1.4	Fail	76.20	≤2.1	Fail	76.2	NA††	Fail	Fail
0.1	1.0	82.9	≤1.4	Fail	78.2	≤2.1	Fail	78.2	NA††	Fail	Fail
0.1	1.0	72.60	≤1.3	Fail	72.90	≤2.1	Fail	72.9	NA††	Fail	Fail
0.01	0.1	9.85	≤1.5	Fail	8.64	≤2.1	Fail	8.64	≤3.8	Fail	Pass
0.01	0.1	5.11	≤1.4	Fail	4.88	≤2.1	Fail	4.88	≤2.4	Fail	Pass
0.01	0.1	5.25	≤1.3	Fail	5.05	≤2.1	Fail	5.05	≤2.4	Fail	Pass
0†	0†	7.51	≤1.5	Fail	6.5	≤2.1	Fail	6.50	≤4.6	Fail	Pass
0†	0†	3.22	≤1.5	Fail	2.89	≤2.1	Fail	2.89	≤2.4	Fail	Pass
0†	0†	2.92	≤1.3	Fail	3.12	≤2.1	Fail	3.12	≤2.6	Fail	Pass

\* lead concentration in original sample. \*\* lead concentration in concentrated 10× sample.

† water for injection. †† pH of sample exceeds allowable range.

NA denotes not applicable.

- Perform the USP <645> “Conductivity” test for process water on the 0.1-ppm lead standard, the 0.01-ppm lead standard, and the water used to prepare the standards.
- Perform the EP 2.4.8 “Method A, Heavy Metals Test” on the 0.1-ppm lead standard, the 0.01-ppm lead standard, and the water used to prepare the standards.
- Test all solutions in triplicate.

#### Evaluation of the concentration requirement before testing.

- Prepare a 0.1-ppm lead standard by diluting the 1.0-ppm lead standard 10:1 with WFI or sWFI.
- Prepare a 0.01-ppm lead standard by diluting the 1.0-ppm lead standard 100:1 or by diluting the 0.1-ppm lead standard 10:1 with WFI or sWFI.
- Reduce the samples of 0.1-ppm lead standard, 0.01-ppm lead standard, and WFI or sWFI by 10×.
- Perform the USP <645> “Conductivity” test on the concentrated 0.1-ppm lead standard, the concentrated 0.01-ppm lead standard, and the concentrated water used to prepare the standards.
- Perform the EP 2.4.8 “Method A, Heavy Metals Test” on the concentrated 0.1-ppm lead standard, the concentrated 0.01-ppm lead standard, and the concentrated water used to prepare the standards.
- Test all solutions in triplicate.

#### Acceptance criteria.

- No heavy metals should be detected in the WFI or sWFI used to dilute the lead standard when conducting the EP “Heavy Metals” test.
- The unconcentrated WFI or sWFI used for dilution must meet current USP conductivity specifications.
- The USP “Conductivity” test should detect the presence of the 0.1 ppm of lead in concentrated and unconcentrated samples.
- The EP 2.4.8 “Heavy Metals” test should detect the presence of the 0.1 ppm of lead in the concentrated sample.

## Results

**Comparison of USP “Conductivity” and EP “Heavy Metals” tests on unconcentrated sample.** Table I summarizes the results from the conductivity and heavy metals tests performed on the unconcentrated samples and WFI. All three 0.1-ppm lead standard replicates passed

the “Heavy Metals” test (by being compared with the 1.0-ppm standard color), but failed all three stages of the “Conductivity” test. The 0.01-ppm lead replicates passed the “Heavy Metals” test, but failed stage 1 of the “Conductivity” test. The replicates passed stage 2 of the USP test. The WFI blanks met both EP and USP requirements. The correlation between the results from these tests demonstrates that a sample containing heavy metals can be detected with conductivity testing at the sensitivity required by the EP without concentrating the sample.

#### Evaluation of the concentration re-

**quirement before testing.** Table II summarizes the test results from the 10×-reduced samples of the 0.1-ppm lead standard, the 0.01-ppm standard, and the WFI. The concentrated 0.1-ppm lead (concentrated level ~1.0 ppm) was detected by the EP “Heavy Metals” and the USP “Conductivity” tests. The lead in the concentrated samples of 0.01-ppm lead (~0.1 ppm) were not detected with the “Heavy Metals” test, although all three replicates failed the “Conductivity” test.

The concentrated WFI passed the EP “Heavy Metals” test, but failed the USP “Conductivity” test. This result is not surprising because the conductivity test responds to all ionic substances present in the sample. Even WFI contains free ions, and a 10-fold concentration of these ions is sufficient to surpass the allowable ionic concentration. It should be noted that the results for the 0.01-ppm concentrated lead sample are significantly higher than those for the WFI, indicating the presence of the lead.

## Conclusion

An aqueous solution’s ability to carry an electrical current can be measured with the conductivity test and is dependent on the ion concentration present. Because heavy metals in an aqueous solution exist in ionic states, they will affect the solution’s conductance. Therefore, as demonstrated by these test results, the USP <645> “Conductivity” test method can be used to effectively determine the presence or absence of heavy metals in process water samples. Furthermore, when using the USP “Conductivity” test, a 10× reduction of samples is unnecessary to detect the EP required limit of 0.1-ppm in high-quality process water.

## References

1. “2.4.8 Method A, Heavy Metals Test,” *European Pharmacopeia* (Council of Europe, Strasbourg, France, 2002), pp. 88–89.
2. “Conductivity” <645>, USP 27–NF 22 (US Pharmacopeial Convention, Rockville, MD, 4th ed., 2003), pp. 2286–2287. **PT**

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