To whom it may concern.

USP vs. EP regarding the details on standard solutions

1. Pharmaceutical water

In many areas USP and EP (CP, Chinese Pharmacopeia) are, where the TOC measurements are of concern, identical. A difference lies in the possible form of the WFI/PW production.

- How is **Water for Injection** (WFI) defined by different Pharmacopeia?
  - USP: "…distillation or a purification process that is equivalent or superior to distillation"
  - EP: "… prepared by distillation"
    - Addendum: **Highly Purified Water (HPW):** "… intended for use in the preparation of products where water of high biological quality is needed, except where WFI is required."[1]
  - JP: "… prepared by distillation or by Reverse Osmosis/Ultra filtration"
  - CP: "… prepared by distillation"

The EP constricts the production method to distillation.
This is probably the reason why 98% off the WFI production units worldwide are based on a distilling process.

This is no concern for the standard solutions.
Another difference lies in the used substances for the production of the standard solution (SST)

2. EP (European Pharmacopoeia)

Here is an extract from the Monograph 2.2.44, which is mandatory to all companies who produce according to the EP Standard

TOC water. Use highly purified water complying with the following specifications:

– conductivity: not greater than 1.0 µS·cm^{-1} at 25 °C,

– total organic carbon: not greater than 0.1 mg/l.

Depending on the type of apparatus used, the content of heavy metals and copper may be critical. The manufacturer's instructions should be followed.

Glassware preparation. Use glassware that has been scrupulously cleaned by a method that will remove organic matter. Use *TOC water* for the final rinse of glassware.

Standard solution. Dissolve *sucrose R*, dried at 105 °C for 3 h in *TOC water* to obtain a solution containing 1.19 mg of sucrose per litre (0.50 mg of carbon per litre).

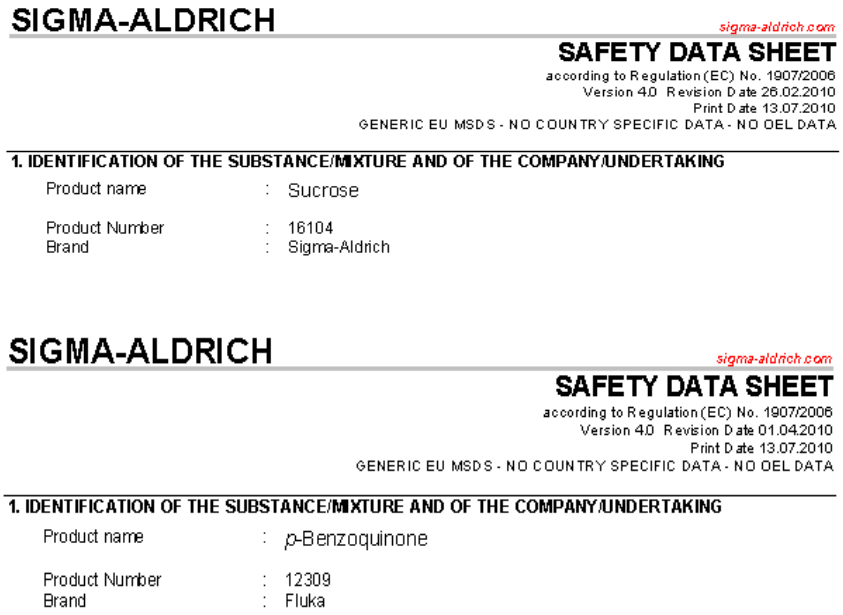
Test solution. Using all due care to avoid contamination, collect water to be tested in an airtight container leaving minimal head-space. Examine the water with minimum delay to reduce contamination from the container and its closure.

System suitability solution. Dissolve *1,4-benzoquinone R* in *TOC water* to obtain a solution having a concentration of 0.75 mg of 1,4-benzoquinone per litre (0.50 mg of carbon per litre).

TOC water control. Use *TOC water* obtained at the same time as that used to prepare the standard solution and the system suitability solution.

According to this regulation substances with a Pharma Grade may be used.

For an example I mentioned 2 MSDS below.



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SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006
Version 4.0 Revision Date 26.02.2010
Print Date 13.07.2010
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

Product name : Sucrose

Product Number : 16104
Brand : Sigma-Aldrich

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SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006
Version 4.0 Revision Date 01.04.2010
Print Date 13.07.2010
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

Product name : *p*-Benzoquinone

Product Number : 12309
Brand : Fluka

These substances are available in standard packs of 25 or 100g.
It is also possible to extract small amounts to produce the desired volume and concentration of a solution. The handling is easy and the price level is acceptable.

When EP rules are applied, our customers are not bounded to one source of delivery. As long as the products match a pharma grade they can be bought from every supplier.

We use the same chemicals for the Function Test solutions.

3. USP (US-Pharmacopoeia)

If a client works according to USP, he must obtain the origin substance from USP. These are available from 10ml Vials to 100mg or 200mg and need to be used all at once.

Enclosed an abstract from the current USP.

USP Reference Standards 11 —*USP 1,4-Benzoquinone RS*. *USP Sucrose RS*.

Reagent Water—Use water having a TOC level of not more than 0.10 mg per L. [NOTE—A conductivity requirement may be necessary to ensure method reliability.]

Standard Solution—Unless otherwise directed in the individual monograph, dissolve in the *Reagent Water* an accurately weighed quantity of USP Sucrose RS, to obtain a solution having a concentration of about 1.2 mg of sucrose per L (0.50 mg of carbon per liter).

System Suitability Solution—Dissolve in *Reagent Water* an accurately weighed quantity of USP 1,4-Benzoquinone RS to obtain a solution having a concentration of 0.75 mg per L (0.50mg of carbon per liter).

Reagent Water Control—Use a suitable quantity of *Reagent Water* obtained at the same time as that used in the preparation of the *Standard Solution* and the *System Suitability Solution*.

The weighing of 1.5mg or 0.75mg in prepared containers is rather difficult. For the conditions at the clients are not always ideal. According to surveys by European pharmaceutical companies such preparations will not be accepted because no final test of the charge is possible with a certified TOC instrument. The traceability is not guaranteed. With a purchased SST Standard which is produced by USP, a measurement report of the actual solution is always included.

Manufactured and certified solutions with an expiration date are, in accordance with the regulations, the best. Should it not be possible because of logistical reasons (for e.g. Import problems or long delivery times), it is possible, after consolation with the client, to produce and use the solution on the spot.

However it should be noted that this indicates a modification and the client muss take this into account when performing the risk analysis (which is part of the validation). In the PQ (SST) the changes has to be noted and signed by the client.

4. Conclusion

Certified prepared solutions according to USP/EP are the best way to avoid troubles and discussions. This method is worldwide accepted and fully traceable. To my knowledge, there was no objection in any audit by using this method.

Other procedures can be implemented but the customer has to agree and assume the responsibility.