

**QUALITY ON THE MOVE  
DYNAMICS OF THE EUROPEAN PHARMACOPOEIA**

**Workshop Session  
Pharmaceutical waters**

**Moderator: J. L. Robert & A. Bevilacqua**

**14:00-15:30**

**Quality on the move:  
Dynamics of the European  
Pharmacopoeia**

**Pharmaceutical Waters  
CHMP/CVMP Note for Guidance**

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National Health Laboratory, Luxembourg  
chair CHMP/CVMP Quality Working Party  
Linda Anderson, Ph.D.  
MHRA, United Kingdom  
Budapest, 5 October 2004

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**Water for Pharmaceutical Use**

- Background
- Regulatory overview
- Current/passed developments
- An assessor's perspective

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**Water for Pharmaceutical Use**

- International Seminar organised by EDQM,  
March 1999  
"Water for Injections"
- Objective:  
To check if "Water for Injections" could be  
prepared by reverse osmosis

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## Water for Pharmaceutical Use

- CHMP/CVMP Note for Guidance on 'Quality of Water for Pharmaceutical Use'
  - First discussed by the CPMP/CVMP Quality Working Party in October 2000
  - Released for consultation February - August 2001
  - Adopted by CPMP/CVMP November 2001
  - Further discussion with industry April 2002
  - Revised guideline adopted May 2002
- European Pharmacopoeia monographs on water

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## Water for Pharmaceutical Use

- Water is one of the major commodities used by the pharmaceutical industry
  - as an excipient
  - in the manufacturing process
- Industry devotes considerable resource to development and maintenance of water purification systems

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## Water for Pharmaceutical Use

### GMP

- Validation and qualification of water purification, storage and distribution systems
  - fundamental part of GMP
  - forms an integral part of GMP inspection

### Marketing Authorisation Application

- Discuss grade of water in the dossier

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## Water for Pharmaceutical Use

### European Pharmacopoeia

- Water for Injections
- Purified Water
- Highly Purified Water

### Potable Water

Must comply with Directive 98/83/EC

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## Water for Pharmaceutical Use

### Purified Water Ph Eur

- chemical purity

### Water for Injections Ph Eur

- chemical purity plus additional control of
- microbial contamination, endotoxins
- conductivity, Total Organic Carbon
- particulates

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## Water for Pharmaceutical Use

### Purified Water PhEur

- distillation
- ion exchange
- any other appropriate method including reverse osmosis

### Water for Injections Ph Eur

- distillation only

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## Water for Pharmaceutical Use

### Water for Injections Ph Eur

- On-going debate over acceptance of WFI prepared by methods other than distillation ie. reverse osmosis etc
- Subject of PhEur consultation in late 1990s
- 1999 major international symposium in Strasbourg
- Representatives from industry, national delegates, assessors and inspectors from Member States and CPMP Working Parties

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## Water for Injections PhEur

### Reverse osmosis

- risk of microbial contamination
- process difficult to validate
- cannot rely on testing
  - sampling problems
  - distribution system
  - sporadic growth

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## Water for Pharmaceutical Use

### Reverse Osmosis

- lacks robustness
- fouling of the membrane (chemical and biological)
- failure of membrane integrity

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## Water for Pharmaceutical Use

WFI produced by Reverse Osmosis

- Products authorised in EU:  
a very small number
- Water said to “meet PhEur specification”  
in terms of test limits, but not production  
method

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## Water for Pharmaceutical Use

USP

- includes RO water for production of  
WFI
- but*
- FDA does not accept RO water for  
production of WFI

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## Water for Injections PhEur

Conclusion of the meeting 1999

*That there was insufficient evidence  
at the present time to support the use  
of RO to produce WFI and in view of  
safety concerns, WFI should be  
prepared only by distillation as laid  
down by Ph Eur.*

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## Water for Pharmaceutical Use

Key Issues emerging from the meeting

### Industry

- need for large volumes
- often used WFI in preference to Purified Water
- lacked data to support stance on RO water
- need for monograph on RO water
- need for guidance

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## Water for Pharmaceutical Use

Key Issues emerging from the meeting

### Regulatory

- lack of transparency
- need for a harmonised position
- need for guidance

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## Water for Pharmaceutical Use

Ph Eur Ad Hoc Working Group on Water

- Industry and Regulatory group
- to discuss use of RO water
- led to development of Ph Eur monograph on Highly Purified Water

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## Water for Pharmaceutical Use

### Highly Purified Water

- *What's in a name? That which we call RO... by any other name!*
- current production methods include double pass RO coupled with ultrafiltration, deionisation
- intended for use where water of high biological quality is needed, except when WFI is required

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## Water for Pharmaceutical Use

### Highly Purified Water

- meets same quality standards as WFI including test for bacterial endotoxins
- but production methods considered less reliable
- monograph adopted by PhEur to be implemented 1st January 2002

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## Water for Pharmaceutical Use

### CHMP/CVMP Quality WP and Inspectors WP

- Draft Note for Guidance on *Quality of Water for Pharmaceutical Use*
- Released for consultation February -August 2001
- Discussed by Working Parties during October and adoption by CPMP/CVMP in November 2001
- Revised version adopted by CPMP/CVMP May 2002

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**Water used as an excipient  
Sterile Products**

<b>Sterile medicinal Products</b>	<b>Minimum Acceptable Quality of Water</b>
Parenteral	WFI
Ophthalmic	Purified
Haemofiltration Solutions Haemodiafiltration Solutions	WFI
Peritoneal Dialysis Solutions	WFI
Irrigation solutions	WFI
Nasal/Ear preparations	Purified
Cutaneous Preparations	Purified

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**Water used as an excipient  
Non-Sterile Products**

<b>Non-Sterile medicinal products</b>	<b>Minimum Acceptable Quality of Water</b>
Oral preparations	Purified
Nebuliser Solutions	Purified*
Cutaneous preparations	Purified**
Nasal/Ear preparations	Purified
Rectal/Vaginal preparations	Purified

\* In certain disease states, e.g. cystic fibrosis, medicinal products administered by nebulisation are required to be sterile and nonpyrogenic. In such cases, WFI or sterilised Highly Purified Water should be used.

\*\* For some products, such as veterinary teat dips, it may be acceptable to use potable water where justified taking account of the variability in chemical composition and microbiological quality.

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**Water used in manufacture  
Sterile Active Ingredients**

Synthesis of intermediates	Potable*
Final isolation/ purification – no requirement for sterility	Potable*
Final isolation/ purification – API not sterile but for use in sterile, non-parenteral product	Purified
Final isolation/ purification – API not sterile but for use in sterile, parenteral product	Purified water with an endotoxin limit of 0.25 EU/ml
Final isolation/ purification – API is sterile and apyrogenic	WFI

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**Water used in manufacture  
but not present in final formulation**

<i>Manufacture</i>	<i>Minimum Acceptable Quality of Water</i>
<b>Granulation</b>	<b>Purified*</b>
<b>Tablet coating</b>	<b>Purified</b>
<b>Use in formulation prior to non-sterile lyophilisation</b>	<b>Purified</b>
<b>Used in formulation prior to sterile lyophilisation</b>	<b>WFI</b>

\* potable water may be acceptable where justified for some veterinary products.

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**Water used for Cleaning / Rinsing etc.  
Sterile products**

<i>Cleaning/Rinsing of Equipment Containers, Closures</i>	<i>Minimum Acceptable Quality of Water</i>
<b>Initial rinse of containers/closures for sterile products</b>	<b>Purified</b>
<b>Final rinse of containers/closures and CIP for sterile non-parenteral products</b>	<b>Purified water or same quality as in product if higher</b>
<b>Final rinse of containers/closures and CIP for sterile parenteral products</b>	<b>WFI</b>

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**Water used for Rinsing containers  
for Sterile Parenteral products**

- **Where a subsequent depyrogenisation step is employed, the use of Highly Purified Water may be acceptable subject to suitable justification and validation data**

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## Water for Pharmaceutical Use

### Conclusions (1)

- Formal consultation period ended August 2001
- Further industry comments received
- Reviewed by QWP, IWP April 2002
- Final revised adopted Nfg (May 2002) contributes to EU harmonisation
- International harmonisation ?

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## Water for Pharmaceutical Use

1999: QWP chairman stated:

" The main concern from the member states was:

Several of its members were of the opinion that, while water manufactured by reverse osmosis will meet the specification for WFI, the reliability of this process has not yet been shown to be equivalent to distillation with regard to removing contaminants and in particular bacterial endotoxins.

From a regulatory prospect, the objective of this meeting is to receive experimental data from industry demonstrating the reliability of the reverse osmosis process. □ □

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## PHARMACEUTICAL WATER ON THE MOVE

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### Agenda

- Modern History of Pharmaceutical Water
- Status of Pharmaceutical Waters in the US, EU, and Japan
  - Bulk WFI and Purified Water
  - Feedwater, Production, and Microbiology requirements
  - Conductivity and TOC Requirements
  - Packaged (sterilized) Waters
- Recent and proposed changes to USP, EP, and JP
- New Monographs and General Chapters
- Summary

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### Why is Water Important?

- Water is the most widely used excipient in Pharmaceutical Manufacturing
- Water systems are a significant part of the quality inspections.
- USP - FDA close informal relationship



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### Who Constitutes the USP?

- ~275 doctors, research scientists, pharmacists, technicians, and administrative support staff.
  - Prepare standards and USP text books
  - Liaison to Expert Committees
- ~600 volunteer members of Expert Committees.
  - 62 Expert Committees
  - The Expert Committees have decision-making authority now
- 1 Pharmaceutical Water Expert Committee
  - Consists of 6 members and staff liaison (Frank Barletta [fbp@usp.org](mailto:fbp@usp.org)).
  - Includes FDA input directly and indirectly
  - Expertise in water production, microbiology, quality, validation, and analytical chemistry

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### Relevant Sections of the USP

- **Pharmaceutical Water Monographs**
  - Purified Water (bulk)
  - Water for Injection (WFI) (bulk)
  - Sterile Purified Water (packaged)
  - Sterile WFI (packaged)
  - Sterile Water for Inhalation
  - Sterile Water for Irrigation
  - Bacteriostatic WFI
  - Water for Hemodialysis – USP 27 – NF 22 supplement 1 effective May 1, 2004
  - Pure Steam - 2005?
- **Test Chapters**
  - [645] Conductivity
  - [643] Total Organic Carbon
  - [71] Sterility
  - [85] Endotoxins
  - [79] pH
- **General Information**
  - [231] Water for Pharmaceutical Purposes
  - [232] Instrumentation for Pharmaceutical Water – approved for USP 28
  - [230] Water for Health Applications – USP 27 – NF 22 supplement 1



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### Last 10 Years of USP and H<sub>2</sub>O

- **1991 - WQC proposes Conductivity and TOC to replace most existing tests for Purified Water and WFI.**
- 1991-1995 – PhRMA/WQC evaluates conductivity and TOC instrumentation.
- 1994 - Thornton involvement begins for conductivity and general water issues.
- 1995 - Thornton publishes "Ammonia-Chloride" model
- **November 1996 - USP 23 supplement 5**
  - Requires [645] Water Conductivity testing for PW and WFI
  - [643] TOC an optional test for PW and WFI

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### Last 5 Years

- 1999-2000 - EP changes analytical chemistry test for bulk waters
  - EP requires conductivity test. Different methods and limits than USP.
  - Requires TOC for WFI. Same test as USP.
  - TOC optional for EP PW.
- 1999-2000 – USP re-organization to include experts in specific areas, including water, and provide authority to them. Pharmaceutical Waters Expert Committee elected by USP.
- 2001 - EP defines *Highly Purified Water*. WFI quality produced by RO. Permitted in some applications.
- 2002 – USP, EP, and JP agree to begin harmonization of *some aspects* of Pharmaceutical Waters.

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### Recent (last 2 years)

- Jan-Feb 2002 – EP publishes proposal to revise conductivity requirements for PW and WFI.
  - platinum sensors???
  - specific calibration requirements???
- March 2002 - Thornton comments on proposed changes to EP Conductivity 2.2.38.
- January 2003 – USP proposes modernizing testing for sterile waters.
- April 2003 – USP proposes definition for "Water for Hemodialysis".
- May 2003 – USP proposed lead Pharmacopoeia for Harmonization.

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### More Recent

- 2004 - EP changes Conductivity limits effective July 1, 2004. USP/Thornton comments accepted and implemented.
  - new WFI conductivity limits same as USP limits, 3 stages
  - new PW conductivity limits different than USP limits, 1-stage
- Sept 2004 – PF 30(5) has major water focus.
  - [232] Instrumentation for High Purity Water Analysis re-proposed
  - [231] Water for Pharmaceutical Purposes revised
  - New Pure Steam monograph proposed
  - New tests for Packaged (Sterile) Waters proposed
  - Ted Meltzer filter Stimuli article
  - New [643] Total Organic Carbon re-proposed
- 2005-2006 – JP 15 and CP plans to implement conductivity and TOC tests similar to [645] and [643]

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**Bulk Purified Water and WFI**  
**What are the requirements for these waters?**

1. Source water requirements
2. "Method of Manufacture" requirements
3. Microbiology requirements
4. Endotoxins requirements (WFI only)
5. [645] Conductivity
6. [643] TOC

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**1. Source Water Requirements**

- USP: Feedwater must meet U.S. EPA Primary Drinking Water Requirements or the drinking water requirements for the EU or Japan or WHO.
- Not all countries from Europe are in the EU.

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**2. "Method of Manufacture" Requirements**

- Purified Water: USP, EP, JP permits production by distillation, reverse osmosis, de-ionization, filtration, or equivalent means.
- WFI
  - USP permits "distillation or ~~reverse osmosis~~ a purification process that is equivalent or superior to distillation in the removal of chemicals or microorganisms"<sup>USP27</sup>
  - EP permits distillation only
  - JP permits distillation or RO/UF
- EP *Highly Purified Water*
  - Produced by RO
  - Meets all the requirements of Aqua ad Iniectionabilia
  - Allowed for limited applications

**New**

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**3. Microbiology Requirements**

- EP limits are ACTION LIMITS in Production section
  - Purified Water...100 cfu/ml
  - WFI.....10 cfu/100ml
- USP limits are “recommended” in [231] general chapter
  - Same limits as EP
- JP limits are enforced in drinking water requirements
  - Same limits as EP

*In practice, this is the most widely audited and monitored attribute of PW and WFI.*

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**4. Endotoxin Requirements (WFI only)**

- <0.25 EU/mL Endotoxin (USP and JP)
- <0.25 IU/mL Endotoxin (EP)
- Same limits and same tests.

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**5. [45] Water Conductivity**

- Prior to November 1996, existing chemistry tests date back to 1840. Chemistry tests are qualitative, subject to bias, and off-line.
  - Carbon dioxide
  - Calcium
  - Ammonia
  - Chloride
  - Sulfate
  - Oxidizable Substances
  - Heavy Metals
- November, 1991 – Conductivity proposed to replace the chemistry tests.



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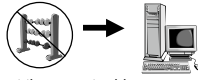
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### 645 Water Conductivity

- Maintain/improve the existing water quality.
- Simplify the testing. Reduce the number of tests.
- Use modern instrumentation.
- Quantify the test results.
- Improve the reliability of the testing. Take out the operator bias.
- Make allowances for on-line, in-line testing.




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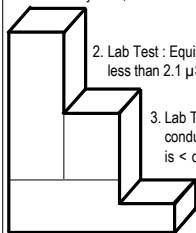
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### USP 645 3-Stage Test Method (effective November, 1996)

1. Measure in-line, non-temperature-compensated conductivity and temperature. Look up conductivity limit for that temperature. If measured uncompensated conductivity is less than conductivity limit, then **Pass - Done. If not:**
2. Lab Test : Equilibrate water sample with atmospheric CO<sub>2</sub> : If conductivity is less than 2.1 μS/cm at 25°C, **Pass - Done. If not:**
3. Lab Test: Saturate previous sample with KCl : Measure pH. Look up conductivity limit for that pH. If measured conductivity (from Stage 2) is < conductivity limit, **Pass - Done. If not:**



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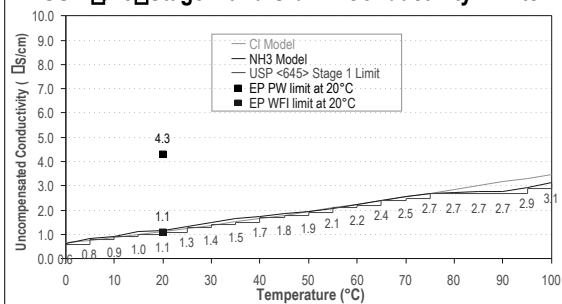
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### USP 645 Stage 1 and Old EP Conductivity Limits




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### Stage 1: Temperature/Conductivity Requirements

(for non-Temperature Compensated Conductivity Measurements)

Temperature (°C)	Maximum Conductivity (µS/cm)	Temperature (°C)	Maximum Conductivity (µS/cm)
0	0.6		
5	0.8	55	2.1
10	0.9	60	2.2
15	1.0	65	2.4
20	1.1	70	2.5
25	1.3	75	2.7
30	1.4	80	2.7
35	1.5	85	2.7
40	1.7	90	2.7
45	1.8	95	2.9
50	1.9	100	3.1

Example: Temperature is 83.7°C and uncompensated conductivity is 1.7 µS/cm. The limit is 2.7 µS/cm at 80°C. PASS!

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### Advantages of On-line, In-line Stage 1 Testing

- Real-time process (conductivity and temperature!) information.
- Immediate alarms and control options.
- Data can be logged . . . provides a water history.
- Easier and *cost-effective*.
- Eliminates sample collection and transportation errors.
- Temperature-compensated conductivity remains an excellent technique to observe water quality changes.
- Maintains the Quality Assurance by improving the integrity of the testing

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### Stage 3: pH/Conductivity Requirements

(for atmosphere-equilibrated samples only)

pH (pH)	Maximum Conductivity (µS/cm)	pH (pH)	Maximum Conductivity (µS/cm)
5.0	4.7		
5.1	4.1	6.1	2.4
5.2	3.6	6.2	2.5
5.3	3.3	6.3	2.4
5.4	3.0	6.4	2.3
5.5	2.8	6.5	2.2
5.6	2.6	6.6	2.1
5.7	2.5	6.7	2.6
5.8	2.4	6.8	3.1
5.9	2.4	6.9	3.8
6.0	2.4	7.0	4.6

Example: Off-line uncompensated conductivity at 25°C is 2.5 µS/cm. Add KCl, and measured pH is 5.5. The limit is 2.8 µS/cm. PASS!

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## Calibration & Performance Requirements for USP $\square 45$

### Meter Calibration/Performance

- Reports uncompensated conductivity or resistivity.
- Display resolution of 0.1  $\square$ S/cm minimum. 1  $\square$ S/cm resolution is unacceptable.
- Verify performance to  $\pm 0.1$   $\square$ S/cm by replacing sensor with traceable precision (0.1%) resistor. For example: 100 k $\square$  resistor with 0.1 cm<sup>2</sup> cell constant should display  $1.0 \pm 0.1$   $\square$ S/cm.
- Temperature measurement circuit should be verified.

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## Calibration & Performance Requirements for USP $\square 45$

### Sensor Calibration/Performance

- Cell constant accurate and known to  $\pm 2\%$ .
- Calibrate sensor in a solution with a stated conductivity (from NIST, chemical supplier, etc...).
- Calibrate sensor in a solution prepared to a specific conductivity (ASTM D1125 standard or ultrapure water).
- Calibrate sensor vs. another calibrated sensor (from mfr. usually).
- *Temperature accurate to 2°C – effective USP 28*

**New**

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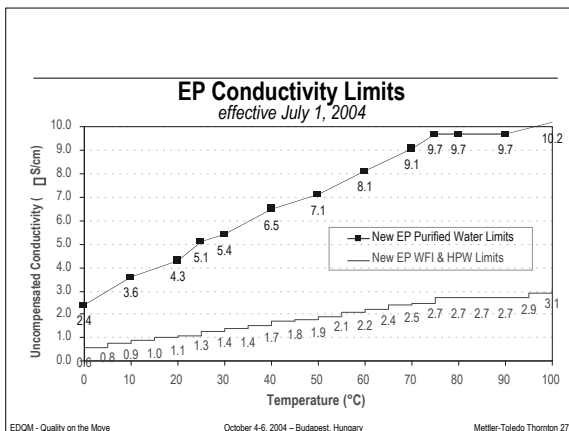
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## New EP Conductivity Requirements

*effective July 1, 2004*

### Sensor Requirements

- "electrodes of a suitable material such as stainless steel"
- "cell constant: within 2% of the given value determined using a certified reference solution with a conductivity less than 1500  $\square$ S/cm."

### Meter Requirements

- "resolution 0.1  $\square$ S/cm on the lowest range."
- "by means of precision resistors or equivalent devices, after disconnecting the conductivity cell, for all ranges used for conductivity measurement and cell calibration (with an accuracy of at least  $\pm 0.1\%$  of the stated value, traceable to the national standard)."

### System Requirements (sensor and meter)

- "If in-line sensors cannot be dismantled, system calibration may be performed against a calibrated conductivity cell placed in proximity to the cell to be calibrated in the water flow."

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## Harmonization: Conductivity Methods & Test Limits

Parameter	USP	<i>effective July 1, 2004</i>		JP
		EP	Future EP	
Conductivity test required	yes	yes	yes	?
Eliminate chemistry tests	yes	no <sup>1</sup>	no	
Separate limits for PWWFI	no	yes	yes	
On-line test	0-100°C <sup>2</sup>	none	same as USP WFI <sup>4</sup>	
Off-line test at temp	25°C <sup>3</sup>	20°C	same as USP WFI <sup>4</sup>	
Instrument requirements	yes	no	yes	

<sup>1</sup> Heavy metals and Nitrates tested required for EP; aluminum test requires for dialysis solutions

<sup>2</sup> Table of values, temperature dependent

<sup>3</sup> Table of values, pH dependent

<sup>4</sup> Different limits for Purified Water

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## Harmonization: Conductivity Methods & Test Limits

Parameter	USP	<i>effective July 1, 2004</i>		JP
		EP	Future EP	
Sensor accuracy	$\pm 2\%$	$\pm 5\%$	$\pm 2\%$	
Sensor calibration method	not specific	specific	not specific	
Calibration solutions	user selected	specific	user selected	
Calibration Method	works	2 stds invalid	works	
Compensation	none	?	None	
Method tested	yes	no	yes	

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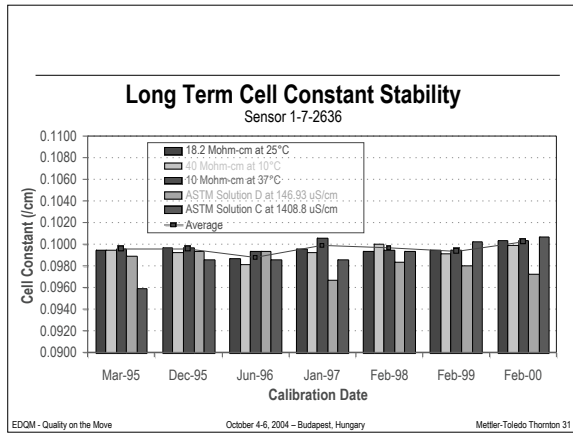
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### 6. Total Organic Carbon (TOC)

- Prior to November 1996, the existing test for "oxidizable organics" was the Oxidizable Substances test. The test is based on the appearance or disappearance of a pink color.
- Same goals as Conductivity – Replace existing tests with a better test.
- In November 1996, [643] TOC was established as an option to the Total Oxidizable Substances test.
- In May, 1998, the Total Oxidizable Substances was deleted (for bulk water testing). Only [643] TOC is required.

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### On-Line TOC by UV Oxidation/Conductivity

- $C_xH_yO_z \xrightarrow{UV} CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$
- Hg lamp emits **185 nm** and **254 nm** UV light
- Light, chemicals, heat, and time move the reaction forward
- Accurate conversion of temperature and conductivity is required
- Many technologies
  - Static UV oxidation - detection by conductivity
  - UV/chemical/membrane oxidation - detection by conductivity
  - Dynamic UV oxidation - detection by conductivity
  - Combustion – detection by IR

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**TOC Instrumentation Requirements for  
USP 643 TOC and EP 2.2.44**

- Limit of Detection of 0.050 mg/L (50 ppb)
- Calibrate according to Manufacturer's recommendations
- Must meet System Suitability testing periodically

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**System Suitability for USP 643 and EP 2.2.44**

- Measure TOC of 0.50 mg carbon/L (as sucrose),  $R_s$ .
- Measure TOC of 0.50 mg C/L (as *p*-benzoquinone),  $R_{ss}$ .
- Measure TOC of water used to prepare these solutions,  $R_w$ . Not to exceed 100 ppb.
- Response shall be between 85 and 115%!

$$\text{Response} = 100 \frac{R_{ss} R_w}{R_s R_w}$$

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**PW, HPW, and WFI Water Requirements for TOC**

- Procure sample. Measure TOC of test water,  $R_u$ .
- Compare  $R_u$  to system response at limit,  $R_s - R_w$ . (~500 ppb).
- USP: Water passes TOC test if  $R_u < R_s - R_w$ .
- EP: Water passes TOC test if  $R_u < 500$  ppb.
- TOC testing not required for EP Aqua Purificata (PW).

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## What's New for USP Pharmaceutical Waters?

### • Monographs

- Definition of WFI production method – see earlier slide
- Write out definitions of all water types; eliminate references
- Addition of new notes
- Update/improve test methods for packaged waters
- New monograph – Water for Hemodialysis
- Pure steam

### • General Information Chapters

- Revisions to [231] Water for Pharmaceutical Purposes
- New [230] Water for Health Applications – see earlier slide
- New [232] Instrumentation for Analysis of High Purity Pharmaceutical Water

### • Test Methods

- Proposed revisions to [643] Total Organic Carbon
- Proposed revisions to [645] Water Conductivity – see earlier slide

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## Monographs

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## Comparison of Sterile WFI Waters

	EP	JP	USP
1. Clarity	+	Not tested	Not tested
2. Colour	+	Not tested	Not tested
3. Extractable volume	+	Not tested	Not tested
4. Nitrate	+	≠ EP	Not tested
5. Heavy metals	+	≠ EP	Not tested
6. Aluminium	+	Not tested	Not tested
7. Acidity/alkalinity	+	≠ EP	Not tested
8. Conductivity	+	Not tested	Not tested
9. Oxidisable substances	+	= EP	= EP
10. Chloride	+	≠ EP	≠ EP ≠ JP
11. Residue on evaporation	+	= EP	Not tested
12. Sulphate	+	≠ EP	≠ EP ≠ JP
13. Ammonium	+	= EP	= EP
14. Calcium/Magnesium	+	Not tested	Not tested
15. Calcium	Not tested	Not tested	+
16. Bacterial endotoxins	+	= EP	= EP
17. Particulate contamination	+	Appears to be the same	Not tested
18. TOC	Not tested at this level	+ ≠ EP & USP bulk waters	Not tested at this level
19. pH value	Not tested	Not tested	+
20. Carbon dioxide	Not tested	Not tested	+
21. Sterility	+	≠ EP	≠ EP ≠ JP

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### USP Packaged Waters Initiative

- Goal: Replace the wet chemistry tests with something more reliable, faster, better
- Issues
  - What are the right tests and what are the limits?
  - Should the limits be the same as the bulk waters?
  - Can we safely eliminate all wet chemistry tests?
- PF 28(4), July-Aug. 2002, pp. 1272-1273
  - Proposal to delete all chemistry tests.
  - 2 Conductivity limits volume dependent (from EP)
  - TOC 6 ppm
- See PF 30(5), Sep-Oct 2004.
  - Same proposal
  - Retain Ox Sub, delete TOC

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### Pure Steam Monograph Proposal

- Pure Steam is water that has been heated above 100°C and vaporized in a manner which prevents source water entrainment.
- Meets source water requirements for Purified Water and Water for Injection: USEPA NPdWR, or drinking water regulations of the European Union, Japan or WHO.
- Contains no added substance.
- Level of steam saturation or dryness, and the amount of non-condensable gases are to be determined by the Pure Steam application.
- [Note: Pure Steam quality is difficult to assess in its vapor state; therefore the attributes of its condensate are used to indirectly test its quality. The process used to create and collect the condensate for analysis must not adversely impact these quality attributes.]
- Bacterial Endotoxins: [85] condensate contains less than 0.25 USP Endotoxin Unit per mL.
- Total Organic Carbon [643] condensate meets the requirement.
- Water Conductivity [645] condensate meets the requirement.

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### General Information Chapters

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### 231 Water for Pharmaceutical Purposes

- Feedwater and impact of THMs on water treatment.
- Listing of all types of water, including non-monograph waters (7+18).
- More discussion of unit purification steps, especially filtration.
- Storage and distribution.
- Enhanced Sanitization discussion.
- Enhanced Sampling considerations.
- Chemical methods of analysis for bulk and packaged waters.
- Enhanced Microbiological considerations.
- Effective USP 28 possible.



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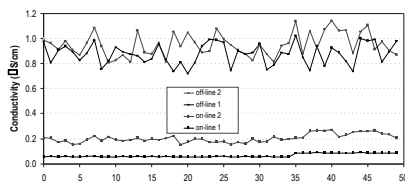
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### 232 Instrumentation for Analysis of High Purity Pharmaceutical Water

- Uniqueness of High Purity Water
- Contamination
  - sample containers: glass or polymer or other?
  - cleaning agents
  - air contamination
- On-line or off-line
- TOC
- Conductivity
- Sample handling



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### General Chapters – Test Methods

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**New §43 Proposal**

- Prepare sucrose and 1,4-benzoquinone solutions at **about** 0.50 mg of carbon per liter (500 ppb)
- Actual solutions weighed are  $C_s$  and  $C_{ss}$
- Calculate response efficiency ( $RE_s$ ) of sucrose -  $100 \cdot (R_s - R_w) / C_s$
- Calculate  $RE_{ss}$  of benzoquinone -  $100 \cdot (R_{ss} - R_w) / C_{ss}$
- TOC System is suitable if  $85\% \geq Re_{s/ss} \geq 115\%$
- Water meets requirements if  $R_u \leq 500$  ppb

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**New §43 Proposal**

**Advantages**

- Makes solution preparation easier for some
- Opens the window for TOC System Suitability

**Disadvantages**

- Moves away from harmonization
- Opens the window for TOC System Suitability

If  $RE_s$  is 85% and  $RE_{ss}$  is 115%, then overall ratio is 135.3%  
If  $RE_s$  is 115% and  $RE_{ss}$  is 85%, then overall ratio is 73.9%

$104.6 \pm 30.7\%$

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**Summary**

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### USP Summary for Bulk Waters

- USP WFI shall be produced by distillation or proven validatable equivalent methods.
- The USP requires that Purified Water and Water for Injection meet specific conductivity [645] and TOC [643] requirements.
- USP [645] is a 3 stage conductivity test. It permits on-line and off-line testing. [645] requires the use of non-temperature-compensated conductivity measurements. [645] requires specific performance requirements for the instruments.
- [643] permits on-line and off-line testing.
- Conductivity and TOC Requirements for USP Bulk waters and very mature and little will change.

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### EP Summary for Bulk Waters

- EP WFI shall be produced by distillation ONLY.
- EP requires that Purified Water and Water for Injection meet specific conductivity (2.2.38) and TOC (2.2.44) requirements. Nitrates and Heavy Metals testing still required.
- Conductivity requirements have changed. WFI conductivity to look like USP requirements. PW conductivity to be changed to allow on-line, but unharmonized.
- TOC testing fully harmonized with USP.
- EP microbiology limits harmonized, but written as part of monograph.

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### JP Summary for Bulk Waters

- JP WFI shall be produced by distillation or RO-UF.
- JP does not require conductivity or TOC testing for Purified Water and Water for Injection, and are being revised.
- JP requires 9 wet chemistry tests.
- JP and USP/EP TOC test method very different for Calibration and System Suitability requirements. Not all TOC technologies will work with both methods.
- Microbiology limits same as USP and EP, but placed in Drinking Water section.
- Plan to change in JP15 - 2005!

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### Packaged Water Summary

- Packaged Water requirements need revision by all groups.
- USP has 9 chemistry tests for SWFI, after preparing WFI!
- USP plans to reduce to 2 tests
  - Conductivity (same limits as EP?)
  - Quantitative organic analysis test (TOC or spectrophotometric OS?)
- EP has ~15 wet chemistry tests for SWFI, plus conductivity
- JP requirements has ~11 wet chemistry tests for SWFI, with no conductivity test

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