（資料２）

ISO/TC198/WG9 “Aseptic processing of health care products” (ISO 13408) 国際会議報告書

１．　会議名：Part 1: General requirements（一般規定要求事項）/ Part 2: Filtration（ろ過）/ Part 3: Freeze drying（凍結乾燥）/ Part 4: Sterilization and cleaning in place（定置滅菌および洗浄）/ Part 6: Isolator/barrier technology（アイソレーター/バリア技術）

２．　開催地：ドイツ　ケルン

３．　開催日：2001 年 12 月 10-12 日

４．　出席者：日本３名、ドイツ５名、アメリカ１名、スウェーデン１名、
議長 Dr.　Claus　Harberer（幹事国　ドイツ）

５．　日本からの出席者：佐々木次雄（国立感染所研究所）、川村邦夫（大塚製薬）、曲田純二（日本ミリポア）

６．　主要議題、議決事項、特に問題となった点および今後の対応についての所見

全体:　今回の会議は 2001 年 10 月開催予定であった ISO/TC198 京都国際会議がアメリカでの同年 9 月のテロ事件により中止になったことを受け、ISO/TC198/WG9 議長から急遽召集された国際会議である。背景には参加国から多くの適切なコメントが WG9 へ寄せられており、これを早期に検討し各国へフィードバックすることにより、医薬品・体外診断薬・医療用具製造業界にとって重要な本国際規格の発効を早めることがある。ただし、テロ事件の影響で所属団体から出張制限を受ける委員が少なからずいたため、参加者数が限定された会議であった。

Part 1: General requirements（一般規定要求事項）

日本の WG9（第 9 作業部会）主査である川村氏より、無菌工程の評価に使用される培地充填試験法の許容限度値について新しい提案が出され、科学的説明がなされた。次回会議でさらに検討される予定である。

イギリスなどから本国際規格の対象を現在の “ヘルスケア製品（医薬品・体外診断薬・医療用具）” から “医療用具” に限定すべきであるとの意見が出されたことに対し、会議出席者間では否定的な意見が占めた。次回会議で最終的に決定されるであろう。

Part 2: Filtration（ろ過）

現在 DIS（＊）である本ドラフトについて日本からも 30 項目以上の訂正提案が出され、特に佐々木氏から補足説明がなされおおむね取り入れられた。全体ではおよそ 80 項目について討議された。変更点の一部の例は下記のとおりである。

ろ過前のバイオバーデンを測定することについては”Should”から”Shall”に変更され、より強い要求事項となった。ただし、過去の実験結果が安定して低いバイオバーデンを示している場合などは除外されている。

メンテナンスと変更管理に関し、フィルター使用者と製造者は同意文書を取り交わすことが追記された。これは特に製造者側に変更届けを義務付けることであり、使用者側の管理として重要な追加事項と思われる。
次回会議でFDISになる予定であり、発効が近い国際規格ドラフトである。
＊　国際規格作成作業はまずWD(Working Draft:**作業分科会原案**)**が作成され、次に**CD(Committee Draft:**委員会原案**)**としてまとめられる。このCDに対する、参加国の投票が行われ、合意されると**DIS(Draft International Standard:**国際規格案**)**となり、ついで同投票後**FDIS(Final Draft International Standard:**最終国際規格案**)**となりこれを経て国際規格発効となる。
Part 3: Freeze drying（凍結乾燥）
Mathot氏から提出されたWDについて討議された。このWDは前回のベルリン会議でのコメント、FDAおよび日本からの事前コメントも取り入れて作成されたものである。
凍結乾燥システムのリークテストについては文書化し、頻度を明確化することや、ベントフィルターシステムの滅菌と完全性試験は定置で実施することが要求されている。
次回会議ではCDにあげられる予定である。
Part 4: Sterilization and cleaning in place（定置滅菌および洗浄）
川村氏よりドラフトが提出された。本作業は定置滅菌に関して滅菌手法がスチームだけではなく、ガスなど幅広いSterilantが含まれているため特に困難なテーマである。WDとして継続検討される。
Part 6: Isolator/barrier technology（アイソレーター/バリア技術）
Damman氏より同様にWDが説明された。
用語の定義として、Isolatorは"a separative enclosure used in aseptic processing(which ***can*** be sealed for bio-decontamination) to exclude operators and surrounding environment from critical processing zone"とされ、Barrier systemの"a separative enclosure used in aseptic processing(which ***can not*** be sealed for bio-decontamination) to exclude operators and surrounding environment from critical processing zone"と区別された。日本から無菌操作対象としてバリア技術まで含めるのは困難なためアイソレーターに限定すべきとの意見が出されたが、議長よりバリア技術の多くが無菌操作工程に利用されている現実があるため対象に加えたいとの意見で継続されることになった。
PQ(Performance Qualification)において、CIP, SIPおよび無菌充填の確立とバリデーションを実施する項目が追記された。なお、ここでのSIP/CIPの要求事項に関しては上述のPart4が適用される予定である。
次回会議でCDにあげられる予定である。

7．次回開催予定：2002年5月13-17日、日本　京都市

20010980

以降P.41－P.57は下記をご参照ください。

ケルン会議で国際規格にするため、FDIS (Final Draft for International Standard)に格上げされた。

ISO TC 198

Date: 2001-02-08

ISO/DIS 13408-2

ISO TC 198

Secretariat: AAMI (ANSI)

Aseptic processing of health care products — Part 2: Filtration

Traitement aseptique des produits de santé — Partie 2: Filtration

添付資料３

製薬用水の国際調和に必要な情報収集と日本薬局方参考情報に導入予定の「製薬用水の製造及び品質管理」の素案作成に関する研究

１．　製薬用水の国際調和に関する EP Position Paper
２．　製薬用水の製造方法及び品質規格に関する３薬局方の比較表
３．　製薬用水の製造管理、規格、規格試験法に関する研究班員リスト
４．　「製薬用水の製造及び品質管理に関する実態調査」への協力願い
５．　製薬用水の製造及び品質管理に関する実態調査表

概要説明：現在、「製薬用水の製造管理、規格、規格試験法に関する研究班」で、製薬用水の国際調和作業に向けて、必要な情報を収集中である。その一環として、日本製薬団体連合会加盟団体を通じ、製薬企業に対し「製薬用水の製造及び品質管理に関する実態調査」を実施中である。また、日局参考情報欄への収載を目指して「製薬用水の製造管理と品質管理」に関するドラフトを作成中である。これらについては、来年度、報告する。

(資料3)

PHARMACOPOEIAL DISCUSSION GROUP
EP POSITION PAPER

WATER FOR PHARMACEUTICAL USE / INITIATION OF INTERNATIONAL HARMONISATION?

1. Introduction

At the November 2001 PDG meeting in Strasbourg, the question was raised whether work should be initiated to harmonise pharmacopoeial monographs on water. A first position paper from the USP was found to lack from an European perspective several important aspects (e.g. history of preceding harmonisation activities in this field, analysis of the current differences in existing monographs). The EP agreed to prepare a document which shall serve at the next PDG meeting as a decision basis on this matter.

2. Background

Water was classified as one of the top 10 excipients selected for international harmonisation in a very early stage of this PDG project. Since water is not a commercial excipient but is prepared in situ it was later not officially included into the list of the top 25 excipients. Nevertheless, harmonisation activities were actively pursued for this widely used excipient.

The USP, which took the initiative in this matter, undertook a major effort to update the existing monographs to the current state in science and technology. Based on comprehensive and well documented work, the USP came up in 1994 with a draft monograph on pharmaceutical bulk water which

- Substituted all tests for inorganic matter by a conductivity test,
- Substituted tests for organic matter (except microbiological purity and bacterial endotoxins) by TOC,
- Did not include microbiological requirements.

The proposed conductivity limit was based on the chloride ion, the ion with the lowest limit of detectability (0.47 ppm) and the lowest conductivity from the ions tested in the previous USP monograph. The resulting extremely low limit of max 1.3 μS/cm at 25 °C requires a complicated labour-intensive 3-step test method to exclude unjustified OOS

rejections.

The USP proposal found great interest and support in Europe, especially since it covered
in-line monitoring of continuously operating water treatment units for most of the critical parameters. However, it was pointed out:

- That the conductivity limit was unnecessarily tight (at the capability limit of water-treatment units (especially the widely used RO technique) and test method and there was no necessity for such a tight limit from the perspective of pharmaceutical application) ;
- That – following the same principle (i.e. basing the conductivity limit on the ion with the lowest limit of detectability) – the EP would have to base the conductivity limit on the nitrate ion (limit of detectability approx. 0.2 ppm) which would result in a conductivity limit of max 0.3 μS/cm (test for nitrate is not included in the previous USP but is in the EP monograph). Nitrate is a regular constituent in potable water. It is from a scientific and technical point of view (e.g. safety concerns, ion slip in reverse osmosis, nutrition of micro-organisms) of much higher relevance than chloride;
- That it is considered inadequate to base the limit for a cumulative test on the limit of detectability of only one ion.

As a consequence, a pragmatic approach with a limit of e.g. 5 μS/cm was proposed from the European side. USP decided to stick to the sodium chloride concept (implementation of the monograp 1996) which finally resulted in a discontinuation of the common work on international harmonisation of waters for pharmaceutical use. Since that point in time, the EP pursued unilaterally the revision of the EP water monographs under the perspective to harmonise as far as possible with the USP.

In addition to conductivity, preparation of WFI by reverse osmosis (RO) (permitted by the USP and the JP but not by the EP), total organic carbon (TOC) and microbiological purity requirements were other important issues during revision. After extensive consultation with the industry and the competent regulatory authorities, the revised monographs were approved by the EP Commission in 1999. Work continued to finalise some adaptations of the conductivity test method, considered still necessary, and to study the necessity to switch for the microbiological purity test from a rich to a low-nutritive culture medium.

TOC determination on WFI prepared by RO is so far the only element of the USP concept adopted by the JP.

3. Differences between present EP, JP and USP water monographs

Water qualities/types: see attachment 1

Bulk water specifications: see attachment 2

Specifications packaged WFI: see attachment 3

Test methods WFI in containers: see attachment 4

4. Conclusions and recommendations to the PDG

4.1 *Water qualities / types*

The overall number of water types described in the 3 Pharmacopoeias amounts to 12. Common to all 3 Pharmacopoeias are only 3:

- Water for injection (bulk),
- Sterilised water for injection (containers),
- Purified water (bulk).

This situation arises from obvious differences in the use/application and commercial distribution of water in the 3 regions. Focus of any harmonisation activities should be on the water types common to all 3 Pharmacopoeias.

4.2 *Testing criteria and specification for WFI and purified water in bulk*

EP has already widely harmonised with the USP at this level. There are remaining differences i.e.:

- No use of RO for WFI production,
- Source water refers to national potable water legislation of EP Convention members (28 countries) not to EU legislation (15 countries),
- Inclusion of microbiological action limits into the binding part of the monographs,
- Different conductivity limit for purified water,
- Test for nitrates and heavy metals maintained,

- Special quality standards (aluminium, bacterial endotoxins) for water used in dialysis,
- Permanganate test alternative to TOC in purified water.

These are the result of extensive consultation with the European industry and the competent European Regulatory Authorities, concluded only recently. These items are therefore not open to harmonisation activities in the near future.

Differences in the lay-out of the monographs between USP/EP on one hand and JP on the other hand are fundamental. Switch of the JP monographs to a concept based on conductivity and TOC would be a big step ahead in international harmonisation.

4.3 *Testing criteria and specifications for sterilised water for injections*

Lay-out differences between the 3 Pharmacopoeias are substantial at this level, which results overall in more than 20 testing criteria. Consistency of monographs for packaged water with those for bulk water is insufficient which results in a considerable number of redundant tests (e.g. EP : calcium + magnesium, sulphate, residue on evaporation besides a conductivity test), or unnecessary repetition of tests like nitrate or heavy metals covered already at the bulk water level, or tests like chlorides or oxidisable substances which might be relevant for WFI in plastic containers but not necessarily in glass containers. Harmonisation at this level would result in a considerable reduction of workload for the industry without adverse effect on the relevant safety standards. Initiation of harmonisation activities at this level seems therefore highly recommendable. Other monographs for packaged water, not common to all 3 Pharmacopoeias, could follow the pattern developed for sterilised WFI in containers.

4.4 *Test methods*

- Water in bulk

The test methods for the 3 testing criteria common to the USP and the EP (i.e. conductivity, TOC, bacterial endotoxins) are equivalent (adaptation of the EP conductivity method to ensure full equivalence with the USP is on the way, see Pharmeuropa 14.1).

JP method for bacterial endotoxins is also equivalent to the USP and EP but not TOC. See attachment 4 with regard to method equivalence between EP and JP.

Even though total aerobic count is a testing criterion neither in the USP nor the JP water monographs, microbial testing plays an important role in the quality control of water. Testing methods differ in all 3 Pharmacopoeias.

- Packaged waters (see attachment 4)

It is recommended to initiate potential harmonisation work on methods only after decision by the JP on the future lay-out for bulk water monographs and mutual agreement on the future lay-out of the monograph for sterilised water for injection in containers.

4.5 *Information chapter on "water for pharmaceutical purposes"*

Such a chapter exists so far exclusively in the USP. EP is considering inclusion of such a chapter. Content of a chapter of this type overlap to a considerable extent with GMP and Inspection aspects and the corresponding guidelines.

Inclusion/Harmonisation of a pharmacopoeial information chapter should be considered only if the existing GMP and Inspection guidelines do not sufficiently cover the relevant facts in this field.

4.6 Cross-references

The various cross-references in use at present between the existing water monographs, turned out to be a source of misunderstanding and misinterpretation and should therefore be abandoned.

Attachment 1

WATER QUALITIES/TYPES

	EP (4th Ed.)	JP (XIII)	USP 24
1. WFI[1]/bulk	+	+	+
2. WFI/sterilised (containers)	+	+	+
3. HPW[2]/bulk	+	–	–
4. PW[3]/bulk	+	+	+
5. PW/containers	+	–	–
6. Water for dialysis (bulk + containers)	+	–	–
7. Bacteriostatic WFI (containers)	–	–	+
8. Sterile water for inhalation (containers)	–	–	+
9. Sterile water for irrigation (containers)	–	–	+
10. Sterile PW/containers	–	–	+
11. Sterile PW/bulk	–	+	–
12. Water (tap, well)	–	+	–

[1] Water for injections

[2] Highly purified water

[3] Purified water

COMPARISON OF BULK PW SPECIFICATIONS

	EP	JP	USP
1. Production Method	All techniques	• distillation • ion exchange • UF[4] • combination of above techniques	• all techniques
2. Source water quality	Potable water acc. to national legislation of EP Convention members	JP water specification	US-EPA drinking water regulations or EU regulations
3. Total aerobic count/ml	Max 100[5]	–	–
4. Conductivity [µS/cm at 20 °C]	Max 4.3[6]	–	Max 1.1
5. TOC [mg/l]	Max 0.5[6]	–	Max 0.5
6. Bacterial endotoxins/ml	Max 0.25 IU[7]	–	–
7. Nitrates [ppm]	Max 0.2	Not detectable	–
8. Heavy metals [ppm]	Max 0.1	Not detectable	–
9. Aluminium[4] [ppb]	Max 10	–	–
10. Acidity/alkalinity	–	Test against colour indicators	–
11. Chloride	–	Not detectable	–
12. Sulfate	–	Not detectable	–
13. Nitrite	–	Not detectable	–

[4] UF alone is not capable of removing inorganic ions, RO is not mentioned for purified water

[5] as action limit in production section

[6] in production section

[7] if used in dialysis

14. Ammonium [mg/l]	–	Max 0.5	–
15. Oxidisable substances [$KMnO_4$ test]	< 0.1 ml[8] 0.02 $KMnO_4$ /100 ml	< 0.10 ml 0.02 $KMnO_4$ /100 ml	–
16. Residue on evaporation	–	Max 1.0 mg/100 ml	–

[8] alternative to TOC

COMPARISON OF BULK WFI SPECIFICATIONS

	EP	JP	USP
1. Production Method	distillation	• distillation • RO + UF, from PW	• distillation • RO
2. Source water quality	Potable water acc.to national legislation of EP Convention members	JP water specifications	• US-EPA drinking water regulation • equivalent regulations of EU and Japan
3. Total aerobic count	Max 10/100ml[9]	–	–
4. Conductivity [µS/cm at 20 °C]	Max 1.1[10]	–	Max 1.1
5. TOC [mg/l]	Max 0.5[7]	Max 0.5[11]	Max 0.5
6. Bacterial endotoxins [per ml]	Max 0.25 IU	Max 0.25 EU	Max 0.25 USP-EU
7. Nitrates [ppm]	Max 0.2	Not detectable	–
8. Heavy metals [ppm]	Max 0.1	Not detectable	–
9. Aluminium[12] [ppb]	Max 10	–	–
10. Acidity/alkalinity	–	Test against colour indicators	–
11. Chloride	–	Not detectable	–
12. Sulfate	–	Not detectable	–
13. Nitrite	–	Not detectable	–

[9] Action limit in production section

[10] in EP in production section

[11] tested exclusively if produced by RO/UF

[12] if used in dialysis

14. Ammonium [mg/l]	–	Max 0.05	–
15. Oxidisable substances [$KMnO_4$ test]	–	< 0.1 ml 0.02M $KMnO_4$ / 100 ml	–
16. Residue on evaporation	–	Max 1.0 mg/100 ml	–

STERILE WFI IN CONTAINERS/COMPARISON OF SPECIFICATIONS

	EP	JP	USP
1. Production method	Distillation To be prepared from bulk water which meets specs. at this level	• Distillation • RO + UF from PW Dito	• Distillation • RO Dito
2. Clarity	Clear	-	-
3. Colour	Colourless	-	-
4. Extractable volume	≥ nominal volume	-	-
5. Nitrate [ppm]	Max. 0.2	Not detectable	-
6. Heavy metals [ppm]	Max. 0.1	Not detectable	-
7. Aluminium [ppb]	Max. 10[13]	-	-
8. Acidity/Alkalinity	Max. 0.1 ml 0.01M NaOH Max. 0.15 ml 0.01M HCl 20 ml/phenol red)	Max. 0.13 ml 0.01M NaOH (phenol red) Max. 0.13 ml 0.01M HCl (bromothymol blue) to change colour (20 ml water)	-

[13] If used in dialysis

9. Conductivity [µS/cm]	Nominal volume ≤ 10 ml : max. 25 Nominal volume > 10 ml : max. 5	-	-
10. Oxidisable substances	< 0.2 ml 0.02 M $KMnO_4$ / 100 ml (5 minutes)	< 0.1 ml 0.02 M $KMnO_4$ /100 ml (10 minutes) [14]	Nominal volume < 50 ml: < 0.4 ml 0.1 N $KMnO_4$ / 100 ml (5 minutes) [15] Nominal volume ≥ 50 ml: < 0.2 ml 0.1 N $KMnO_4$ / 100 ml (5 minutes)
11. Chlorides [ppm]	Nominal volume ≤ 100 ml : max. 0.5 Nominal volume > 100 ml not detectable	Nominal volume ≤ 10 ml : max. 0.5 Nominal volume > 10 ml : not detectable	Max. 0.5
12. Residue on evaporation	Nominal volume ≤ 10 ml : max. 0.004 % Nominal volume > 10 ml : max. 0.003 %	Nominal volume ≤ 10 ml : max. 0.004 % Nominal volume > 10 ml : max. 0.003 %	-
13. Sulphate	Not detectable	Not detectable	-
14. Ammonium [ppm]	Max. 0.2	Nominal volume ≤ 10 ml : max. 0.02 Nominal volume > 10 ml : max. 0.01	Nominal volume < 50 ml : max. 0.6 Nominal volume ≥ 50 ml : max. 0.3

[14] In case of production by RO, TOC determination mandatory

[15] 0.4 ml 0.1N K MnO_4 equivalent to 0.4 ml 0.02 M $KMnO_4$

15. Calcium + magnesium	Not detectable	-	-
16. Calcium	-	-	Not detectable
17. Sterility	Meets requirements	Meets requirements	Meets requirements
18. Bacterial endotoxins per ml	< 0.25 IU	max. 0.25 EU	max. 0.25 USP-EU

19. Particulate contamination: subvisible particles	<u>Method 1:</u> Containers > 100ml: Particles ≥ 10 µm: □ = max 25 /ml particles ≥ 25 µm □ = max 3 /ml Containers ≤ 100ml: Particles ≥ 10 µm: □ = max 6000/container particles ≥ 25 µm □ = max 600/container <u>Method 2:</u> Containers > 100ml: Particles ≥ 10 µm: □ = max 12 /ml particles ≥ 25 µm □ = max 2 /ml Containers ≤ 100ml: Particles ≥ 10 µm: □ = max 3000/container particles ≥ 25 µm □ = max 300/container		Specification (for all sizes) appear to be identical with EP specifications for containers ≤ 100 ml Specification (for all sizes) appear to be identical with EP specifications for containers ≤ 100 ml
20. Nitrite	-	Not detectable	-
21. TOC (mg/l)	(-)[16]	Max 0.50[17]	(-)[4]
22. pH value	-	-	5.0-7.0

[16] Covered at bulk level

[17] Applicable exclusively for WFI produced by RO

23. Carbon dioxide	-	-	Not detectable

STERILE WFI IN CONTAINERS/

COMPARISON OF TEST METHODS

	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, detailed check still necessary	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