OFFICIAL RECOMMENDATIONS FOR QUALITY OF FLUIDS IN DIALYSIS – THE NEED FOR STANDARDISATION

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SUMMARY

Recommendations/guidelines regarding the microbiological and chemical quality of fluids in dialysis are increasing in numbers, both nationally and internationally. As dialysis is a worldwide issue, with many elements being similar regardless of geographical area, it is logical to have the same quality requirements on fluids used in dialysis. At present, there are large differences between the different documents. This situation makes studies where several nations participate more difficult to interpret as the fluids used in dialysis are crucial for the dialysis session.

A special situation applies for substitution fluid produced 'On-Line' for haemodiafiltration (HDF) and haemofiltration (HF), where some recommendations are questionable from a scientific standpoint.

The International Organisation for Standardisation (ISO) is in the process of finishing a collection of standards including guideline for fluids in dialysis (water, concentrates, dialysis fluid, substitution fluid) and equipment used for water preparation. To have the same quality for reference worldwide will facilitate the interpretation of international studies as well as give dialysis patients treatments based on the same quality baseline.

KEY WORDS **Chemistry • Fluids in dialysis • Microbiology • Quality • Standards**

INTRODUCTION

The quality of fluids in dialysis is a topic in which there is a large interest. A number of authorities and organisations have recently issued recommendations, or are in the process of doing so. These recommendations are mostly for microbiological limits, but there are also some addressing chemical limits.

The situation of having a large number of national and international recommendations with different limits is not satisfactory. The world is coming closer together and there are many reasons to have harmonised standards on how to define the quality of fluids in dialysis, both in terms of limits and methods of follow-up.

- Dialysis is a similar treatment regardless of geographical area.
- Patients are more or less 'the same' and have similar problems.
- Equipment from many manufacturers is used worldwide and is nearly identical.
- Scientific studies that have more than one country participating.

Seen from this perspective it would seem logical to have an International harmonised set of standards for the chemical and microbiological quality of dialysis fluid. There are both national and international recommendations in progress. But unfortunately, these documents are not identical. They are not identical in the limits specified, nor in the recommended microbiological assay methods.

BIODATA

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One organisation, ISO (International Organisation for Standardisation), has a harmonised set of standards for the preparation for fluids in dialysis. This includes:

- a standard for water (ISO/FDIS 13959),
- a standard for concentrates (ISO/FDIS 13958),
- a standard for dialysis fluid and substitution fluid (ISO/FDIS 11663),
- a standard for water equipment (ISO/FDIS 26722) and
- a standard as a guideline with rationale and advice for the four standards mentioned (ISO/NP 23500).

Some 40 countries are participating in this work, representing roughly 65% of the world population and 75% of the world's dialysis units. Dialysis today involves several different fluids with different quality requirements. The range is from the incoming feed water (normally drinking water) to the critical substitution fluid used in 'On-Line' haemodiafiltration (HDF) and haemofiltration (HF). In this paper comments are given on the different fluids and the national and international recommendations/guidelines.

WHY STANDARDISATION?

The need for standardisation is illustrated by the following example, where the microbiological analysis of a water sample was carried out using three different methods:

Media	TVC limit CFU/ml	Incubation	Sample CFU/ml
TGEA (tryptone glucose extract agar) (Nystrand 1999)	100	7 days at 17°C–23°C	5600
R2A (Reasoners agar no.2) (Reasoner & Geldreich 1985)	10^2	5 days at 28°C	510
TSA (tryptic soye agar) (AAMI RD52)	200	48 hours at 35°C	0

Table 1: Water sample analysis comparisons.
TVC: total viable count; CFU: colony-forming units.

When the same sample is analysed, the difference can be seen to be considerable, which emphasises the need for standardisation.

THE DIALYSIS SYSTEM AND FLUIDS

- In dialysis, the following fluids can be identified: incoming feed water (drinking water)
- Water in the pre-treatment parts of the water system (charcoal filter, softener, particle filter)
- Water used for dilution of haemodialysis concentrates
- Water used for haemodiafiltration
- Concentrate acid (may partly be purchased as dry powder)
- Concentrate basic (often a dry powder)
- Dialysis fluid
- Dialysis fluid Ultra pure (could be dialysis fluid prior to final filter in HDF/HF "On-Line")
- Substitution fluid (in HDF/HF)

INCOMING FEED WATER (DRINKING WATER)

The incoming feed water is normally drinking water that has to meet the applicable local drinking water standard. The chemistry of drinking water is complex. For example, for aluminium, the state of aggregation (Al^{3+}, $AL(OH)_4^-$, AlO(OH), $Al(OH)_3$, Al_2O_3) is influenced by pH and, the nonion aggregates may pass the reverse osmosis (RO) membrane. The microbiological limit for the total viable count is normally 100 CFU/ml, and up to 5000 is acceptable according to Livsmedelsverkets Författningssamling (LIVSFS 2005, p.10). The endotoxin content of drinking water is mostly in the range 5–20 (Endotoxin Units/ml [EU/ml]). In home dialysis situations with private wells, findings might be higher.

Drinking water requirements include special values for some specific microorganisms, such as *Escherichia coli* and *Pseudomonas aeruginosa*, which are often included with a limit of $<$1CFU/100ml.

WATER IN PRE-TREATMENT

In the pre-treatment phase the water is treated chemically in order not to give rise to problems in the connection with the RO unit. The microbiological findings are mostly in the region of 100–3000 CFU/ml but values as high as 50,000 CFU/ml are seen. The endotoxin content can be up to 100 EU/ml. Pre-treatment installations are characterised by having installations with large surfaces and no disinfection. Disinfection of the pre-treatment equipment is not practical because the incoming water has so many microorganisms that would immediately negate the results. It must also be noted that most disinfectants are neutral molecules that may pass RO membranes. The chemical treatment of water in the pre-treatment includes: removing the free chlorine, chloramines and organics by charcoal filter, and exchanging Calcium and Magnesium ions with Sodium ions in the softener. In addition, one or two particle filters may be included as the last step before the RO unit. It is often disputed as to what regulations should be applicable for the 'manipulated' water in the pre-treatment phase.

Document national and international standards	Year of issue	Microorganisms CFU/ml	Endotoxin EU/ml	Note
JSDT (Japanese Society for Dialysis Therapy) (Morii *et al*. 1998)	1998	– *	0.25	*No cultivation
ISO 13959	2002	10^2	1 – (5)	
EDTNA guidelines technical section	2002	$<10^2$	<0.25	
EDTA European best practice guideline	2002	$<10^2$	<0.25	
AAMI RD 52	2004	200 (Action50)	2 (Action 1)	Cultivation method: TSA 48 hours at 35°C
Denmark Dansk Nefrologisk Selskab (draft)	2004	0.1	0.05	
Italy, Alloatti et al. (2005)	2005	$<10^2$	<0.25	*P. aeruginosa* <1 CFU/250 ml
Germany hygiene guideline Arbeitskreis für angewandte Hygiene	2005	$<10^2$	<0.25	
Norway Norsk Nyremedicinsk Forening (draft)	2007	100	<0.25	
USP XXXI	2008	100	2	
Ph Eur 6th ed <1167>	2008			
Sweden SLS	2008	$<10^{2\dagger}$	<0.25	†of which $<10^1$ fungi and/or yeast
Germany Dialysestandard	2006 /2008	10^2	0.25	No coliform bacteria *P. aeruginosa* <1 CFU/100 ml
ISO/FDIS 13959 (draft)	2008	100	0.25	Cultivation method: TGEA or R2A 7 days at 17°C–23°C
France NF S93 – 315 (Afnor)	2008	100	0.25	

Table 2: Water for dilution of haemodialysis concentrates International recommendations/guidelines.

WATER FOR DILUTION OF HAEMODIALYSIS CONCENTRATES (TABLE 2)

Water for dilution of the haemodialysis concentrates has normally passed a RO unit. In principle, all RO systems on the market intended for dialysis water, produce water that meets the requirements for chemical quality in all of the recommendations.

For the microbiological quality, the situation is different. The microbiological quality of the water that has been filtered by the RO membrane also meets all the requirements recommended. However, due to different strategies of disinfection and different recommendations for cultivation technique, the microbiological quality of the water used for dilution, that is, the product water in the loop after the RO varies.

LOCAL RECOMMENDATIONS/GUIDELINES (TABLE 2)

In the United States and other countries that use the Association for the Advancement of Medical Instrumentation (AAMI) RD52 standard, the recommended values are high (microorganisms 200 CFU/ml and 2 EU/ml for endotoxins) compared to European standards. AAMI RD52 is also used as reference for many Asian countries.

In Denmark, a Dansk Nefrologisk Selskab (DNS) draft (DNS 2004) indicates very low levels for microorganisms at 0.1 CFU/ml and 0.05 EU/ml for endotoxins. It is worth noting that of the 34 systems in Denmark, none of them can continuously meet the microbiological limit of <0.1 CFU/ml when a sensitive method of cultivation is used.

In Japan, endotoxins have been used as a marker for microbiological quality but recently, cultivation is increasingly used after discussions about the sensitivity of endotoxin testing (Nystrand 2005).

In Europe, most recommendations are in line with the recommendation in European Pharmacopoeia (Ph Eur 2008) <1167>, although cultivation methods differ between the countries.

In Sweden, the Svensk Läkemedelsstandard (SLS) recommends four different cultivation media and claims that the media must be 'salt free and nutrient poor' (SLS 2008). None of the recommended media, TGEA, CLED, Blood agar and Saboroud agar, fulfil these claims. It can be noted that, recently, a claim for 'Ultrapure water' defined as <0.1 CFU/ml for microorganisms

and <0.03 EU/ml for endotoxins has been required by some hospitals in Sweden in their purchase specifications.

In Germany (Dialysestandard 2006), Italy (Alloatti *et al.* 2005) and Austria (Arbeitskreis für Krankenhaushygiene 2002) there are special requirements for *P. aeruginosa* and *coliform bacteria*. For *P. aeruginosa*, a value of <1CFU/100ml means that the general limit of 100 CFU/ml is overruled and the disinfection activities are to be on a level that can handle a situation that is 10,000 times more stringent (no one can tell in advance when *P. aeruginosa* will appear).

All these various standards again emphasise the need for standardisation.

INTERNATIONAL RECOMMENDATIONS/GUIDELINES (TABLE 2)

In ISO 13959, both microbiology and chemistry are addressed. Limits for microorganisms are stated with action limits for disinfection, also included. The recommended cultivation technique uses the principle of low temperature, long time and a general cultivation medium (Nystrand 2008). For the chemical quality the elements are divided into three groups:

a. Contaminants with documented toxicity in haemodialysis.
b. Electrolytes normally included in dialysis fluid.
c. Trace elements in dialysis water.

For metals, the analytical work can include either the full 'picking list' of AAMI RD52 or the principle of 'heavy metals' used in Ph Eur <1167>.

WATER USED FOR HAEMODIAFILTRATION AND HAEMOFILTRATION (TABLE 3)

In some recommendations (see Table 3), special requirements are given for water used for HDF and HF. The microbiological quality is required to be <0.1 CFU/ml for microorganisms. There is no water system (identified as: clean side of reverse osmosis membrane, distribution piping, inlet lines to dialysis machines) that can continuously meet this requirement. The best microbiological quality that can be achieved with present water systems and disinfection strategies is 0.1–1 CFU/ml (Nystrand 2007). For endotoxin levels, recommendations for water used for haemodiafiltration varies between <0.03 and 0.25 EU/ml.

One reference position for water is the mixing point of it with concentrates. Only 'On-Line' dialysis machine systems equipped with an endotoxin filter for water will, on a continuous basis, be able to conform to the standards requiring 0.1 CFU/ml for the water (Nystrand 2004).

SPECIAL DEMANDS IN THE NETHERLANDS

The Netherlands (Dialyse Groep Nederland) (DGN 2003) has a standard for water with a value for conductivity corresponding to Ph Eur <1927> (2008), 'Water, highly purified', which is given as 1.1 μS/cm at 20°C (Ph Eur <1927>; Table 2). It is also to be noted that in Ph Eur <1927> (Table 2), pH and conductivity for temperature and atmosphere equilibrated samples, the conductivity at pH 7 is 4.6 μS/cm. It is important to know what impact pH and dissolved gases may have on the conductivity as no water systems for dialysis are equipped with degassing units.

In order to comply with low conductivity of 1.1 μS, it is, in principle, necessary to have an electrodeionisation (EDI) unit in the system. Furthermore, the Dutch recommendation (DGN 2003) contains a section dealing with carbohydrates and benzene derivates in connection with haemodiafiltration. For the chemical quality, standards otherwise have the same requirements regarding limits as for water for dilution of haemodialysis concentrates.

Document national and international standards	Year of issue	Microorganisms CFU/ml	Endotoxin EU/ml	Note
EDTA European best practice guideline	2002	<0.1	<0.03	This quality is recommended for high flux dialysis but is suggested to be used for all dialysis modalities
Germany dialysestandard	2006 addition 2008	<0.1	<0.03	This quality is recommended for hemodiafiltration / hemofiltration but is suggested to be used for all dialysis modalities
France Circulaire 52	2007 (28)	<0.1	0.25	
France NF S93—315 (draft) (Afnor)	2008	<0.1	0.25	

Table 3: Water for haemodiafiltration and haemofiltration.

Document National and international standards	Year of issue	Micro organisms CFU/ml	Endotoxin EU/ml	Note
EN 13867	2002	10^2	0.5	Tests are to be carried out according to methods addressed in EN 13867
AAMI RD52	2004	Limits for diluted concentrate same as for dialysis fluid 200 (action 50)	Limits for diluted concentrate same as for dialysis fluid 2 (action 1)	
Ph Eur 6th ed <0128>	2008	-	<0.5*	
Sweden SLS	2008	-	<0.5*	
ISO/FDIS 13958	2008	No value given. Requirements in ISO/FDIS 13959 and ISO/FDIS 11663 must be fulfilled.	No value given. Requirements in ISO/FDIS 13959 and ISO/FDIS 11663 must be fulfilled.	

Table 4: Concentrates (acid and basic).
**Diluted to user concentration.*

CONCENTRATES (TABLE 4)

Concentrates are available in both fluid and dry powder form. The use of central systems is increasing for acid concentrates, and dry powder use is increasing for basic concentrates. The recommendations, both for microorganisms and endotoxins, refer to concentrate diluted to user concentration. In ISO/FDIS 13958, there are no limits set neither for microorganisms nor endotoxins. However, there are two requirements in the user situation.

1. Water according to ISO/FDIS 13959 must be used.
2. It must be possible to produce a dialysis fluid that is in agreement with the requirements in ISO/FDIS 11663.

CONCENTRATES FOR 'ON-LINE' APPLICATIONS

A special situation may apply where concentrates are used as raw materials for producing substitution fluid in 'On-Line' applications. Substitution fluid is, in some countries, considered to be a drug. In this case, the concentrates have to meet requirements in applicable pharmacopoeia, such as Ph Eur (Ph Eur <0128> 2008).

DIALYSIS FLUID (TABLE 5)

Dialysis fluid is not a commercial product and hence it is not mentioned in Ph Eur and US Pharmacopoeia (USP 2008). Recommendations for dialysis fluid for standard haemodialysis are often the same as for water. However, as no producer of concentrates has a process with steps to remove endotoxins in concentrates, it must be taken into consideration that some additional endotoxins may be present when the concentrate is added to water.

In a situation where the participants have fulfilled the requirements for water in the dialysis centre (0.25 EU/ml), with A-concentrate (0.5 EU/ml diluted) and B-concentrate (0.5 EU/ml diluted) added, the result can be as high as 1.2 EU/ml (Calculated with 136 litres of water used, 4 litres of A-concentrate, 4 litres of B-concentrate, time 4.8 hours 500 ml/min). In ISO/FDIS 11663, this has been considered and the limit for *endotoxins* for dialysis fluid is set at 0.5 EU/ml.

Document National and international standards	Year of issue	Microorganisms CFU/ml	Endotoxin EU/ml
JSDT (Morii *et al*. 1998)	1998	100	0.1
EDTNA guidelines technical section	2002	$<10^2$	<0.25
EDTA European best practice guideline	2002	$<10^2$	<0.25
AAMI RD 52	2004	200 (action 50)	2 (action 1)
Germany Hygiene Guideline Arbeitskreis für angewandte Hygiene	2005	$<10^2$	<0.25
France Circulaire 52	2007	$<10^2$	<0.25
Sweden SLS	2008	$<10^2$	<0.25
ISO/FDIS 11663 (draft)	2008	100 (action 50)	0.5

Table 5: Dialysis fluid.

ULTRAPURE DIALYSIS FLUID (TABLE 6)

The term 'ultrapure dialysis fluid' (0.1 CFU/ml) was identified by Ledebo and Nystrand (Ledebo & Nystrand 1999), and was intended to be used for dialysis fluid to define the microbiological quality prior to the final filter in an 'On-Line' dialysis machine system. The value 0.1 CFU/ml is adopted in other recommendations but the value for endotoxins varies between <0.03 and 0.25 EU/ml.

Document national and international standards	Year of issue	Microorganisms CFU/ml	Endotoxin EU/ml
EDTNA guidelines technical section	2001	<0.1	<0.03
EDTA European best practice guideline	2001	<0.1	<0.03
The Netherlands Dialyse Groep Nederland	2003	<0.1	<0.03
AAMI RD 52	2004	0.1	0.03
Denmark Dansk Nefrologisk Selskab (draft)	2004	<0.1	<0.05
France Circulaire 52	2007	<0.1	<0.05
Norway Norsk Nyremedicinsk Forening (draft)	2007	<0.1	<0.025
France NF S93 – 315 (Afnor)	2008	0.1	0.25
Sweden SLS	2008	<0.1	<0.1
ISO/FDIS 11663 (draft)	2008	<0.1	<0.03

Table 6: Ultrapure dialysis fluid prior to last filter for haemodiafiltration 'on-line'.

SUBSTITUTION FLUID PRODUCED 'ON-LINE' (TABLE 7)

Substitution fluid produced 'On-Line' is a difficult issue, with different opinions in different documents. In documents from organisations such as European Dialysis & Transplant Association (EDTA) (European Best Practice Guideline 2002), European Dialysis & Transplant Nurses Association/European Renal Care Association (EDTNA/ERCA) (EDTNA/ERCA 2002), DGN (DGN 2003), AAMI (AAMI RD52 2004) it is expressed as '10^{-6} CFU/ml'. Documents from other authorities use the word 'sterile', Ph Eur and the Swedish SLS refer to Ph Eur Monograph 2.6.1 (2008) of sterility testing. In the French (Nefrology Française) standard NF S93–315 (Afnor 2008) and Circulaire 52, 2007, a practical testing requirement appears as 0 CFU/500 ml. In ISO/FDIS 11663, the requirement is 'sterile' interpreted as SAL 6 (Sterility Assurance Level) for the whole dose.

By definition, it is not possible to take out a sterile product from an unsterile system. It must also be quite clear that a disinfection procedure is not a method of sterilisation unless it has been validated and found to have the power of a sterilisation procedure (this is difficult with heat procedures 80°C–90°C).

Rationale and advice are included in the *new standard (guideline) ISO/NP 23500*. In ISO/NP 23500, information and advice about microbiology, biofilm disinfection, chemical limits, water system construction principles and installation qualifications are found. For *endotoxins*, different levels are given in different documents ranging from 0.03 to 0.25 EU/ml.

Today, it is not unusual to have HDF with 50–90 litres of substitution fluid. Substitution fluid, as stated previously, is a drug in some countries, and the amount of *endotoxins* given to the patient is limited to 5 EU/kg bodyweight/hour (Ph Eur <2.6.14> 2008). For a four-hour HDF session with 20 litres of substitution fluid, the maximum concentration of *endotoxins* will be 0.07 EU/ml (in total 350 EU, patient 70 kg). It is interesting to note the German recommendation (Deutsche Arbeitsgemeinschaft für klinische Nephrologie 2008) that states that for substitution fluid 'sind die qualitativen Anforderungen an das Substituat höher zu stellen als an Infusionslösungen, dies gilt sowohl für Mikroorganismen, Exotoxine, Endotoxine und Partikeln" = "quality requirements

Document national and international standards	Year of issue	Microorganisms CFU/ml	Endotoxin EU/ml
EDTNA guidelines technical section	2002	$<10^{-6}$	<0.25
EDTA European best practice guideline	2002	$<10^{-6}$	<0.25
The Netherlands Dialyse Groep Nederland	2003	$<10^{-6}$	<0.03
AAMI RD 52	2004	$<10^{-6}$	<0.03
Germany Hygiene Guideline Arbeitskreis für angewandte Hygiene	2005	Sterile	Nonpyrogenic
France Circulaire 52	2007	0 CFU/500 ml	<0.05
Norway Norsk Nyremedicinsk Forening (draft)	2007	Sterile	<0.025
Ph Eur 6th ed <0861>	2008	Sterile	<0.25
Sweden SLS	2008	Sterile	<0.1
ISO / DIS 11663 (draft)	2008	Sterile	Nonpyrogenic
France NF S93 – 315 (Afnor)	2008	0 CFU/500 ml	<0.05

Table 7: Substitution fluid 'on-line'.

on substitution fluid are to be more stringent compared to infusion solutions both for micro-organisms, *exotoxin, endotoxin* and particles'. For microorganisms the requirement on infusion solutions is 'sterile'. What is beyond this requirement?

For the chemical quality, most standards have the same requirements as for dialysis fluid. The Dutch recommendation (DGN 2003) has additional recommendations about water, as specified above.

DISCUSSION

For fluids in dialysis, many of the national standards in use, or in preparation, are not logical regarding limits and microbiological cultivation methods for verification. Some have both high limits and nonoptimal verification methods. Others have too stringent limits but lack detailed information about any verification method. When it comes to disinfection of a water system, the situation where an insensitive microbiological cultivation technique is used for setting up and verifying disinfection strategies will lead to inadequate disinfection and hence to microbial growth, biofilm and metabolites that may pass the membrane in the dialyser. For substitution fluid the situation is peculiar: in one country it is accepted when showing a 'no growth' in 500 ml (Afnor 2008), while others claim that sterility is necessary as, in fact, substitution fluid is an infusion solution.

In the documents from some organisations the definition of microbial cleanliness, that is, substitution fluid, is expressed as '10^{-6} CFU/ml'. Why per ml? Why not per μl, cl, dl or l? There is, in principle, no scientific support for this definition. A dose of substitution fluid can be up to more than 100 litres (= 100,000 ml). In practical terms, if using substitution fluid of 100 litres per treatment, we only need to perform 10 treatments in order to have used 1,000,000 ml. This is far from the safety of '1 in a million' as is the meaning of Sterility Assurance Level (SAL) defined as 10^{-6}, where *dose* is the unit. Sterility is an issue of probability that cannot be proven by testing 'on site'. '1 in a million' means only one living microorganism in 1 million doses used. It is also significant to note that CE marking of dialysis machines intended for 'On-Line' must be carefully reviewed as important issues are not included, such as filters and their management, disinfection/sterilisation and product (substitution fluid) quality. Conditions for 'On-Line' giving the strategy for disinfection and how to achieve sterile conditions in critical parts of the system are not included in any of today's standards.

CONCLUSION

The current situation is not satisfactory as has been discussed in this paper. There is a need for a harmonised standardisation regarding quality of fluids in dialysis. As this paper demonstrates, no reason can be seen to keep the situation as it is today.

The efforts of International Organisation for Standardisation to have a well-organised collection of standards (ISO/FDIS 13959, ISO/FDIS 13958, ISO/FDIS 11663, ISO/FDIS 26722) with a guideline (ISO/NP 23500), which includes information and advice about microbiology, biofilm disinfection, chemical limits, water system construction principles and installation qualification, offers a solution to this problem, provided that the standards are adopted by all. This acceptance of standards, universally, is of great importance to all health providers and patients.

BENEFITS CAN EASILY BE DEFINED

- To make comparison of research results from different geographical areas possible.
- To improve quality, as more sensitive microbiological techniques can be used in connection with disinfection methods, which will lead to preventive disinfection protocols.
- Results of investigations will be more relevant.
- To facilitate co-operation between different countries.
- To make international studies more reliable.
- Uniform quality requirements will make it easier for industry to develop relevant products.
- Guidance on methods of disinfection, endotoxin filter changes, etc.

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