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SCIENCE MEDICINES HEALTH

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Assessment report for Dialysis solutions from Baxter group of companies and associated companies produced at Castlebar

Procedure number: EMEA/H/A-31/1290

Referral under Article 31 of Directive 2001/83/EC

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature redacted (under the format of a black box: [redacted]).

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 17 January 2011[1] the European Commission triggered a referral under Article 31 of Directive 2001/83/EC, as amended. The Committee for Medicinal Products for Human Use (CHMP) was requested to give its opinion on whether measures are necessary to ensure the safe and effective use of dialysis solutions from Baxter group of companies and associated companies produced at Castlebar.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

In December 2010 the CHMP was informed that a small proportion of certain Baxter peritoneal dialysis (PD) solutions (Dianeal, Extraneal and Nutrineal) produced at Castlebar (Baxter's manufacturing plant in Ireland) could potentially contain endotoxins. The root cause was traced to small stress cracks in two mixing tanks (Tanks F and G) used at the Castlebar manufacturing plant. The cracks caused solution to leak into a cavity leading to the formation of a biofilm which then released bioburden back into the solution tank at random intervals, resulting in increased levels of endotoxin in some units. Based on testing of recalled samples only a small minority of units in a batch were considered by Baxter to be affected but as these could not be identified all batches of Extraneal, Dianeal and Nutrineal produced using this manufacturing line and within expiry date were considered to be affected. Tanks F and G were removed from use and the manufacturing line subject to extensive cleaning. Exposure to endotoxin was found to be associated with an increased risk of aseptic peritonitis. At the request of the United Kingdom (UK), the CHMP started a procedure under Article 5(3) of Regulation (EC) No 726/2004 to provide recommendations to the Member States on the management of this situation. A full recall of the potentially affected products was not considered possible as there were insufficient alternatives available. Based on the information provided by Baxter, the CHMP was satisfied that the root cause had been identified and that measures had been taken to eliminate the endotoxin from the Castlebar plant. The CHMP issued recommendations to manage the problem of the presence of endotoxins and supply on 16 December 2010[2].

Further out-of-specification endotoxin results were observed in new batches manufactured as of 17 December 2010 and the Castlebar manufacturing plant was shut down and subjected to further extensive cleaning [redacted] considered effective at targeting biofilm. The production facility was cleaned and subjected to a total disinfection using a fog dispersal system. A good manufacturing practice (GMP) inspection by the Irish Medicines Board (IMB) of the Castlebar site in January 2011 raised concerns that the biofilm had spread due to the routine recirculation of sanitising agents through various tanks in a particular manufacturing area and the infrequent transfer of bulk solution from Tank F to Tank M[3], (and a subsequent Health Hazard Assessment from the MAH also implicated Tank H). Concern was also raised that contaminating organisms developed resistance to routine cleaning measures. This suggested that additional batches of Dianeal, Extraneal and Nutrineal and sodium chloride 0.9% solution for haemodialysis and the additional product Monosol solution for haemodialysis could also potentially be affected.

Following the receipt of further information from Baxter, indicating that their manufacturing problem was not resolved and the root cause not identified, an Article 31 referral procedure of Directive 2001/83/EC, as amended was initiated by the European Commission (EC). An extensive list of

[1] On 18 January 2011, the EC circulated an updated notification, superseding and replacing the previous one received. A correction was introduced in the list of products affected.

[2] For further information on the recommendations adopted, see the published Assessment report for Art 5(3) procedure: Presence of endotoxins in Baxter peritoneal dialysis solutions

[3] The IMB raised concerns that cleaning solution from Tank M had been transferred to tanks used in the manufacture of Physioneal on a weekly basis thereby suggesting a possible risk with Physioneal. However, no out-of-specifications for endotoxin was reported for Physioneal.

questions was addressed to Baxter in the framework of the Article 31 procedure to allow a thorough review of the matter.

Recommendations were given to minimise the use of affected product from Castlebar[4]. Taking into account the crucial nature of these medicinal products, and the means by which unaffected batches of PD solutions could be made available to patients across the EU in the shortest possible timeframe, alternatives were sought. In view of severe supply limitations for Dianeal, Extraneal and Nutrineal and the risk of switching patients to alternative PD solutions or therapies, the CHMP considered that the use of comparable products produced by Baxter at alternative manufacturing sites outside the EEA (European Economic Area) should be prioritised. Dialysis solutions[5] were thus imported from Canada, Singapore, Turkey and USA. All products were tested in accordance to currently approved EU specifications, as applicable. Whilst awaiting full availability of these products in the EU, a limited selected number of batches produced at Castlebar which had passed all approved specifications and an additional intensive testing for endotoxins, needed to be used to avoid interruptions of patients treatment. To meet supply demands importation of PD solutions from other sites (Canada, Turkey and USA) increased. The MAH chose to import only once from Singapore, and this manufacturing plant was no longer used as an alternative. Once sufficient quantities of the unaffected batches of PD solutions were available, a stepwise recall of Castlebar PD solutions was initiated. The CHMP agreed that until an adequate root cause and corrective measures have been identified it would not be acceptable to release new PD solutions from the Castlebar plant.

Considering the likelihood of prolonged use of large quantities of unlicensed (imported) PD solutions on the EU market, and in order to ensure continued supply of licensed medicinal products to the EU, the necessary data packages to support the inclusion of additional manufacturing sites were expedited within the ongoing article 31 referral procedure.
The available data to support inclusion of sites from which products are currently being imported (Canada, Turkey and USA) into the existing PD solutions marketing authorisations were submitted. The necessary data packages to support the inclusion of one more additional manufacturing site located in Europe (Poland) which is expected to become fully operational soon, was also expedited. In light of the current uncertainty over the root cause and the future re-instatement of supply from Castlebar, the addition of manufacturing sites to the marketing authorisations aimed at mitigating future supply problems arising for PD solutions in Europe, ensuring that sufficient PD solutions are available.

A total of 12 data packages were submitted by Baxter including Alliston, Canada, Lublin, Poland, Istanbul, Turkey and North Cove, USA, and information was provided per site and per product. Modules 2 and 3 of the common technical document (CTD) were affected. Only CTD sections which were different to the approved CTD sections were included in the submission, and this was considered acceptable.
A combined assessment for all PD solutions was presented, including product specific differences highlighted when appropriate. Dianeal contains Glucose, Extraneal contains Icodextrin and Nutrineal contains [redacted] (an amino acid mix), however, the products share many similarities for instance, they contain the same ingredients, are made in the same way, are packed similarly and sterilised by the same method.

A tabular overview of which products can be produced at each manufacturing site is provided below:

Manufacturing Site	**Product Manufactured**			
	Extraneal	**Nutrineal**	**Dianeal PD1**	**Dianeal PD4**
Alliston, Canada	X	X		X
Istanbul, Turkey	X	X	X	X
Lublin, Poland			X	X
North Cove, USA	X			X

The CHMP reviewed all the data available for each of the four sites concerned. In April, the information available on the USA site was insufficient to conclude on its addition, pending the outcome of a recent inspection carried out at this site. However, sufficient data was available to recommend the variation to the marketing authorisations consisting in the inclusion of Canada, Poland and Turkey as additional

[4] Production of all products using the affected lines at the Castlebar plant ceased on 26 January 2011. In order to eliminate the biofilm the MAH proposed to replace all solution contact points and surfaces in the manufacturing line (Twinbag/mainline Mix/Fill Complex) in addition to resurfacing and polishing all tanks.
[5] There were no supply shortages identified for sodium chloride 0.9% solution for haemodialysis and Monosol solution for haemodialysis.

manufacturing sites, as no major quality issues were identified at these sites. A first opinion on the inclusion of these three sites was issued by the Committee in April, and the corresponding decision from the Commission was issued on 12 May 2011.
Presently, the information available on the USA site is also sufficient to conclude on its addition as an alternative site, as the results of a recent inspection carried out at this site were satisfactory.
The opinion on the Castlebar site cannot be finalised at this stage as issues remained for resolution by the marketing authorisation holder.

The review of the issues identified at Castlebar, with the interruption of supply from this site, led to the need to authorise additional manufacturing sites to ensure supply of PD solutions in Europe. Whilst all data to finalise the ongoing article 31 is not available, a stepwise approach is followed for the assessment, resulting in subsequent opinions being adopted by the CHMP.

Therefore, without prejudice to the ongoing article 31 procedure, the CHMP considers that sufficient information is available to issue a second opinion for this article 31 procedure recommending the addition of the USA manufacturing site to the relevant PD solutions' marketing authorisations, subject to conditions set out in the Annex IV of the opinion. The specificities of authorisation for this site are discussed below.

2.2. Scientific discussion on chemical, pharmaceutical and biological aspects

2.2.1. Addition of the United States of America finished product manufacturing site

The administrative details for the USA site are shown below.

Name:	Baxter Healthcare Corporation
Address:	Highway 221 North Marion, North Carolina, 28752, US
Peritoneal dialysis produced at the site	Dianeal PD4 (Glucose 1.36%) Dianeal PD4 (Glucose 2.27%) Dianeal PD4 (Glucose 3.86%) Extraneal

Good manufacturing practice (GMP)
A GMP inspection was performed in March 2011 in connection to the inclusion of this site, which is considered GMP compliant.

Drug substance
The name and address of the supplier and drug substance specification for each active substance was provided. Some active suppliers are common to the EU products, e.g. Icodextrin is supplied by [redacted] In the case of active substances common to EU no further data was required. Some suppliers of active substance have not been used in EU products and active substance master files (ASMF's) or equivalent data were not submitted for these suppliers. It is to be noted that the product currently supplied to the USA market complies with the USP. Although minor differences in quality standards may be highlighted, the product currently released into the EU market through importation complies with the EU requirements. The appropriate data should be submitted to formally harmonise specifications in accordance with the current EU standards.
Summary details of relevant new sources of drug substances (and relevant differences between products) were provided and are described below.

Dianeal PD4
Dextrose Anhydrous
Dianeal PD4 made at North Cove, USA uses Dextrose anhydrous [redacted] This is a new source of active, not present in EU approved product, and should be supported by an ASMF or equivalent data package to be submitted. The product is in compliance with the USP. An appropriate change management plan should be submitted.

Extraneal
Icodextrin
The source of icodextrin is [redacted] and the drug substance from this site was previously approved. Further information was not considered necessary.

All PD solutions

Sodium Chloride

[redacted] are proposed as additional suppliers for Sodium Chloride not previously licensed in the EU approved PD solutions. In order to support their inclusion in the licence an ASMF or equivalent data package should be provided for sodium chloride produced at 1) [redacted] (a Ph. Eur. compliant alternate supplier) and 2) [redacted] (a USP compliant alternate supplier).

Sodium S-Lactate

Baxter Healthcare Corp., North Cove, USA is proposed as additional supplier for Sodium S-Lactate solution and this was not previously licensed in the EU approved PD solutions. An ASMF or data package in support of this active substance should be provided. The product complies with the USP. Lactic Acid, used as starting material for production of Sodium S-Lactate, is tested in compliance with USP. Tests for the following are not performed as they are performed on the starting material: reducing sugars and sucrose; methanol; chloride; oxalate and phosphate; and sulphate. It is considered necessary to fully explain the control of the lactic acid starting material, including the comparability of assay limits to the Ph. Eur. Aluminium and barium are not controlled in Sodium S-lactate from [redacted] Unless justified these tests should be added to the specification for Sodium S-Lactate. An appropriate change management plan should be submitted.

Calcium Chloride and Magnesium Chloride

Calcium Chloride and Magnesium Chloride are made by the same manufacturers as Castlebar. These sources are accepted and therefore further information was not considered necessary.

Control of microbial contamination / endotoxins

Some of the salt starting materials contain water for crystallisation or water, which can be risk factor for microbial contamination / microbial impurities. In addition, Ph. Eur. 5.1.1 states 'Microbiological monitoring and setting of suitable action limits may be advisable for ingredients which are liable to be contaminated because of their origin, nature or method of preparation.'

Given the concerns raised regarding the product manufactured at Castlebar (possibly associated with biofilm) together with the difficulties so far in identifying the root cause, the CHMP considered that routine microbial monitoring of all the starting materials (including excipients) should be undertaken and the appropriate change management plans submitted.

Drug product

Description and composition of the drug product

The composition of Dianeal PD4 drug product is presented in the table below.

Comparison of composition of Dianeal PD4 manufactured at Castlebar and North Cove

Glucose concentration	**1.36 % (anhydrous glucose corresponding to 1.5 % glucose monohydrate)**		**2.27 % (anhydrous glucose corresponding to 2.5 % glucose monohydrate)**		**3.86 % (anhydrous glucose corresponding to 4.25 % glucose monohydrate)**		**%age of Castlebar**
Manufacturing site	Castlebar	North Cove	Castlebar	North Cove	Castlebar	North Cove	
Active ingredients	Per 1000 ml	Per 1000 ml	Per 1000 ml	Per 1000 ml	Per 1000 ml	Per 1000 ml	
Glucose monohydrate / dextrose monohydrate	15.0 g	15.0 g	25.0 g	25.0 g	42.50 g	42.50 g	same
Sodium chloride	5.38 g	5.38 g	5.38 g	5.38 g	5.38 g	5.38 g	same
Calcium chloride dehydrate	0.184 g	0.183 g	0.184 g	0.183 g	0.184 g	0.183 g	99.45%
Magnesium chloride Hexahydrate	0.051 g	0.051 g	0.051 g	0.051 g	0.051 g	0.051 g	same
Sodium S-lactate solution	4.48 g	4.48 g	4.48 g	4.48 g	4.48 g	4.48 g	same
Water for injection	To 1000 ml	qs	To 1000 ml	qs	To 1000 ml	qs	same

As shown in the table above, the composition of Dianeal PD4 manufactured in Castlebar and in North Cove is equivalent. There is a minor difference in the quantity of Calcium Chloride dehydrate, which is less than 1% and considered insignificant.

Extraneal

The composition of Extraneal drug product is presented in the table below.

	Product manufactured in Castlebar	**Product manufactured in North Cove**	**% of Castlebar**
Name of ingredients	**Formula in g/l (100 % formulation)**	**Formula in g/l (100 % formulation corresponding to label claim)**	**-**
Icodextrin	75.0	75	100%
Sodium chloride	5.4	5.35	99.07 %
Calcium chloride dihydrate	0.257	0.257	100%
Magnesium chloride hexahydrate	0.051	0.0508	99.60%
Sodium lactate solution	4.5	4.48	99.55 %
Water for injection	To 1000 ml	To 1000 ml	Same
Sodium hydroxide or Hydrochloric acid	qs to required pH*	as required	Same

A slight difference in sodium chloride, magnesium chloride and sodium S-Lactate concentrations was noted but the difference is less than 1% and considered insignificant.

Pharmaceutical development

The development pharmaceutics are the same as those currently approved.

Manufacture

Manufacturing, chemical testing, packaging
BAXTER HEALTHCARE CORPORATION
Highway 221 North Marion, North Carolina 28752

Chemical testing, packaging, final release
BAXTER HEALTHCARE S.A.
Moneen Road
Castlebar, County Mayo
Republic of Ireland

Testing
[redacted]

Batch formula

Dianeal PD4

The scale of manufacture at North Cove is [redacted]
The scale of manufacture at Castlebar is [redacted]

Extraneal

The scale of manufacture at North Cove is [redacted]
The scale of manufacture at Castlebar is [redacted]

Description of Manufacturing Process and Process Controls

The method of preparation is essentially the same as for other sites. Dissolution and mixing of ingredients occurs. The solution is [redacted] and filled into pre-printed PVC bags. The bags are sterilised by moist heat.

The maximum time the bulk solution may be held in the mix tank is [redacted]
The drug product is terminally sterilised. The units are subject to a steam sterilisation cycle that aimed at a minimum F_0 of [redacted] at a cycle temperature of 121°C. The maximum processing time between the start of mixing and the start of sterilisation is [redacted]
The same type of autoclaves is used at Castlebar and North Cove, but there are some differences in approach. While the US validated process has a minimum target of F_0 = [redacted] at the end of the exposure, the Ph. Eur. indicates a minimum target of F_0 = [redacted] The MAH confirmed that release of product to the EU market will not occur unless F_0 is at least [redacted] North Cove has been producing PD solutions without incident for some time and is licensed [redacted] in the USA. This gives assurance with regard to sterility. It is noted that a different biological indicator than that required by the Ph. Eur. is used in the validation of sterilisation at North Cove, in accordance with the USP. The sterilisation process should be re-validated using the biological indicators as per Eur. Ph. 5.1.1. and 5.1.2. An appropriate change management plan should be provided.

Controls of critical steps and intermediates
In-process controls are similar to Castlebar. Bioburden limits are the same order of magnitude at both sites [redacted] generally accepted in the EU for moist heat sterilisation. Overall the same process controls are applied to all products at North Cove. [redacted]
Confirmation of the bioburden limits should be supplied with regard to spores and spore forming organisms. Further explanation of how spores are monitored should be provided. The product is validated using a spore with a D value of [redacted] The limit for the product bioburden is stated as being not more than [redacted]
Bioburden specifications of the filled containers should be harmonised with current EU standards. An appropriate change management plan should be provided.

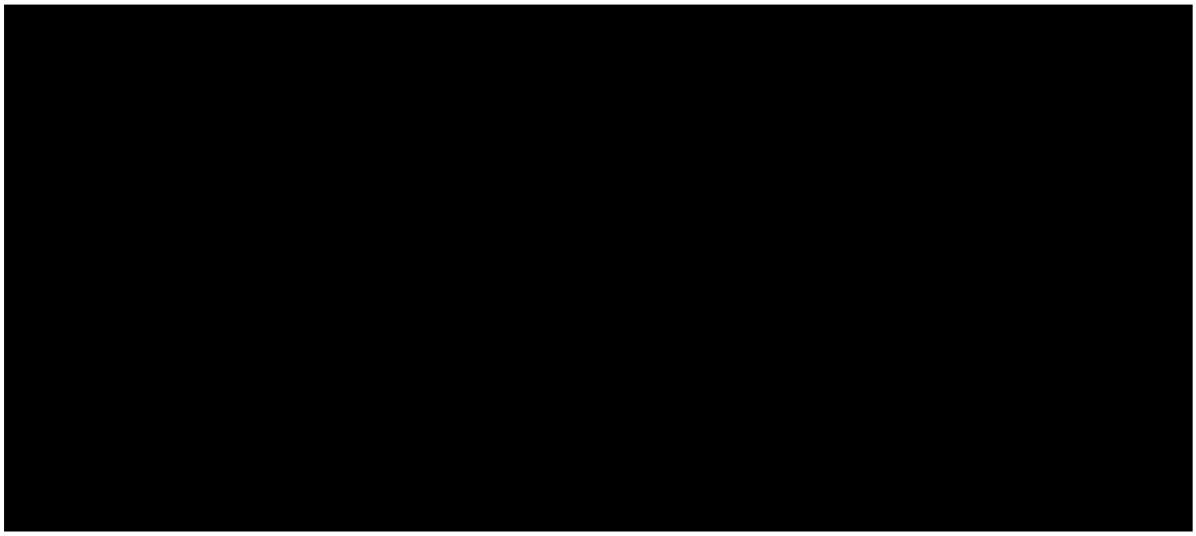
Control of excipients
The following excipients are present in both Dianeal and Extraneal: water for injection; hydrochloric acid; and sodium hydroxide. The excipients are controlled according to the USP.
Water for injections is produced by distillation but presently not tested for compliance with the Ph.Eur. It complies with the USP. Hydrochloric acid and sodium hydroxide are not presently tested to the Ph.Eur., but comply with the USP.
All excipients should be tested to the Ph.Eur. Given the concerns over control of bioburden and endotoxin, this should be tested for all excipients.

Control of drug product
Baxter provided tables and EU specifications for North Cove products. Some tests have been omitted in the US specification and some limits are wider than allowable in the EU specification.
It is to be noted that licensed medicines being imported into the EU from a non-EU country are tested according to the EU specifications, [redacted] As previously agreed at CHMP in the framework of the ongoing article 31 for all imported products, batches which do not meet in their totality the approved EU specifications are not released to the market. The appropriate efforts should be undertaken by the MAH to harmonise specifications across sites with EU requirements.

Dianeal PD 4
Batch analysis was provided for 10 batches. All batches comply with the specifications.

Extraneal
Batch analysis was provided for 10 batches. All batches comply with the specification.

Container closure system
Dianeal and Extraneal are packed in bags made of the same material. The compositions of the bags used in the USA are slightly different to those licensed in the EU. Both formulations are identical with the exception of the stabiliser and the lubricant.



The new packaging raises no safety concerns and is considered acceptable. The container has been on the market for many years.

Stability
In all cases, summary stability data are provided.

Dianeal PD 4
Up to 24 months data stored at 25°C/40%RH was presented for various presentations and all remained within specification. Weight loss remained within the expected limits.

	Dianeal Europe	Dianeal North Cove
Shelf life	24 months	24 months
Storage statement	Do not store below 4 °C	Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. It is recommended the product be stored at room temperature (25°C/77°F).

Extraneal
The samples were stored for up to 18 months at 25°C/40%RH. All parameters remained within specification. Weight loss results were within the expected limits.

	Europe	North Cove
Shelf life	24 months	18 months
Storage statement	Do not store below 4 °C	Store at 20 –25°C (68–77°F). Excursions permitted to 15 –30°C (59–86°F) [See USP Controlled Room Temperature]. Store in moisture barrier overwrap in carton until ready to use. Protect from freezing.

It is noted that there are differences in the shelf life for the products manufactured in North Cove to those manufactured at Castlebar. The shelf-life expiration dating of peritoneal dialysis (PD) solutions is primarily dependent on the rate of water loss over time. This is because flexible container systems are water vapor permeable and the resultant water loss contributes to the concentration of solutes over time. The thickness of the [redacted] overpouches used for these products also affects water loss from the primary containers. Other contributing factors to water loss are container geometry, container surface area to solution volume, sterilisation heat history, loading pattern, and

container fill volumes. Actual product weight loss for specific products varies between facilities due to differences in container configurations (e.g., fill volume), container surface area to solution volume, sterilisation heat history and loading pattern.
The stability data from the products manufactured at North Cove provides reassurance on their stability profile. However, as stability data of these products manufactured in compliance with EU requirements is currently not available, a conservative approach of recommending a 12 month shelf-life across all products produced at North Cove was agreed. Stability data, including long term and accelerated in product produced in accordance with EU specifications should be provided. A change management plan should be submitted by the MAH.
The real time stability data from product produced at North Cove have shown similar trends with the approved products manufactured at Castlebar. On this basis, then the special storage conditions remain unchanged.

Regional information
Not applicable.

Product information
Product information (PI) will be provided in all the relevant EU languages. However, due to the undertaking by the MAH to ensure EU supply from sites originally supplying non-EU markets, a delay in the availability of the PI according to EU languages is expected. In the meantime, the current agreed standards for importation of product into EU, should continue to be followed.
Information on changes to the PI can be found in section 2.4.

Conclusions on quality on adding North Cove as an additional manufacturing site
The CHMP considered that the data provided was acceptable and showed that inclusion of the USA site does not present major quality concerns.
However, the MAH should address the following:

1. All drug substances should be supported by active substance master files or appropriate data and comply with European Pharmacopoeia (Ph. Eur.) requirements.

Suppliers of active substance listed below have not previously been used in EU product and active substance master files (ASMF's) or equivalent data packages should be submitted for these suppliers. A change management plan, including timelines for implementation should be submitted within one week of Commission Decision. In addition, where applicable, they should be tested and shown to comply with the European Pharmacopoeia (Ph.Eur.), prior to the release of PD solutions to the EU market under the EU marketing authorisation.
In particular:

- Dextrose anhydrous from [redacted]
- sodium chloride produced at 1) [redacted] and 2) [redacted]
- Sodium S-Lactate from [redacted]

2. The excipients water for injections, hydrochloric acid and sodium hydroxide are controlled according to the United States Pharmacopoeia. These should be tested and results submitted to show they comply with the Ph. Eur. prior to the release of PD solutions to the EU market under the EU marketing authorisation.

3. The current minimum standards for critical process parameters and limits e.g. for terminal sterilisation should be reviewed and improved, in compliance with process capabilities and best practice. Terminal sterilisation has to be expressed as a minimum exposure time to a minimum temperature as per Ph. Eur. and should be harmonised at all involved sites. Consequently bioburden specifications of the filled containers should also be harmonised. The sterilisation process should be re-validated using biological indicators as per Ph. Eur. A change management plan, including timelines for implementation should be submitted within one week of Commission Decision.

4. Routine microbial monitoring of all the starting materials (including excipients) should be undertaken and the appropriate change management plan, including timelines for implementation should be submitted within one week of Commission Decision.

5. Stability data, including long term and accelerated in products produced in accordance with EU specifications should be provided. An appropriate change management plan should be submitted within three weeks of Commission Decision.

6. Standard QP release should apply for all products released under the terms of EU marketing authorisations; in particular the QPs must be satisfied that the active substances are manufactured in accordance with EU GMP requirements. The declaration should be provided prior to the release of PD solutions to the EU market under the EU marketing authorisation.

Pending conclusion of the ongoing Article 31, the MAH should implement in all its sites the outcome of lessons learned from the findings at Castlebar, to ensure a safe product supply. In particular

7. A more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing should be introduced. A change management plan, including timelines for implementation should be submitted within three weeks of Commission Decision.

8. The full description of manufacture (3.2.P.3) for the site together with its critical review should be submitted. A change management plan, including timelines for implementation should be submitted within three weeks of Commission Decision.

Additional measures may be requested subsequently for all sites, but pending conclusion of the ongoing article 31 these cannot be identified.

2.3. Overall conclusion

An article 31 referral procedure of Directive 2001/83/EC, as amended was initiated by the European Commission (EC) following receipt of information from Baxter indicating that their manufacturing problem related to out-of-specifications results for endotoxins in peritoneal dialysis produced at Castlebar was not resolved and the root cause had not been identified.
Taking into account the crucial nature of these medicinal products, and the need for unaffected batches of PD solutions to be made available to patients across the EU in the shortest possible timeframe, alternatives were sought. In view of severe supply limitations for Dianeal, Extraneal and Nutrineal and the risk of switching patients to alternative PD solutions or therapies, the CHMP considered that the use of comparable products produced by Baxter at alternative manufacturing sites outside the EEA (European Economic Area) should be prioritised. These dialysis solutions were thus imported from Canada, Singapore, Turkey and USA. To meet supply demands, the unprecedented importation of PD solutions from Canada, Turkey and USA increased. The Singaporean manufacturing plant was only used once and no longer considered as an alternative.

Considering the likelihood of prolonged use of large quantities of unlicensed (imported) PD solutions on the EU market, and in order to ensure continued supply of licensed medicinal products to the EU, the necessary data packages to support the inclusion of additional manufacturing sites were expedited within the ongoing article 31 referral procedure.
The available data to support inclusion of sites from which products are currently being imported (Canada, Turkey and USA) into the existing PD solutions marketing authorisations were submitted. The necessary data packages to support the inclusion of one more additional manufacturing site located in Europe (Poland) which is expected to become fully operational soon, was also expedited. In light of the current uncertainty over the root cause and the future re-instatement of supply from Castlebar, the addition of manufacturing sites to the marketing authorisations aimed at mitigating future supply problems arising for PD solutions in Europe, ensuring that sufficient PD solutions are available.

The CHMP reviewed all the data available for each of the four sites concerned. In April 2011, the Committee considered that the information available on the USA site was insufficient to conclude on its addition, pending the outcome of a recent inspection carried out at this site. However, sufficient data was available to recommend the variation to the marketing authorisations consisting in the inclusion of Canada, Poland and Turkey as additional manufacturing sites. A first opinion on the inclusion of these three sites was issued by the Committee in April, and the corresponding decision from the European Commission was issued on 12 May 2011.

At this stage of the article 31 review procedure, sufficient data is now available to recommend the variation to the marketing authorisations consisting in the inclusion of the site located in the USA as additional manufacturing site, as no major quality issues were identified and the results from the inspection were satisfactory.
The opinion on the Castlebar site cannot be finalised at this stage as issues remain for resolution by the marketing authorisation holder.

The review of the issues identified at Castlebar, with the interruption of supply from this site, led to the need to authorise additional manufacturing sites to ensure supply of PD solutions in Europe. Whilst all data to finalise the ongoing article 31 is not available, a stepwise approach is followed for the assessment, resulting in subsequent opinions being adopted by the CHMP.

Therefore, without prejudice to the ongoing article 31 procedure, the CHMP considers that sufficient information is available to issue a second opinion for this Article 31 procedure recommending the addition of the USA manufacturing site to the relevant PD solutions' marketing authorisations, subject to conditions set out in the Annex IV. Overall, the following should be taken into account:

- All drug substances should be supported by active substance master files or appropriate data and comply with Ph Eur requirements.

- All starting materials (including excipients) should be subject to satisfactory routine control of microbial contamination and, unless justified, endotoxin testing.

- Water for injections, and other excipients, should fully comply with Ph Eur monograph requirements, where applicable.

- The current minimum standards for critical process parameters and limits e.g. for terminal sterilisation should be reviewed and improved, in compliance with process capabilities and best practice. Terminal sterilisation has to be expressed as a minimum exposure time to a minimum temperature as per Ph. Eur. and should be harmonised at all involved sites. Consequently bioburden specifications of the filled containers should also be harmonised.
The sterilisation process should be re-validated using biological indicators as per Ph. Eur.

Standard QP release should apply for all products released under the terms of EU marketing authorisations; in particular the QPs must be satisfied that the active substances are manufactured in accordance with EU GMP requirements.

Pending conclusion of the ongoing Article 31, it is expected that the MAH implements in all its sites the outcome of lessons learned from the findings at Castlebar, to ensure a safe product supply. The introduction of a more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing and the re-submission of the full description of the manufacturing processes for all sites together with its critical review should thus be undertaken. Additional measures may be requested subsequently for these sites, but pending conclusion of the ongoing article 31 these cannot be identified.

The CHMP considers of extreme importance to retain coordination of the review of the conditions presently identified for the site in the USA. A harmonised European approach to supply has been in place since identification of the concern at Castlebar and the article 31 procedure remains ongoing pending resolution of the outstanding issues. The present opinion is the second of a series of entwined opinions, which may result subsequently in additional measures being requested for the site subject of the current opinion. The coordinated review by the CHMP of the conditions of the site in the USA, as done for the sites subject to the first opinion, will enable the appropriate harmonious adjustments with minimum impact on supply of PD solutions to the EU market.

2.4. Changes to the product information

Proposed minor amendments to the PI take into account the quality particulars in relation to the addition of the site to the marketing authorisations, in particular the shelf-life and nature and contents of container differences. The CHMP agreed with the amendments to the product information, as detailed below:
Changes are shown as greyed boxed wording

Summary of Product Characteristics

DIANEAL PD4
6.3 Shelf life

The shelf life of the product as packaged for sale is 24 months
12 months (for medicinal products manufactured at Alliston, Canada and North Cove, USA only).
The product, once removed from its overpouch, should be used immediately

EXTRANEAL
6.3 Shelf Life

2 years
12 months (for medicinal products manufactured at Alliston, Canada and North Cove, USA only).
The product, once removed from its overpouch should be used immediately.

6.5 Nature and Contents of Container

Flexible PVC container holding 1.5, 2.0 or 2.5 litres.

The lineo connector that may equip the Y transfer line of the twin bag, contains 10.5% of Povidone iodine ointment

1.5 L	8 units per box	Single bag Sy II (luer connector)
1.5 L	8 units per box	Single bag Sy III (spike connector)
1.5 L	8 units per box	Twin bag Sy II (luer connector)
1.5 L	8 units per box	Twin bag Sy III (spike connector)
1.5 L	6 units per box	Single bag Sy II (luer connector)
1.5 L	6 units per box	Single bag Sy III (spike connector)
1.5 L	6 units per box	Twin bag Sy II (luer connector)
1.5 L	6 units per box	Twin bag Sy III (spike connector)
1.5 L	6 units per box	Twin bag (lineo connector)
2.0 L	8 units per box	Single bag Sy II (luer connector)
2.0 L	8 units per box	Single bag Sy III (spike connector)
2.0 L	8 units per box	Twin bag Sy II (luer connector)
2.0 L	8 units per box	Twin bag Sy III (spike connector)
2.0 L	6 units per box	Single bag Sy II (luer connector)
2.0 L	6 units per box	Single bag Sy III (spike connector)
2.0 L	6 units per box	Twin bag Sy II (luer connector)
2.0 L	6 units per box	Twin bag Sy III (spike connector)
2.0 L	5 units per box	Single bag Sy II (luer connector)
2.0 L	5 units per box	Single bag Sy III (spike connector)
2.0 L	5 units per box	Twin bag Sy II (luer connector)
2.0 L	5 units per box	Twin bag Sy III (spike connector)
2.0 L	5 units per box	Twin bag (lineo connector)
2.5 L	5 units per box	Single bag Sy II (luer connector)
2.5 L	5 units per box	Single bag Sy III (spike connector)
2.5 L	5 units per box	Twin bag Sy II (luer connector)
2.5 L	5 units per box	Twin bag Sy III (spike connector)
2.5 L	4 units per box	Single bag Sy II (luer connector)
2.5 L	4 units per box	Single bag Sy III (spike connector)
2.5 L	4 units per box	Twin bag Sy II (luer connector)
2.5 L	4 units per box	Twin bag Sy III (spike connector)
2.5 L	4 units per box	Twin bag (lineo connector)

Not all pack sizes may be marketed

Patient Information Leaflet

EXTRANEAL
5. How to store EXTRANEAL

- Keep out of the reach and sight of children.
- Store in the original package.
- Do not store below 4°C.
- Do not use EXTRANEAL after the expiry date. The date is stated on the carton label and on the bag after the abbreviation Exp. and the symbol ⌛. The expiry date refers to the last day of that month.
- Dispose EXTRANEAL as you have been trained

Patient Information Leaflet

Volume	Number of units per box	Product configuration	Type of connector(s)
1.5L	8	Single bag (APD)	luer /spike
1.5L	8	Twin bag (CAPD)	luer / spike
1.5L	6	Single bag (APD)	luer /spike
1.5L	6	Twin bag (CAPD)	luer / spike /lineo
2.0L	8	Single bag (APD)	luer/spike
2.0L	8	Twin bag (CAPD)	luer/spike
2.0L	6	Single bag (APD)	luer/spike
2.0L	6	Twin bag (CAPD)	luer/spike
2.0L	5	Single bag (APD)	luer / spike
2.0L	5	Twin bag (CAPD)	luer / spike / lineo
2.5L	5	Single bag (APD)	luer/spike
2.5L	5	Twin bag (CAPD)	luer/spike
2.5L	4	Single bag (APD)	luer / spike
2.5L	4	Twin bag (CAPD	luer / spike /lineo

The Lineo connector contains iodine.
Not all configurations may be marketed.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanations, the CHMP concluded that the data are sufficient to support inclusion of the additional manufacturing sites located in the USA into the existing marketing authorisations of relevant Baxter PD solutions.

Therefore, the CHMP recommends the variations to the terms of the marketing authorisation for the medicinal products referred to in Annex I concerning the addition of the USA manufacturing site as set out in the Annex II and for which the relevant sections of the summary of product characteristics and package leaflet, are set out in Annex III of the opinion. The conditions affecting the marketing authorisations are set out in Annex IV of the opinion.

This opinion is the second opinion[6] issued by the Committee, and will be followed by subsequent opinion(s) pending resolution of the outstanding manufacturing issues at Castlebar (Ireland).

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.

[6] A first opinion for this Article 31 procedure recommending the addition of Canada, Poland and Turkey manufacturing sites to the existing PD solutions' marketing authorisations was issued in April 2011. The corresponding decision from the commission was issued on 12 May 2011.