Annex IV

Conditions of the marketing authorisation

The following conditions (identified below per site) should be fulfilled by the marketing authorisation holder.

The CHMP considers of extreme importance to retain coordination of the review of the conditions presently identified for the sites in Canada, Poland and Turkey. 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 first of a series of entwined opinions, which may result subsequently in additional measures being requested for the sites subject of the current opinion. The coordinated review of the conditions by the CHMP will enable the appropriate harmonious adjustments with minimum impact on supply of PD solutions to the EU market. Therefore, data in relation to the following conditions should be submitted and reviewed by the CHMP.

Canadian manufacturing site
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 monohydrate
- sodium chloride
- Sodium S-Lactate

2. The excipients water for injections and sodium hydroxide are controlled according to the United States Pharmacopoeia. These should be tested and results submitted to shown 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 all sites together with its critical review should be submitted. A change management plan, including timelines for implementation should be submitted within three week of Commission Decision.

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

Polish manufacturing site
The MAH should address the following:

1. 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.

2. The maximum batch size at Lublin should be stated and the actual validation data for these batch sizes should be provided within three weeks of Commission Decision.

3. Specifications for the excipients sodium hydroxide and hydrochloric acid should be stated along with the results of analysis. This should be submitted 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

4. 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.

5. The full description of manufacture (3.2.P.3) for all sites together with its critical review should be submitted. A change management plan, including timelines for implementation should be submitted by 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.

Turkish manufacturing site
The MAH should address the following:

1. For glucose anhydrous the limit test for endotoxin in the drug substance should be tightened prior to the release of PD solutions to the EU market under the EU marketing authorisation. Updated certificates of analysis should also be provided.

2. 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.

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. 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

5. 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.

6. The full description of manufacture (3.2.P.3) for all sites together with its critical review should be submitted. A change management plan, including timelines for implementation should be submitted by 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.