The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

19 December 1997
Revised
CPMP/1138/97

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 33rd plenary meeting on 16-17 December 1997. This also included a meeting with representatives from patient organisations related to HIV/AIDS (European AIDS Treatment Group - EATG).

Centralised Procedures

The Committee adopted by consensus the following opinions:

- One positive opinion on a centralised application was adopted under exceptional circumstances. It relates to a biological/biotechnological product (Part A) indicated for the treatment of multiple sclerosis.
- Two positive opinions were adopted for centralised type I variations following the type II procedure and four positive opinions for centralised type II variations.

The Committee noted the withdrawal of one application (Part A).

Since the CPMP meeting in November 1997, the European Commission has granted a marketing authorisation for CEREZYME (imiglucerase), indicated for long term enzyme replacement therapy in patients with a confirmed diagnosis of type I Gaucher Disease and who exhibit clinically significant manifestations of the disease. A summary concerning this product is given in Annex III. In anticipation of future EU Policy for orphan medicinal products the EMEA had granted a partial fee exemption for this application.

An overview of centralised applications is given in Annex I and II.

Scientific Advice

The CPMP adopted by consensus six scientific advice on preclinical and/or clinical issues and development plans concerning products indicated for the treatment of asthma, chronic obstructive pulmonary disease, migraine, breast cancer, prostate cancer and chronic constipation.

Referrals under Article 10 of Council Directive 75/319/EEC, as amended

One positive opinion for arbitration referred to the EMEA under the Mutual Recognition procedure was adopted by consensus and will be forwarded to the Commission.

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Working Parties, Ad Hoc Expert Groups and Organisational Matters

The CPMP heard reports from its Quality, Biotechnology, Safety, Efficacy and Pharmacovigilance Working Parties and the Ad Hoc groups of Experts on Update of Guidance on SPCs and on Herbal Medicinal Products. Work Programmes for 1998 were adopted for the Efficacy, Safety and Pharmacovigilance Working Parties.

Biotechnology Working Party:

The CPMP adopted a Position Paper for Production of Tallow Derivatives for Use in Pharmaceuticals (CPMP/1163/97). The first joint workshop between the Biotechnology Working Party, the European Plasma Fractionation Association (EPFA) and the European Association of the Plasma Products Industry (EAPPI) on plasma-derived medicinal products was hosted by the EMEA on 8 December 1997. The objective of the workshop was to share scientific information and views with the aim of reaching a common understanding.

The topics addressed included issues related to:

- Plasma source material.
- Inactivation/removal of viruses, with a focus on removal of viruses by filtration.
- Consideration of potential effects of viral inactivation or removal processes on biological activity of plasma-derived medicinal products.

A more detailed report of the meeting is being prepared and will be made available in early 1998.

Safety Working Party:

The following documents were adopted:

- Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95).
- CPMP Position Paper on the Genotoxic and Carcinogenic Potential of Phenolphthalein (CPMP/818/97).
- Points to Consider in the Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products (CPMP/986/96).

Efficacy Working Party:

The following documents were adopted:

- Note for Guidance on the investigation of drug interactions (CPMP/EWP/560/95).
- Note for Guidance on clinical investigation of drugs used in weight control (CPMP/EWP/281/96).

The Chairperson of the CPMP, Prof. J-M Alexandre thanked CPMP members at the end of this term for their important contributions during the transition period following the introduction of the new EU-systems in 1995. Membership will either be renewed or changed for the January 1998 meeting, and elections for chairperson and vice-chairperson are anticipated for 27 January 1998.

Mutual Recognition

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) (15 December 1997) which is circulated together with this press release.

Prof. R. Bass
Head of Human Medicines Evaluation Unit

Annex I: Centralised Applications: Statistics
Annex II: New Community Marketing Authorisations
Annex III: Product Summary for CEREZYME
Annex IV: Meeting with European AIDS Treatment Group (EATG)
Annex V: Herbal Medicinal Products (press release November 1997)
Annex VI: Position Paper of the CPMP for Production of Tallow Derivatives for Use in Pharmaceuticals (CPMP/1163/97)

This press release and other documents are available on the Internet at the following address: http://www.eudra.org/emea.html

ANNEX IV to **CPMP - December 1997**
Press Release

The CPMP held a second meeting with EATG to exchange views on the document recently released "Points to Consider in the assessment of anti HIV medicinal products" (CPMP/602/95 rev. 1 dated 19 November 1997). The significant overall progress made in this field was reviewed and the following outstanding points were discussed including the definition of treatment failure, emergence of resistance, drug-drug and drug-food interaction, compliance, impact of new combination therapy in quality of life and opportunistic infections. Further meeting might be useful to exchange views on the advances expected in this pharmaco-therapeutic area.

The European Agency for the Evaluation of Medicinal Products
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ANNEX I to **CPMP - December 1997**
Press Release

CENTRALISED APPLICATIONS TO THE EMEA

	CENTRALISED		TOTAL*
	Part A	***Part B***	
Applications submitted since 01.01.95	48	85	133
Withdrawn	3	8	11
Review ongoing	19	40	59
Opinions given by CPMP	27	37	64**
Marketing Authorisations granted by Commission	25	27	52***

* These figures include the 18 ex-concertation procedures submitted before January 1995 of which 14 have been authorised and 4 withdrawn before end 1996
** 64 Opinions corresponding to 49 substances
*** 52 Marketing Authorisations corresponding to 42 substances

	PENDING		FINAL		TOTAL
	Part A	***Part B***	***Part A***	***Part B***	
Variations type I	6	6	64	65	141
Variations type II	5	8	18	30	61
Extensions	25	2	10	2	39
Scientific advice	4		46		50

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Update 19 December 1997

ANNEX II to **CPMP – December 1997**
Press Release

Medicinal Products granted a Community Marketing Authorisation under the Centralised Procedure

Status: December 1997

Product a) Brandname b) INN c) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) ATC b) Indication	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Opinion received on b) Date of decision c) Date of notification d) OJ No.
a) **Cerezyme** b) imiglucerase c) Part A	a) Genzyme B.V b) NL	a) A16AB02 b) enzyme replacement therapy in patients with a type I Gaucher disease	a) Powder for infusion b) 200 IU c) 2 Presentations	a) 17.01.97 b) 23.07.97 c) 175 Days d) 30 Days	a) 22.08.97 b) 17.11.97 c) d)

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ANNEX III to **CPMP - December 1997**
Press Release

CEREZYME

International Non-proprietary Name (INN): **Imiglucerase**

On 17 November 1997, the European Commission issued a Marketing Authorisation valid for the entirety of the European Union for the medicinal product Cerezyme, which contains Imiglucerase. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 23 July 1997. The Marketing Authorisation Holder responsible for this medicinal product is Genzyme B.V., The Netherlands.

The approved indication is for use as a long-term enzyme replacement for the treatment of patients with a confirmed diagnosis of type I Gaucher disease who exhibit clinically significant manifestations of the disease. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in this EPAR and is available in all European Union official languages.

The active substance of Cerezyme, Imiglucerase, is a recombinant macrophage targeted β-glucocerebrosidase. The targeting is achieved by modification of oligosaccharides of β-glucocerebrosidase to expose mannose-terminated β-glucocerebrosidase which leads to a selective uptake of the enzyme by macrophages that are present in liver, spleen and bone marrow. Imiglucerase was developed as a recombinant product as substitute to the placental derived enzyme, alglucerase.

Clinical trials were designed to investigate efficacy of placental and recombinant DNA derived products using as primary parameters the increase in hemoglobin level, an increase in platelet count and decrease in liver and spleen volume as assessed by MRI or CT.

It has also been shown that patients may safely switch from alglucerase to imiglucerase treatment.

Safety measures monitored throughout the studies include the formation of antibodies, routine clinical laboratory values and adverse events. Alglucerase and imiglucerase have a comparable safety profile. Theoretically imiglucerase has a lower risk of viral contamination than alglucerase.

The CPMP, on the basis of the overall benefit/risk ratio considered that Cerezyme showed a satisfactory safety profile and adequate evidence of efficacy in the therapy of type I Gaucher disease and therefore recommended that the Marketing Authorisation should be granted.

The marketing authorisation holder has been requested to submit additional information on chemical, pharmaceutical and biological aspects. All additional data will be carefully monitored and the results will be reviewed by the CPMP.

This text is also published as Abstract of the EPAR for CEREZYME.

The European Agency for the Evaluation of Medicinal Products
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ANNEX V to **CPMP - December 1997**
Press Release

Press Release

AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS* MEETING
24-25 NOVEMBER 1997-12-18
EMEA, 7 Westferry Circus, Canary Wharf, London E14 4HB

The third meeting of the Ad Hoc Working Group on Herbal Medicinal Products, which was held at the EMEA offices in London on 24-25 November 1997, concluded the first series of meetings related to the facilitation of marketing authorisation of herbal medicinal products via the Mutual Recognition Procedure.

Over its three meetings this year and in accordance with its mandate defined last June by the EMEA Management Board, the group reviewed the criteria set out in Council Directive 75/318/EEC for the demonstration of chemical and pharmaceutical quality, pre-clinical safety, safety and clinical efficacy in the case of marketing authorisation applications for herbal medicinal products. Such criteria must be fulfilled to allow successful mutual recognition.

In the field of quality, the group reviewed existing guidance for Good Manufacturing Practice (GMP) which was considered acceptable. Minor modifications would suffice for updating Annex 7 'Manufacture of Herbal Medicinal Products' of GMP for medicinal products. Concerning documentation on pharmaceutical quality existing guidance is appropriate at present, although modifications would be necessary, in particular to the Note for Guidance "Quality of Herbal Remedies". Taking into account potential difficulties for the testing of complex mixtures, development of further guidance should be considered.

Guidance regarding requirements for non-clinical testing of herbal drug preparations was derived from available draft guidance on requirements for old substances with long term marketing experience. The proposed guidance takes into account experience available in humans for well-established herbal drug preparations.

Although efficacy was recognised as being the most difficult issue, the group agreed on some general principles and reached agreement on a core SPC for *Valerianae radix*. The group considered that the drafting of such core SPCs would be the most appropriate way to develop general guidance on criteria to assess efficacy data based on bibliographical documentation. ESCOP made a presentation to the working group on their study on the pharmacovigilance of herbal medicinal products.

The outcome of the work achieved by the working group was presented to Interested Parties who unanimously supported the continuation of this work beyond 1997. Industry upon request confirmed their willingness to co-operate in encouraging new research in the field of clinical pharmacology and clinical efficacy in order to obtain modern clinical data on herbal medicinal products. They also expressed a great interest in commenting on all proposals for revision of documents prepared by the working group. These proposals will be released by the EMEA Secretariat for consideration by Interested Parties including learned societies.

Full report will be given to the Management Board of the EMEA and to the European Commission for consideration and circulated to CPMP and Mutual Recognition Facilitation Group. Proposals for future work include establishment of listings of herbal medicinal products available in the Member States, preparation of core SPCs and drafting a Points to consider document on criteria to assess efficacy of herbal medicinal products and review fixed combinations.

* The ad hoc group on Herbal Medicinal Product had been created within the EMEA upon the initiative of the European Commission and the EMEA Executive Director

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

ANNEX VI to **CPMP - December 1997**
Press Release

(CPMP/1163/97)

POSITION PAPER OF THE CPMP FOR PRODUCTION OF TALLOW DERIVATIVES FOR USE IN PHARMACEUTICALS

1. Background

Tallow derivatives are frequently used as excipients in medicinal products, or are used in their manufacturing process. Examples of tallow derivatives include magnesium stearate (contained in tablets), glycerol (used as an excipient or as a reagent in manufacturing processes for biotechnology products), and polysorbates (used as a stabiliser in medicinal products or as a reagent in a viral inactivation step applied to many plasma derived medicinal products).

Tallow is not used as such in medicinal products, but it is the starting material used for the production of tallow derivatives. Production of tallow involves the melting of fat in tissues or carcasses, and its separation (by filtration and centrifugation) from proteineous material, followed by washing steps. The exact equipment used will vary from one renderer to the other and, therefore, the range of temperatures will vary. Rendering processes are described in EU legislation (Commission Decisions 92/562/EC). Experimental transmission studies performed by Dr. Taylor[1] demonstrated that tallow, produced from typical slaughterhouse offal (bones, organs, fat) from BSE infected cattle, using the mildest conditions[2] approved under the EU legislation (Commission Decision 92/562/EC), showed no detectable infectivity. Infectivity was detected, however, in the bone meal resulting as a by-product of this tallow production.

Manufacturing conditions for the preparation of tallow derivatives involve additional steps which include the use of high temperatures and/or high alkalinity.

2. Recommendations

Tallow used as the starting material for the manufacture of tallow derivatives should be produced by a method at least as robust as those referred to in Commission Decision 92/562/EC.

For the manufacture of pharmaceutical grade tallow derivatives, the following manufacturing conditions should be used :

- Transesterification or hydrolysis at not less than 200 °C for not less than 20 minutes under pressure (glycerol, fatty acids and fatty acid esters production)
- Saponification with NaOH 12 M (glycerol and soap production)
  - Batch process : at not less than 95 °C for not less than 3 hours ;
  - Continuous process: at not less than 140 °C, 2 bars for not less than 8 minutes, or equivalent.

[1] Taylor et al., The Veterinary Record, December 9 1995, 1327, 605-610.
[2] During these ‘mild’ conditions, the temperature reached 120 °C after 20 minutes or 117 °C after 17 minutes.

It is also recommended that there is a pooling of European expertise from all EU scientific committees with a similar interest for minimising the risk of transmission of TSE, in order to develop harmonised European standards for tallow derivatives across all sectors.

Report from the meeting held on 15th December 1997

The MRFG noted that 10 new mutual recognition procedures have been finalised recently as well as 19 type I and 7 type II variations.
The status as of 15th December 1997 of procedures under mutual recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures from Type I variations finalised	Procedures from Type I variations pending	Procedures from Type II variations finalised	Procedures from Type II variations pending	Arbitrations referred to CPMP
1997	136	51	99	19	152	66	1 N.A. + 1 Var.

16 new procedures (regarding 36 products) have been started since 17th November. The categories of these procedures are as follows:

New active substance[1]	Line extensions[2]	Fixed combinations	Generics	Herbal products[3]	OTC[4]	Others[5]
7	3	1	2	1	0	2

1. When in one of the involved Member States it concerns a new active substance according to the definition in the Notice to Applicants Part IIA;
2. Line extensions are those applications which extend a range of products, e.g. an additional strength, or a new pharmaceutical form from the same Marketing Authorisation Holder;
3. In this category products are classified as herbals when the RMS has considered them as herbal product;
4. In this category products are classified as OTC products when the RMS has approved it for OTC use, although the legal status is not part of the Mutual Recognition Procedure;
5. When the product is not classified in the previous six categories.

Each application can be classified in only one category.

Number of countries involved in the started new applications procedures since 17th November 1997:

Reference Member State (number of products involved in the procedure)	Number of CMS involved in the procedure
DE (1)	11
DE (1)	14
DE (1)	9
DE (1)	12
DE (2)	1
FR (3)	14
FR (3)	11
NL (2)	14
NL (1)	13
SE (2)	1
UK (2)	1
UK (1)	4
UK (1)	13

UK (1)	13
UK (7)	14
UK (7)	1

General issues

- The MRFG received a report on EudraTrack from its sub group which had met to review the progress of the 3 months pilot implementation of the system. The group noted that some progress had been made but the previously agreed updates had not been installed and that significant problems remained to be resolved. The pilot phase would therefore be extended and the group would review the situation again at its January meeting.
- The group also received a report from its influenza vaccine sub group. The procedures for harmonising the influenza vaccines through the mutual recognition procedure is progressing well and a meeting with the EVM (European Vaccines Manufacturers) will be held in January. The Influenza Vaccines sub-group had finalised their Proposal for a harmonised SmPC for influenza vaccines. Representatives of the European Vaccines Manufacturers (EVM) present at the meeting agreed that the applicant will draft new SmPCs for their Core dossiers taking account the Proposal agreed by the sub-group. These SmPCs will be submitted to the Concerned Member States in the beginning of January.
- A resource document on the availability of video-conference facilities available to the competent authorities was finalised.
- The MRFG agreed a format for the response document of the applicant after day 60. The document is attached to this report and copies have been sent to the trade organisations. Copies will also be available on the member state internet web-sites. It is hoped that this document will further help the MR-procedure. The new document should be used immediately by applicants.
- The diagnostic review of break-out meetings and of procedure withdrawals was commenced and a fruitful discussion was held.
- The MRFG heard a report of the meeting between the European Commission, the EMEA and the Drug Authorities of Central and Eastern European Countries and started a consideration over how the discussion on mutual recognition might be taken forward.
- The MRFG noted that companies were seeking procedural advice directly from the group. It was agreed that applicants should discuss issues with the RMS or potential RMS. The member state concerned should give advice to the applicant or bring the issue to the attention of the Commission or to the MRFG. Such a filtering procedure was considered to be the most efficient use of resources.
- The group was pleased to welcome the Commission to its meeting and took the opportunity to discuss a series of issues related to the end of the transition period.
- The next meeting of the MRFG will be held on the 26th January 1998.

Information on the above mentioned issues can be obtained by the presiding chair of the MRFG:

Dr David Jefferys
Medicines Control Agency
Market Towers
1 Nine Elms Lane
UK - London SW8 5NQ *Phone: +44.171.273.0454 or*
+44.171.273.0451

MRFG

Mutual Recognition Facilitation Group

APPLICANT'S RESPONSE DOCUMENT IN MUTUAL RECOGNITION RECOMMENDED FORMAT

Version 4
15th December 1997

It is important to emphasise that a well prepared response document greatly facilitates the task of the competent Authorities in evaluating the dossier.
Moreover, since the Concerned Member States have a short time period to assess the response document, it should be clear, brief and focused on the questions raised.

Prerequisite

1- The applicant should provide a draft response document in due time to the Reference Member State, so that the Reference Member State should comment on the responses and then support the applicant's response document, considered as satisfactory, with a letter.

2- The applicant should send the whole response document to the Concerned Members States (CMS) in due time: the response document should be with the CMS **not less than five days** before the scheduled date for the next MRFG meeting in order to facilitate assessment and if necessary, discussion during the break-out session (see Notice to Applicants-July 1997-page 31).

3- Answers to questions from one or more CMS (which were not solved by the company's first answer) should also be sent to **all** CMS.

4- Additional studies are not acceptable during the procedure.

FORMAT OF THE RESPONSE DOCUMENT

The document is divided in four Parts (I, II, III and IV) according to the initial dossier, as follows:
- Part I: answers to questions on SmPC
- Part II: answers to questions on chemical/pharmaceutical and biological documentation
- Part III: answers to questions on toxico-pharmacological documentation
- Part IV: answers to questions on clinical documentation.
- Appendices: a copy of CMS questions should be appended to the document.

However, for purpose of flexibility, the option to provide a presentation per member state remains available.
The applicant should answer all the questions raised by the Concerned Member States. A general table of contents should facilitate examination of the dossier.
The document should preferably not mention any cross-reference to the initial dossier. If applicable, supportive information or modified pages should be included to the relevant part, as an attachment.
A copy of CMS questions should be appended to the document.

PART I

Part IA

The applicant should answer questions, if any, on Part IA (administrative data, samples, manufacturing and marketing authorisations).

Part IB

This part should include the new proposed SmPC and the relevant SmPC tabular format with the answer to the questions raised by the CMS on the different sections of the SmPC.

1. New proposed SmPC

In agreement with the RMS, the applicant should propose a new version of the SmPC including all revised wording clearly identified.

The words, sentences or paragraphs to be deleted should be still written but crossed out, i.e: ~~words, sentences or paragraphs to be deleted~~.

The words, sentences or paragraphs to be added should be written using bold and italic types, i.e: ***words, sentences or paragraphs to be deleted.***

2. Questions raised on SmPC: tabular format (*landscape paper format*)

The tabular format may be adapted as necessary for an individual marketing authorisation application by expanding or contracting sections or omitting sections where not relevant. Alternative tabular presentations may be used. However, the heading of such tables must be of the same structure, i.e:

Initial Proposed SmPC plus proposed revisions (with deletions marked by strike through and additions marked in bold italic)	**Objections/Points for consideration raised by Concerned Member States**	**Company response (with cross reference to the response document when applicable)**

Each objection or question should be mentioned and followed by the initials of the Concerned Member State.

The final proposal should include clear and appropriate answer to support the new proposal.

PART II, III and IV

The applicant must answer questions, if any, on Part II (chemical, pharmaceutical and biological documentation), on part III (toxicological and pharmacological documentation) and on part IV (clinical documentation).

The response document should follow the same presentation as the initial dossier (see The Notice to Applicants, Vol 2B, Jan 97).

The applicant should answer all questions raised by the concerned member states.

Each objection or question should be mentioned and followed by the initials of the Concerned Member State. Cross-references could be useful from one response to another. If applicable, all modified pages of the initial dossier or references should be added and appended to each concerned Part.

APPENDICES

It could be helpful to append at the end of the response document a copy of the objections and comments raised up to Day 60 by the Concerned Member States.

NUMBER OF COPIES OF THE RESPONSE DOCUMENT

The number of copies of the Applicant's response document for submission to the Concerned Members States are set out in the Notice to Applicants/Vol 2A/July 97, page 169.

Note: i) when possible, the written response should be bound in separate volumes so that the pharmaceutical assessor can review the response to Parts I and II, the pre-clinical assessor the response to Part I and III and the clinical assessor the response to Part I and IV.

ii) on the request of the Reference Member State, the Applicant should provide the response document in electronic form.

TEMPLATE

Table of Contents

Part I

I.1 Proposal for revised SmPC

1. NAME OF THE MEDICINAL PRODUCT
XXX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
XXX

3. PHARMACEUTICAL FORM
~~Tablet~~ Capsule

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
XXX is indicated for the treatment of YYY ***in adult.***
4.2 Posology and method of administration
4.3 Contra-indications
~~None known~~ ***Renal insufficiency***
4.4 Special warnings and special precautions for use
4.5 Interaction with other medicinal products and other forms of interaction
4.6 Use during pregnancy and lactation
4.7 Effects on ability to drive and use machines
4.8 Undesirable effects
4.9 Overdose

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
5.2 Pharmacokinetic properties
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6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
6.2 Incompatibilities
6.3 Shelf life
6.4 Special precautions for storage
6.5 Nature and contents of the container
6.6 Instructions for use/handling

7. MARKETING AUTHORISATION HOLDER
8. MARKETING AUTORISATION NUMBER
9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION
10. DATE OF (PARTIAL) REVISION OF THE TEXT

I.2 Questions raised on SmPC: Tabular format

Initial Proposed SmPC plus proposed revisions (with deletions marked by strike through and additions marked in bold italic)	**Objections/Points for consideration raised by Concerned Member States**	**Company response (with cross reference to the response document when applicable)**
XX is indicated...	Question: XXX *(FR)* Question: XXX *(NL)*	Response: we agree on the proposal (see new proposed SmPC). Response: we do not agree because...

Part II: answers to questions on chemical/pharmaceutical biological documentation

Part II A
Question: XXX (FR)
Response:

Part II B
Question: YYY (AU)
Question: ZZZ (DE)
Response:

Part II C, D, E, F, Q

Part III: answers to questions on toxicolo/pharmacological docum entation

Part III A	Toxicity
Part III B, IIIC	Reproduction /Fertility/Embryotoxicity
Part III D,E	Mutagenic potential / Carcinogenic potential
Part III F, G, H, Q	Pharmacodynamics / pharmacokinetics (in vitro/animal)

Part IV: answers to questions on clinical documentation

Part IV A	Pharmacodynamics / Pharmacokinetics (human)
Part IV B	Clinical trials

Post-Marketing experience

Annexes

Copy of Day 60 letters from Concerned Member States.