EFPIA: Avenue Louise 250 Boîte 91 - B-1050 Bruxelles - Belgique
EMEA: 7 Westferry Circus - Canary Wharf - LONDON E14 4HB - Great Britain

EFPIA INFO DAY

2000 MINUS 2

Performance Indicators of the Centralised Procedure

20 NOVEMBER 1998
CABOT HALL - LONDON

EFPIA INFO DAY
2000 MINUS 2

PERFORMANCE INDICATORS OF THE CENTRALISED PROCEDURE

20 NOVEMBER 1998
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EFPIA INFO DAY 1998

Performance indicators of the centralised procedure

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1. EFPIA INFO DAY PROGRAMME

EFPIA-INFO DAY- NOVEMBER 1998

"2000 minus 2"

PROGRAMME

20 November 1998 - Cabot Hall

Cabot Place West, Canary Wharf, GB - London E14 5AB - Tel.: +44.171.418.27.85/418.27.95

Morning Session
The Centralised Procedure

09.00 Opening remarks
Strachan HEPPELL - EMEA

09.05 Welcome and general introduction
Brian AGER - EFPIA

Performance since the 1997 EFPIA Info Day

09.10 Chairman's introduction
Yves JUILLET - Hoechst-Marion-Roussel

09.20 The challenges of the centralised procedure : evolution or revolution ?
Prof. Jean-Michel ALEXANDRE - CPMP

09.35 Joint EFPIA/EMEA survey: concrete improvements in the results
Jim RITCHIE - SmithKline Beecham + Patrick LE COURTOIS - EMEA

09.50 EFPIA/EMEA interactions : Validation / pre-submission, from opinion to decision, scientific advice
Jean-Pierre OSSELAERE - Schering-Plough + David LYONS - CPMP + Prof. Rolf BASS - EMEA

10.05 Panel discussion: assessment of the year three
All speakers + Dave GILBERT- Novartis + Françoise DE CREMIERS - Wyeth-Ayerst

10.35 Coffee break

CONCRETE PROPOSALS FOR IMPROVING THE PROCESS

10.50 Chairman's introduction
Fernand SAUER - EMEA

11.00 Regulation 2000 : what is it and what is it not ?
Vaila MARSHALL - Pfizer

11.20 Commission approach to the future
Patrick DEBOYSER - DG III

11.40 What would we like to achieve ?
Emily DONNELLY - SmithKline Beecham

12.00 Panel discussion: How to be better prepared for the next century ?
All speakers + Bo LUMHOLTZ - CPMP + Hans WINKLER - CPMP

12.30 Buffet lunch

Afternoon Session
The Mutual Recognition Procedure

Performance since the 1997 EFPIA Info Day

14.00 Chairman's introduction
Christa WIRTHUMER-HOCHE - MRFG

14.10 From transition to reality : the main differences
Christa WIRTHUMER-HOCHE - MRFG + David JEFFERYS - MRFG

14.30 EFPIA and MRFG initiatives to achieve a "real mutual recognition spirit"
Blandine PICON - French Medicine Agency + Ekkerhard BAADER - HMR

14.50 Panel discussion : assessment of the year three
All speakers + Agnete KJAERVIG - Novo -Nordisk

15.20 Coffee break

CONCRETE PROPOSALS FOR IMPROVING THE PROCESS

15.40 Chairman's introduction
Roger BOLTON - Zeneca Pharmaceuticals

15.50 Accelerated arbitration : is it a solution ?
Gabriele DISSELHOFF - Merck KGaA

16.10 Clarifications on the procedure with the help of the Commission communication
Philippe BRUNET - DG III

16.30 The common efforts of Member States to improve the process of mutual recognition
Thomas LÖNNGREN - MRFG

16.50 Panel discussion : how to be better prepared for the next century ?
All speakers + David ROBERTS - Almirall Prodesfarma + Birka LEHMANN - BfARM + Olivier AMEDEE-MANESME - SNIP

Closing remarks

17.20 **Strachan HEPPELL - EMEA**

17.25 **Brian AGER - EFPIA**

17.30 Adjourn

2. JOINT EFPIA-EMEA PRESS RELEASE

2. JOINT EFPIA-EMEA PRESS RELEASE

REPORT ON EFPIA INFO DAY - 20 NOVEMBER 1998

The fifth EFPIA-Info day organised by EFPIA with the collaboration of the EMEA and the CPMP was held in London on 20 November 1998. It was opened by the Chairman of the EMEA Management Board, S. Heppell. Over 200 delegates attended this meeting, including a large number of industry representatives, CPMP members and EMEA staff.

Performance Assessment and Centralised Procedure

The first part of the meeting addressed the performance of the centralised procedure and especially the latest results of the joint EFPIA/EMEA continuous survey procedure. Analysis of the responses showed that since the 1997 results, overall timelines have been better respected, oral explanation meetings are more fruitful, and the overall quality of the translations improved. However, the survey revealed more criticism of the quality of the initial dossier and the expert reports, more outstanding objections and an increase in the number of hearings. Some concerns remain regarding the quality and the clarity of the issues raised in the assessment reports.

The CPMP Chairman, Prof. J. -M. Alexandre made the following recommendations on how to achieve a more efficient EU registration system. A network involving national experts and resources but free from national interference should help consolidate a robust European system. He stressed the need to work together, and explained why more dossiers are being withdrawn or are receiving a negative opinion from the CPMP: a few bad candidate molecules, sometimes a poor development, premature dossiers, CPMP more demanding and requesting clearer therapeutic benefits.

The overall attitude was positive and constructive, and all parties expressed their commitment to continue to work together towards better performance. EMEA and EFPIA jointly presented the results of a series of workshops aiming to resolve the issues arising during the pre-submission phase, during the time from opinion to decision, and in the case of variations. The availability on the Internet of the pre-submission guidance document was welcomed as it supports interaction prior to submission and validation of centralised dossiers.

Applicants are encouraged to continue to seek scientific advice and accept guidance at an early stage of the development to avoid problems later on. The EMEA will continue to help applicants to improve the quality of documents and translations. A continued interaction between applicants and EMEA CPMP before submission and throughout the procedure is recommended.

The questionnaire for the survey on the centralised procedure is considered useful in its present form. It will continue to serve as a tool and will focus on major steps of the survey (impact of scientific advice) and will include negative opinions and withdrawals. The accuracy of the survey will depend on increasing the response rate especially from industry but also from (Co-) Rapporteurs. In addition the reasons for problematic issues detected will be explored, e.g. in workshops on case studies involving EMEA CPMP and concerned applicants.

The Way Forward

Looking forwards to the future, EFPIA has started discussions quite some time ago as V. Marshall from Pfizer told the audience. This overview has been published concerning relevant principles and concepts towards defining the optimal long term future structure for regulatory resources in Europe to deliver globally competitive performance by the pharmaceutical industry and the EU regulators ("Regulation 2000"). Following brainstorming and a variety of surveys this paper is expected to be built up towards industry consensus (EFPIA policy 1999) which would then be promoted for implementation until 2001, and a "one-stop-service" will be requested from EU regulators.

Looking towards the future EMEA Executive Director, F. Sauer pointed out that it is about time to prepare for a re-design of the EU-procedures and thus to consolidate the success acclaimed currently. Mutual Recognition can be guided into decentralised networking which may be able to profit from the "ex-concertation procedure" experience. This can only be achieved by partnership between all national competent agencies concerned and the EMEA and the European Commission. The centralised procedure would certainly benefit from further streamlining including the decision making process thus facilitating consistent scientific input starting with scientific advice and measured for performance throughout.

Mutual Recognition

The afternoon session addressed the performance of the mutual recognition procedure. The improvements since 1997 presented by the two latest Mutual Recognition Facilitation Group (MRFG) Chairpersons (Dr. C. Wirthumer-Hoche and Dr. D. Jefferys) included a falling number of withdrawals and break-out sessions, an increase in visibility and transparency with the launch of the Heads of Agenciesí web site, the MRFG press releases, and the soon to be published Product Index.

The impact of the automatic validation procedure has recently been evaluated by an EFPIA study of users of the mutual recognition procedure. Results of this survey were encouraging, pointing to an 82% positive verdict on this new procedure.

The lack of formalised duties and responsibilities and the proper financing for the MRFG were stressed as operational problems. These did not however impede the functioning of the procedure, which was facilitated by common efforts from Member States. It was also pointed out that Member States find it financially difficult to send experts to participate in breakout sessions.

The EMEA Management Board Chairman and the EFPIA Director General, B. Ager concluded the day by welcoming the fruitful discussions, and stressing the need for industry and authorities to go on working constructively, to achieve the best world class registration system.

For further information please contact:

EFPIA, Mr. Brian Ager
Tel: +32-2-626-2540
Fax: +32-2-626-2566

EMEA, Prof. Rolf Bass
Tel: +44-171-418 8411
Fax: +44-171-418 8551

3. EFPIA INFO DAY REPORT

WELCOME AND OPENING REMARKS

Mr. Strachan HEPPELL
Chairman of the Management Board
European Agency for the Evaluation of Medicinal Products (EMEA)

Mr. Heppell welcomed participants and expressed satisfaction with the very good attendance. He stressed three important elements concerning regulatory relationships. First, he stressed the need to be realistic about what regulators can do. Secondly, he highlighted the fact that it is essential there is no “regulatory capture” : regulators have to be fully independent. Finally, he recommended an open dialogue among regulators and pharmaceutical industry, and stressed the importance of sharing views on and debating current and future regulatory issues.

Mr. Brian AGER
Director General
European Federation of Pharmaceutical Industries and Associations (EFPIA)

Mr. Ager welcomed participants, and thanked Mr. Heppell, Mr. Sauer and Professor Alexandre for their personal support for this annual event. He stressed the need to optimise performance on all sides : CPMP, EMEA, Commission, Member States and companies. All these partners share the same goal : to have in Europe the best regulatory system in terms of public health, in supporting innovation, and in delivery to patients. He informed participants that the day would be divided into two parts : centralised and decentralised, looking at what has been accomplished since the previous year's EFPIA info day, and then discussing how we can further improve the performance of the European registration system. The key features would be performance indicators for the centralised procedure, an important joint initiative which demonstrated industry's continued support for the EMEA and for the centralised procedure as well as its commitment to their continuing success and high performance. Next, the results of the EFPIA's survey on the mutual recognition procedure, and especially on the automatic validation process, would be presented. Both EFPIA and Mutual Recognition Facilitation Group (MRFG) were working actively together to identify the areas to be ameliorated, and a joint survey would begin soon. Finally, Mr. Ager explained that unfortunately, due to last-minute emergencies, some participants were unable to attend, and in particular the Commission representatives who were working on the Bangemann Round Table.

MORNING SESSION
THE CENTRALISED PROCEDURE

PERFORMANCE SINCE THE 1997 EFPIA INFO DAY

CHAIRPERSON'S INTRODUCTION

Dr. Yves JUILLET
Director of the Public and Pharmaceutical Affairs
Hoechst Marion Roussel, France

Dr. Juillet remarked that since the previous EFPIA Info-day, regulators and industry people had gained a lot of experience in the use of the centralised procedure. He presented the aims of the session, which were to show how the performance activities had given some results and, as a consequence, had inspired the prospective activities. Participants would also examine the results of joint workshops between the EMEA and EFPIA where different issues had been addressed : validation-pre-submission, scientific advice, from opinion to decision, and variations. First, he noted the changes that had happened at the EMEA since 1995, and especially the increase in administrative activities. Secondly, he described developments at the CPMP, including a consensus reached at the start of 1995, growing recourse to votes and ever more withdrawals. The session would enable participants to give some explanations regarding these new facts. Dr. Juillet also identified the increasing EMEA and CPMP workload, with a number of new active substances submitted, but also a lot of line extensions, a lot of variations, and ever more pharmacovigilance cases.

THE CHALLENGES OF THE CENTRALISED PROCEDURE : EVOLUTION OR REVOLUTION ?

Professor Jean-Michel ALEXANDRE
Chairman of the Committee for Proprietary Medicinal Products (CPMP)

Professor Alexandre highlighted the objective of an efficient European registration system. Europe is the biggest market in the world, health, employment, investment, research, clinical development and contributions to the public health. He outlined two possible ways to achieve this objective : the first, as proposed by Regulation 2000, is to set up purely centralised system. The second is to function on a network-based system, using national resources and expertise. This network should be free of national constraints and hindrances. Professor Alexandre gave some personal views on the mutual recognition procedure. He considered that mutual recognition is a principle which has never been implemented. The two main obstacles are that marketing authorisations are not granted on the same basis from one Member State to the next because regulations and guidelines are interpreted in a variety of ways, and that there is competition among Member States. Professor Alexandre considered that a decentralised system is necessary and that the only way to achieve it is to work together. The Member States' differences should not be obstacles but a source of wealth and efficiency. Professor Alexandre congratulated the MRFG for the work already done and noted an increase in mutual trust and respect.

Concerning the centralised procedure, Professor Alexandre informed participants that CPMP had issued 76 positive opinions and given about 80 recommendations in the form of scientific advice. Recently, two negative opinions had been adopted, and there had been more and more withdrawals. The reasons for these negative opinions or withdrawals are : bad candidates for marketing authorisation, poor development, or premature dossiers. There is also the possibility that the CPMP is gradually becoming more severe, especially regarding the need for a clear therapeutic benefit. EPARs should include in their conclusions the clinical interest/benefit of the approved medicinal products, i.e. the demonstration of pharmacodynamic effects is not sufficient. The place of the new medicinal product in the existing therapeutic arsenal and its interest for patient, should also be taken into account.

Professor Alexandre then summarised the contents of the November 1998 CPMP meetings (see 24 November 1998 CPMP press release). He stressed that CPMP is efficient, deadlines are respected and that the key to success is to have the possibility to work together. Participants should know that a CPMP opinion reflects the contribution of all CPMP members and may be different from the initial rapporteur and co-rapporteur assessments. Moreover, the CPMP's work-

load had drastically changed over the last year. In 1997, there had been four to six delegations which had intervened frequently. Now, all delegations are highly actively contributing to the discussion. Furthermore, the system is more and more open to outside experts, which are invited to contribute to the CPMP activities.

Professor Alexandre concluded that the future system can be based partly on what exists today. He believed that, with respect to the scientific assessment, the CPMP should obtain a better balance of competence (i.e. : currently only one toxicologist, no specialist in pharmacovigilance, no methodologist, no epidemiologist, no statisticians, etc.). Bureaucratic assessment must be avoided. The CPMP should work in such a way as to stay abreast of the best clinical practice.

JOINT EFPIA - EMEA SURVEY : CONCRETE IMPROVEMENTS IN THE RESULTS

Dr. Patrick LE COURTOIS
Head of Sector "New chemical substances"
European Agency for the Evaluation of Medicinal Products (EMEA)

Dr. James RITCHIE
Director of Pre-clinical and Regulatory Strategy
SmithKline Beecham

Dr. Le Courtois and Dr. Ritchie together presented the results of the joint EFPIA - EMEA survey on the centralised procedure (see attached slides). This third phase covered the marketing authorisations granted between mid-October 1997 and mid-October 1998, and did not include withdrawals.

First, Dr. Le Courtois informed participants about the responses from rapporteurs, co-rapporteurs and EMEA project managers. Overall, the 1998 results had shown a high level of satisfaction (over 70% or 80%), but there had been a slight increase of dissatisfaction compared to the 1997 results. This had concerned the quality of the initial dossier, the expert's reports, the applicants' responses, as well as the communication among all partners and the general consistency. The time of submission of initial assessment reports had substantially improved since 1997. About half of delegates had commented on the assessment reports, generally in good time, and those comments had largely been considered relevant. The average time for clock stop had been 169 days for part A products, and 103 days for part B products. This had shown a similar time for part A products, and a double time for part B products. Concerning the quality of the translations provided to the EMEA by the applicants, the 1998 results were more balanced than the 1997 ones.

Next, Dr. Ritchie presented the EFPIA results, which represented 13 out 26 procedures. He therefore stressed the need to be cautious with interpretation of the corresponding statistics. Dr. Ritchie highlighted the main outcomes of the survey : the pre-submission phase (in which there remained some administrative issues), the quality of the assessment report (with a high level of satisfaction for the rapporteur's report, but still some concerns on the clarity of the issues raised), an overall satisfaction on the oral explanation, translations improved and a high level of satisfaction with the final EPARs. Overall, companies were satisfied with the procedure, but less so than with the 1997 results. Finally, Dr. Ritchie concluded by stressing that overall timelines were well respected by all parties and there were many areas with high level of satisfaction. However, some companies complained about the availability of specialised expertise in relevant scientific areas and about the burden of administrative issues. Dr. Ritchie invited pharmaceutical companies' attendees to improve their participation in the survey to allow valid interpretation of the results.

Finally, Dr. Le Courtois presented the general conclusions, explaining the actions taken on key issues identified in 1997. He recommended that applicants continue to seek scientific advice, and underlined the need for interaction between all partners. He indicated that the next phase of the survey would include negative opinions and withdrawals.

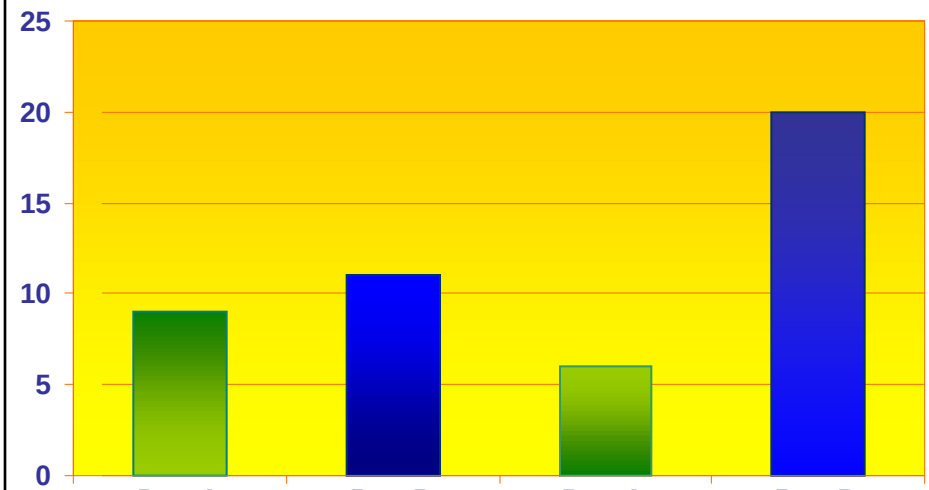
Joint EMEA/EFPIA Survey on Performance Indicators 1998

Patrick Le Courtois - EMEA

Analysis of the Responses from EMEA, CPMP and Applicants

- Criteria of Inclusion: Completed centralised procedures (Commission Decision) since last phase of the Survey covering a time period between: 18 Jun. 1996 - 17 Oct. 1998
- Number of Centralised Procedures included: 26
- Date of receipt of the last response: 10 Nov. 1998
- Number of responses received from:
  - EMEA-Project Mgrs.: 26
  - Rapporteurs: 19
  - Co-rapporteurs: 13
  - Applicants: 13

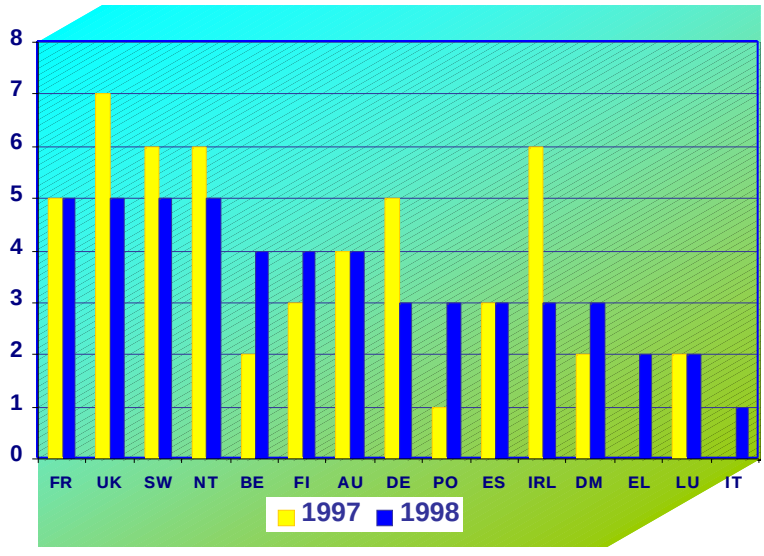
Authorised Part A and Part B Products enrolled in the Survey



26 Procedures

EFPIA Infoday 20 November 1998

Delegation acting as (Co-)Rapporteur for enrolled procedures



26 Procedures

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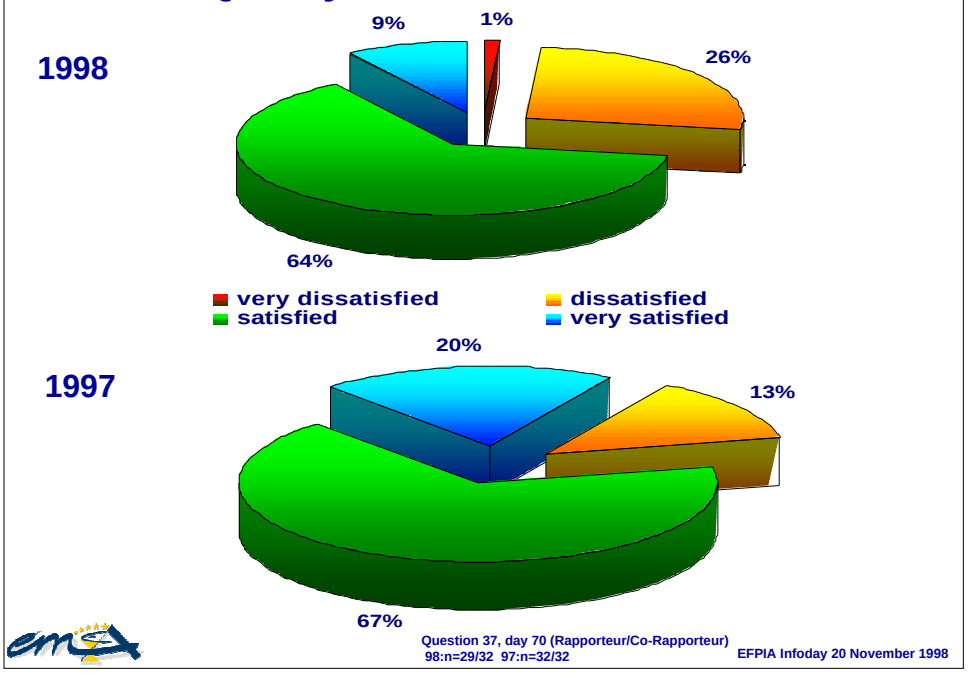
Quality of the Initial Dossier



Question 37, day 70 (Rapporteur/Co-Rapporteur)
98:n=29/32 97:n=32/32

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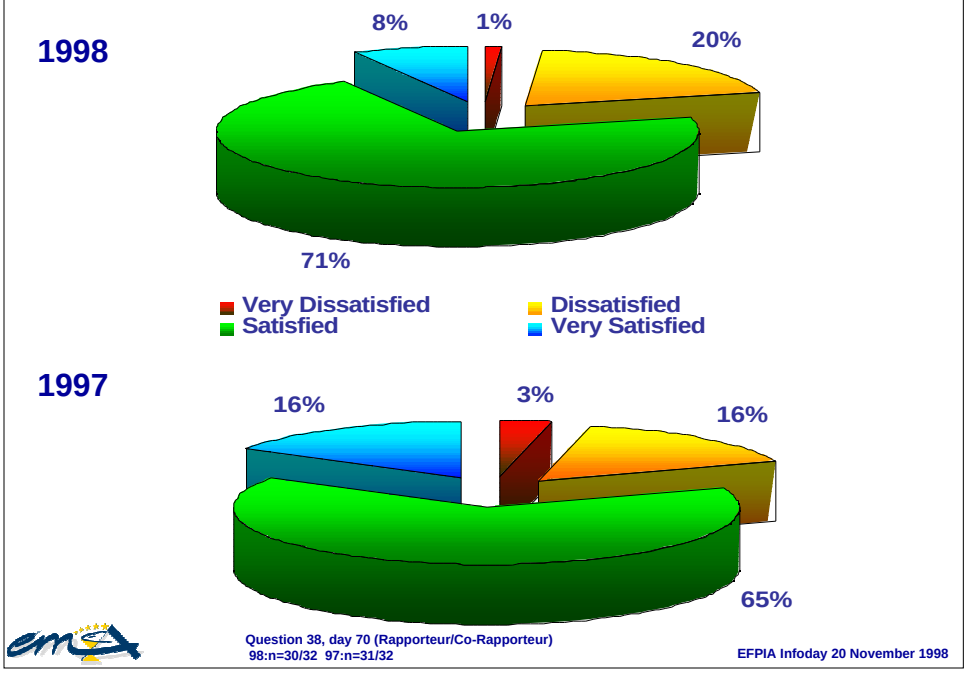
Quality of the Applicant's Expert Reports



Question 38, day 70 (Rapporteur/Co-Rapporteur)
98:n=30/32 97:n=31/32

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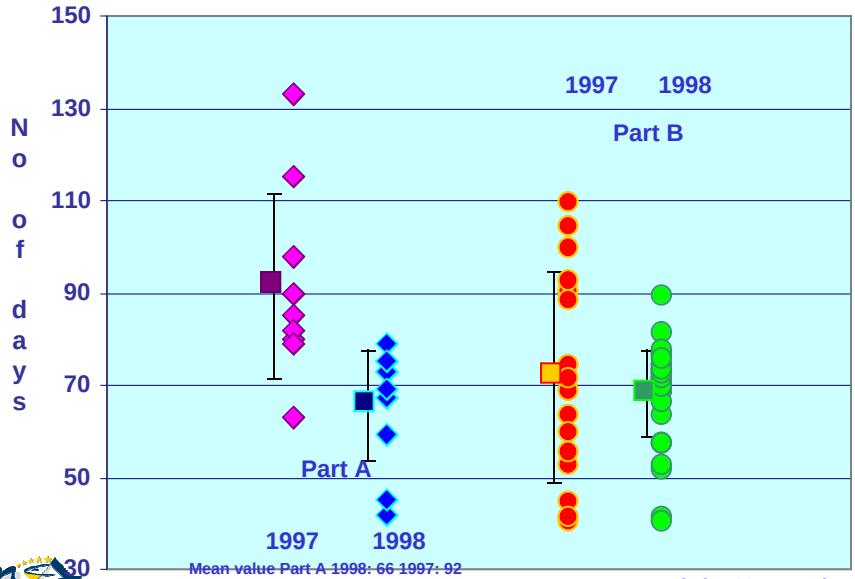
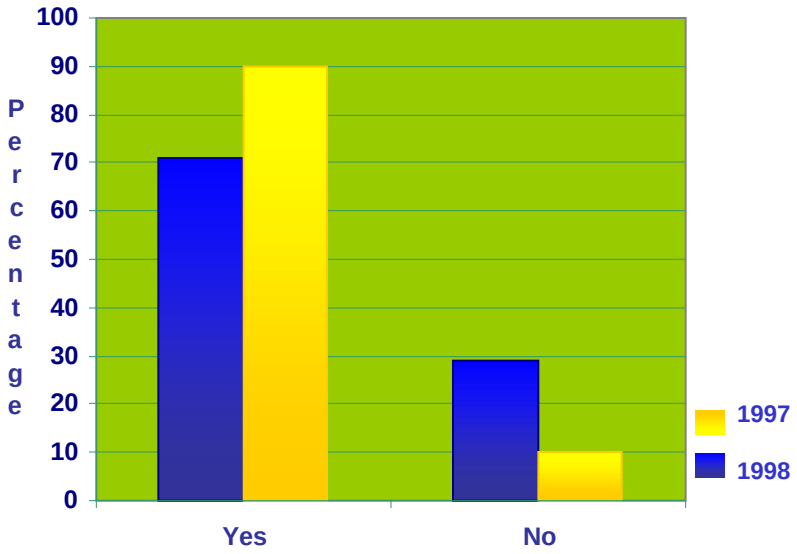
Time of Submission of Initial Assessment Report



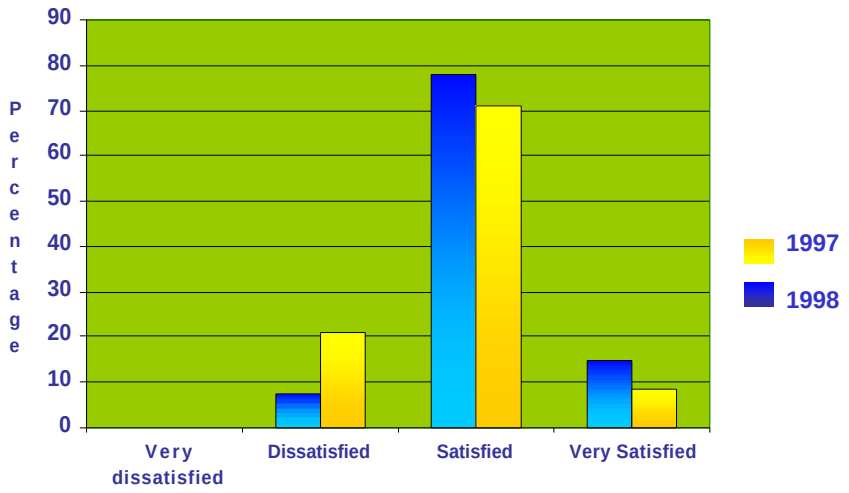
Mean value Part A 1998: 66 1997: 92
Mean value Part B 1998: 69 1997: 72

Punctuality of CPMP Members' Comments



Question 40, Day 170 (Project Manager)
1997: n=20/26 1998: n=24/26

Relevance of CPMP Members' Comments on the Assessment Report



Question 42 (Rapporteur/Co-Rapporteur)
1997: n=32 1998:n=27/32

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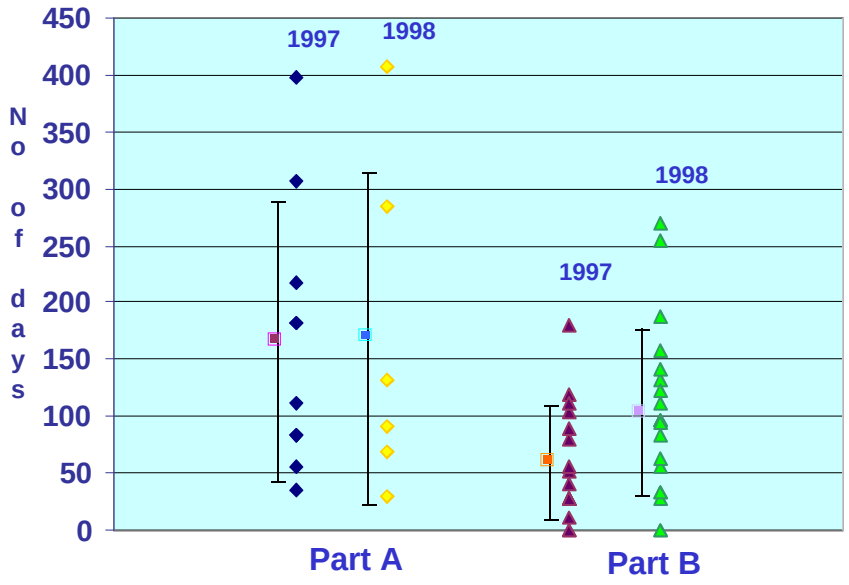
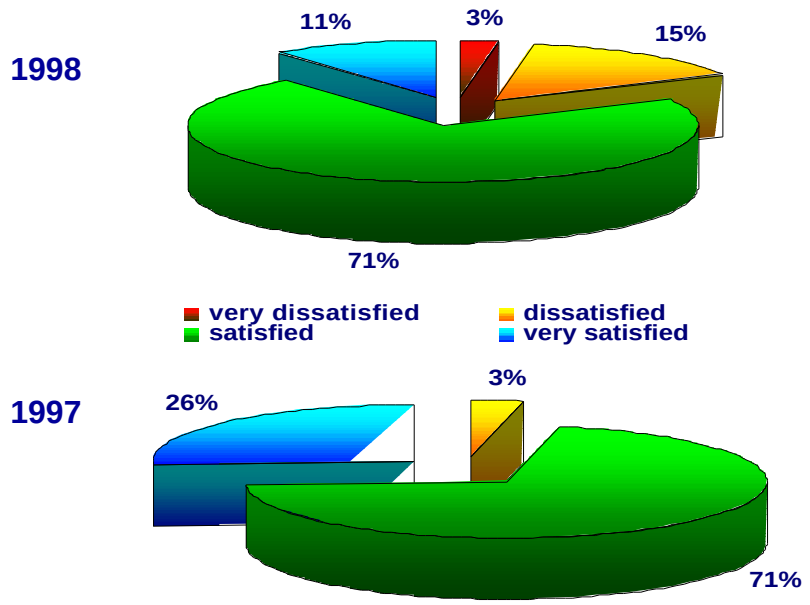
Clock Stop



Mean Value for Part A: 1997 (166) 1998 (169)
Mean Value for Part B: 1997 (56) 1998 (103)

EFPIA Infoday 20 November 1998

Quality of the Applicant's Written Responses



Question 53, day 121 (Rapporteur/Co-Rapporteur)
98:n=31/32 97:n=31/32

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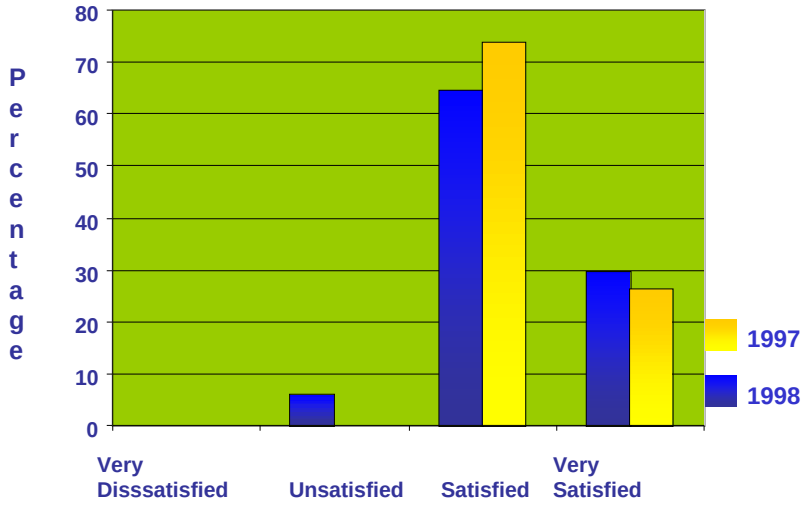
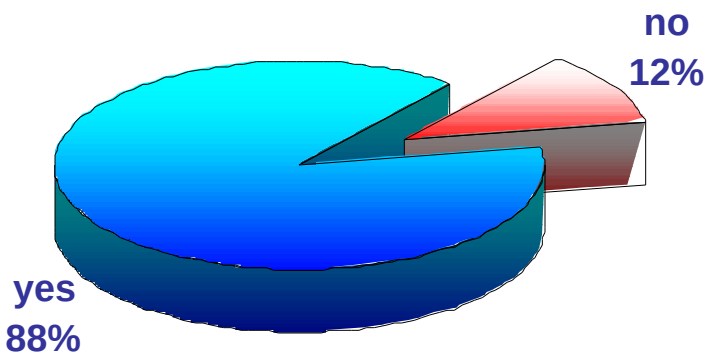
Quality of the Applicant's Responses during the Oral Explanation



Question 71, Day 181 (Rapporteur/Co-rapporteur)
1998: n=17/32 1997: n=11/24

EFPIA Infoday 20 November 1998

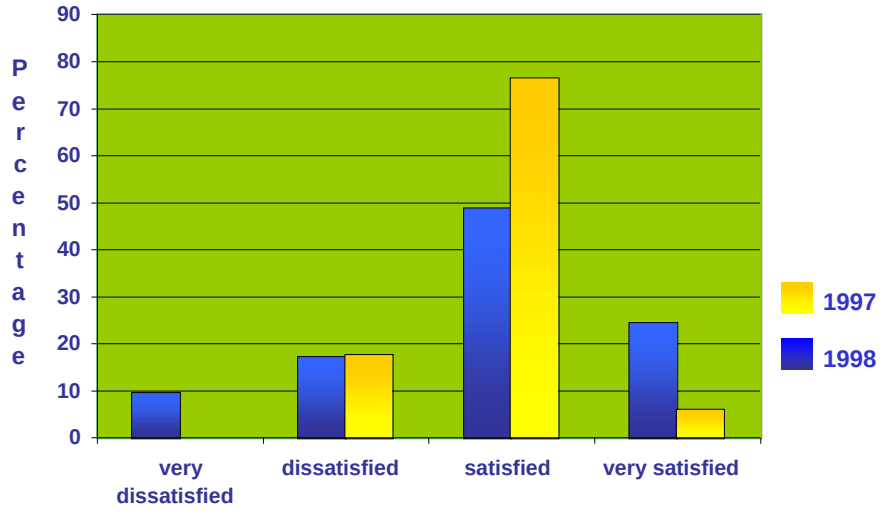
Usefulness of the Oral Explanation



Question 72, Day 181
(Rapporteur/Co-rapporteur)
n=11/24

EFPIA Infoday 20 November 1998

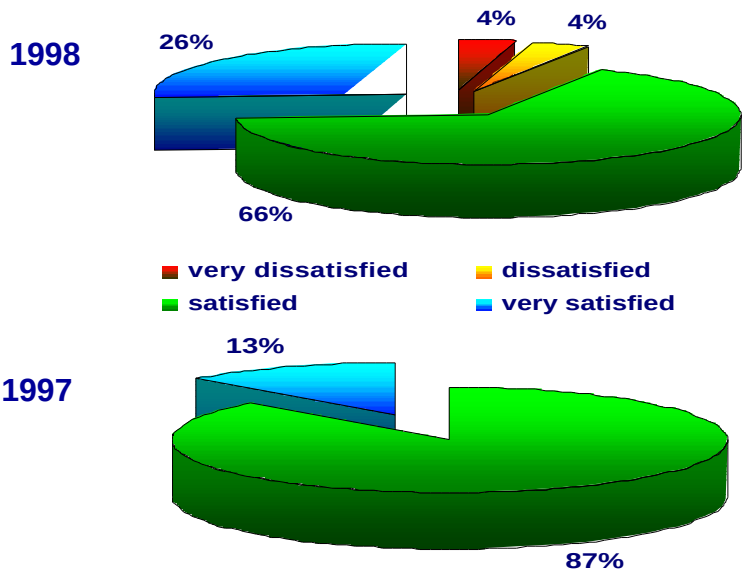
Quality of the Translations provided by the Applicant at Day 195



Question 77, Day 195 (Project Manager)
1997: n=17/24 1998: n=21/26

EFPIA Infoday 20 November 1998

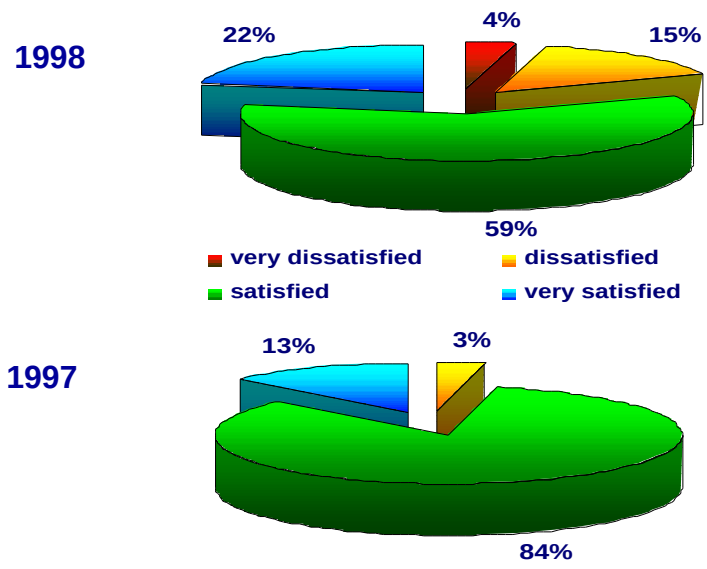
Communication between all partners: EMEA, CPMP, Applicant



Question 93, (Rapporteur/Co-Rapporteur)
98:n=27/32 97:n=31/32

EFPIA Infoday 20 November 1998

General Consistency: Dossier Assessment, Issues raised, Responses given



Question 92, (Rapporteur/Co-Rapporteur)
98:n=27/32 97:n=31/32

EFPIA Infoday 20 November 1998

Pre-submission

- 2/13 (15%) sought scientific advice from CPMP; 7/13 (54%) sought scientific advice from national authorities
- choice of rapporteur - 23% dissatisfied (5% in 1997)
- pre-submission meetings:
  - mostly satisfied, dissatisfaction generally related to clarity on administrative issues
- EMEA requests for further information in 7/13 cases (admin 6/13, Quality 3/13, Preclin 1/13, Clinical 3/13)
- problems during validation in 3/13 cases (minor admin)

Joint EMEA/EFPIA Survey: EFPIA Data

Assessment Report

- high level of satisfaction with quality of rapporteurs assessment report (Q 1/13, S 0/13, E 1/13 dissatisfied)
- lesser level of satisfaction with quality of co-rapporteurs assessment report (Q 2/13, S 4/13, E 3/13 dissatisfied)
- some concern over clarity of issues raised in assessment report (3/13 dissatisfied)
- concern also over clarity of issues raised in assessment report on responses (3/13 dissatisfied)

Joint EMEA/EFPIA Survey: EFPIA Data

Consolidated List of Questions

- only 1/13 were formally dissatisfied with clarity but 4 comments indicated potential for improvement
- overall conclusion indicated approvable (6/13), non-approvable (5/13) or no indication (2/13) [note 5 non-approvable were all eventually approved]
- if product was approvable questions in Q (5/13), preclin (4/13), clin safety (6/13), efficacy (4/13)
- if product was non-approvable questions in Q (3/13), clin safety (2/13), efficacy (4/13)

Joint EMEA/EFPIA Survey: EFPIA Data

Oral Explanation

- requested on 8/13 occasions - requested by applicant or, applicant on advice of rapporteur (5/8), or by CPMP (3/8)
- related to preclin (1/8), clin safety (3/8) or efficacy (4/8)
- preparatory meeting held with rapporteur, co-rapporteur and project manager in 7/8 cases - considered very useful in 4/8 cases but not satisfactory in 3/8 cases
- quality of oral explanation in relation to both scientific discussion and facilities etc.: satisfied 5/8, dissatisfied 2/8
- issues resolved during oral explanation? Yes 4/8, No 2/8, and was the oral explanation useful? Yes 5/8, No 1/8

Joint EMEA/EFPIA Survey: EFPIA Data

Translations and Final EPAR

- receipt of last comments on translations from CPMP members:
  - in time? Yes 1/13, No 6/13
  - if delay, how many days? 2-19 days
  - no. of delegations sending comments? 5-12
  - relevance of comments? 4/13 not satisfied, 3/13 satisfied

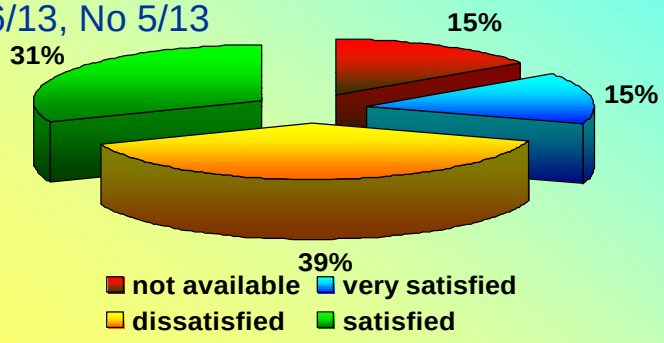
- satisfied with final EPAR on:
  - objectivity? Yes 10/13, No 0/13
  - clarity and legibility? Yes 7/13, No 0/13
  - level of data protection? Yes 11/13, No 0/13

Joint EMEA/EFPIA Survey: EFPIA Data

Overview of the Procedure

- satisfied with transparency, dialogue and advice from:
  - EMEA? Yes 9/13, No 2/13
  - rapporteurs/co-rapporteurs? Yes 9/13, No 3/13

- overall satisfaction with the procedure?
- Yes 6/13, No 5/13



Joint EMEA/EFPIA Survey: EFPIA Data

Overall Conclusions

- Overall timelines were well respected by all parties
- some concern over availability of specialised expertise in relevant scientific areas (particularly for co-rapporteurs)
- Administrative issues still an issue (e.g. additional admin data, mockups to be submitted at the beginning of the procedure, translation issues etc.
- Many areas with high level of satisfaction (e.g. quality of rapporteurs assessment report, oral explanation, EPARs)
- Low level of response from industry must be improved to allow valid interpretation of survey data

Joint EMEA/EFPIA Survey: EFPIA Data

CONCLUSION

Actions taken on key issues identified in 1997 (I):

- Scientific advice
  - improvement of procedure
  - more support by CPMP and additional resources
- Presubmission meetings
  - Increase of opportunities of meetings
  - Streamlined organisation
  - Pre-submission meeting request form, guidance document for users

Actions taken on key issues identified in 1997 (II):

- Good quality of public documents and translations from the start
  - Implementation of PIQ
  - Checking of documents and improved activities of QRD
  - Updated templates, convention, QRD terminology
- EMEA/ EFPIA Workshops on
  - Presubmission
  - Validation
  - Translations
  - Variations

MAIN RESULTS OF THE SURVEY 1998

Development of issues identified in 1997:

- More criticism concerning the quality of the initial dossier
- Oral explanation more useful
- Improvement in the overall quality of the translations

New issues identified in 1998:

- More outstanding objections in 1998 increase in the number of hearings
- Answers from both rapporteurs/co-rapporteurs and project managers more critical this year
  - more difficult issues coming to EMEA
  - initial dossier less satisfactory?
  - premature applications (more withdrawals)
  - CPMP members more demanding ?

Way forward

- Applicants to continue to seek scientific advice and to accept guidance at an early stage of the development to avoid later problems
- EMEA to continue to help applicants to improve quality of documents and translations
- Continue interaction between applicants, EMEA and CPMP before submission and throughout the procedure, especially for applicants choosing for the first time the centralised procedure

Further Steps

- Revised Version of the Questionnaire focussing on major steps of the survey and including negative opinions and withdrawals
- No electronic version available
- Explore reasons for problematic issues detected (in workshops or other ways?)

EFPIA - EMEA INTERACTIONS : VALIDATION / PRE-SUBMISSION, FROM OPINION TO DECISION, SCIENTIFIC ADVICE

Professor Rolf BASS
Head of Unit for the Evaluation of Medicinal Products for Human Use
European Agency for the Evaluation of Medicinal Products (EMEA)

Dr. David LYONS
Irish member of the Committee for Proprietary Medicinal Products (CPMP)

Dr. Jean-Pierre OSSELAERE
Managing Director
Schering-Plough Europe

Dr. Osselaere introduced the subject by briefly presenting the goal and the outcomes of the joint EFPIA/EMEA workshops held on different topics.

Next, Professor Bass gave an overview of the main meetings held in 1998 between the EMEA and EFPIA on numerous topics : workshops on validation, pre-submission, from opinion to decision, scientific advice, patient information quality/ quality review of documents (PIQ/QRD), variations, pharmacovigilance and regular contacts on the centralised procedure survey. He detailed the recent EMEA pre-submission guidance, which includes the answers to questions frequently asked to the EMEA. He also presented the EMEA pre-submission meeting request form. Better use of scientific advice by the industry could contribute to reduce the number of applications withdrawn from the centralised procedure.

Dr. Lyons highlighted the substantial recent increase in the applications which had not obtained a CPMP positive opinion. He distinguished two types of premature applications. In the first, an applicant announced the submission of a dossier for a specific date, but for whatever reason was not able to provide the designated rapporteur and co-rapporteur with this dossier at the agreed date. Such behaviour impeded good planning. In the second, the dossier was submitted in good time, but presented a temporary analysis, which represented only a part of the final analysis, and therefore was not approvable. In the first case, the CPMP can do nothing. In the second, deadlines for applicants' responses were 6 months. If the applicant was not able to respond in time, the dossier had to be withdrawn. Dr. Lyons recommended making greater use of the scientific advice procedure to prevent such issues. He also advised companies which are using the centralised procedure for the very first time to get advice from the EMEA and EFPIA for practical concerns and calendar for submission.

Dr. Osselaere welcomed the EMEA pre-submission guidance, underlining the need for it to be fully consistent with the legislation and suggesting that it be made a part of the Notice to Applicants. He informed participants that the new EMEA templates were now frozen, and welcomed the QRD convention and decisions on stylistic matters and on the use of terms. Concerning the phase from opinion to decision, he recommended that participants take special care in drafting the product information document. He also stressed that pharmaceutical companies are satisfied with the EPARs and that the CPMP would like them to better reflect the CPMP discussions and the reasons for approval. He explained the need for industry to obtain a quick scientific advice, and mentioned the increasing number of “follow-up” advice and consultation of various CPMP and EMEA working parties and expert groups.

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

EMEA/EFPIA INTERACTIONS 1998

Rolf Bass
EMEA London

EFPIA Info Day
20 November 1998

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

EMEA/EFPIA MEETINGS HELD IN 1998 IN RELATION TO PROCESS IMPROVEMENT

- **Workshop 3 March 1998**
  - **Validation**
  - **Pre-submission**
  - **Opinion/Decision**
  - **Scientific Advice**

  ⟹ **draft Pre-Submission Meeting Guidance/Request Form**

- **Workshop 3 July 1998**
  - Opinion/Decision
  - PIQ/QRD
    - ⇒ Handling of templates
    - ⇒ Reduction of administrative work

- **Workshop 22 September 1998**
  - Variation
    - ⇒ More and better interaction

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- **Technical discussion PhV 12 May 98**

  ⇒ Notice to MAH
  (future Volume IX)

- **EMEA/EFPIA Questionnaire**
  - 28/4/98 agreement on changes
  - 28/10/98 preparation for review panel
  - 16/11/98 review panel

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Human Medicines Evaluation Unit

EMEA Pre-submission Guidance

- **Answer to frequently asked questions.**
- **Emea position on issues adressed at PSM.**

PSM ↓ ! IMPORTANCE !

☛ **PSM focus on more complex issues related to a specific application.**

☛ **Applications meeting all requirements and ready for validation.**

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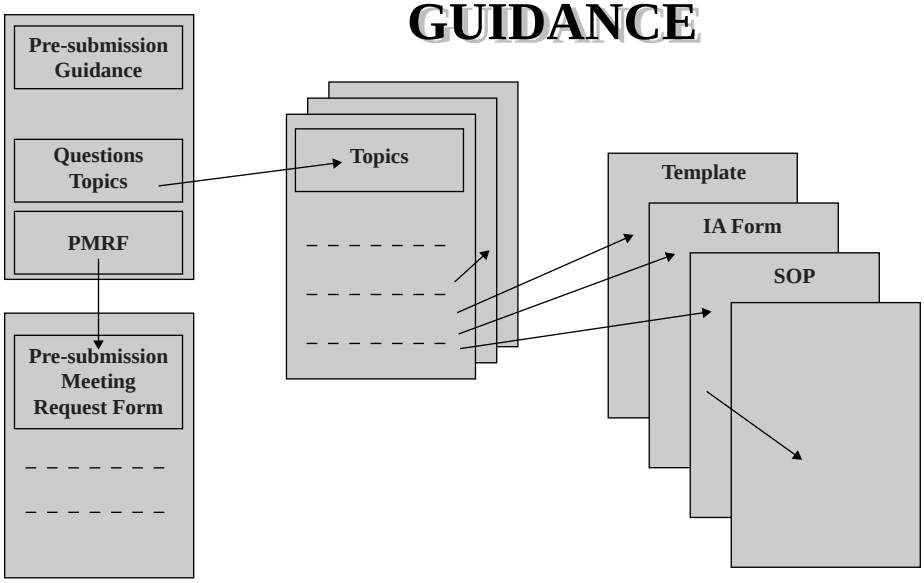
PRE-SUBMISSION GUIDANCE



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EMEA Pre-submission Meeting Request Form

- List topics addressed in the EMEA Guidance document

- To obtain further clarification on a certain topic during a Pre-Submission Meeting, complete the form as follows:

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Human Medicines Evaluation Unit

EMEA Pre-submission Meeting Request Form

- ♣ **tick the topic** concerned
- ♣ **describe** which aspect of this topic you would like to be addressed by the EMEA during the Pre-Submission Meeting
- ♣ complement your question(s) with **useful background information**

→ **Return Request Form to EMEA**

EMEA Pre-submission Guidance - Topics (examples)

- How and when shall I apply for Part B status?
- How will I know if the proposed (trade) name of my medicinal product is acceptable from a public health point of view?
- When and how are Rapporteur and Co-Rapporteur appointed?
- What fee do I have to pay and how is the fee calculated?

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EMEA Pre-submission Guidance

- When shall I submit mock-ups and/or specimens?
- Do I have to submit samples together with my application?
- What batch release arrangements in the EEA are required for my medicinal product?
- How shall I submit an European Drug Master File (EDMF)?

EMEA Pre-submission Guidance

- How, when and to whom shall I submit my dossier? (dates of CPMP meetings, adresses)
- How shall my application be evaluated (timetable)?
- When can I expect a pre-approval GMP inspection and how are they conducted?
- How is a Pre-Submission Meeting conducted at the EMEA?

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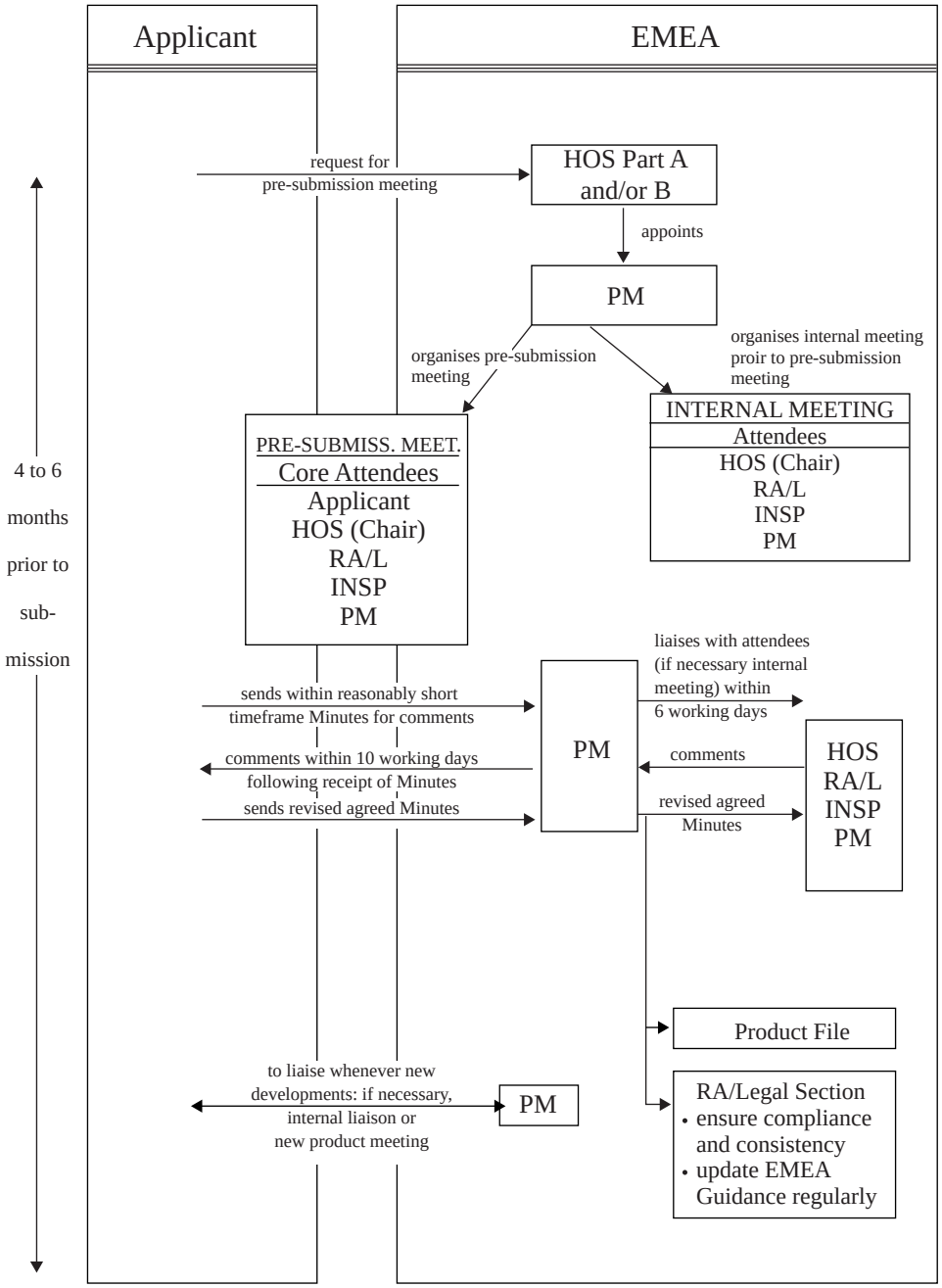
EMEA PRE-SUBMISSION FLOW-CHART



HOS= Head of Sector
PM= Project Manager
RA/L= Regulatory Affairs/Legal Section Representative
INSP= Inspections Sector Representative

EFPIA/EMEA INTERACTIONS

- **WORKSHOPS HELD ON DIFFERENT TOPICS**

  - **GOAL: IMPROVEMENT OF THE EMEA/CPMP PROCEDURES WITHIN THE CURRENT REGULATORY FRAMEWORK**

  - **OUTCOME: CLARIFICATION OF DIFFERENT STEPS AND AGREEMENT ON POSSIBLE IMPROVEMENTS**

  - **RESULTS SHOULD BE PROMPTLY MADE PUBLIC (PAPER VERSION AND INTERNET)**

EFPIA/EMEA INTERACTIONS

- **VALIDATION/PRE-SUBMISSION:**

  - **PRE-SUBMISSION GUIDANCE DOCUMENT**

    - **DOCUMENT WELCOME!**
      - **USER FRIENDLY AND INFORMATIVE**
    - **SHOULD BE MADE PART OF THE "NOTICE TO APPLICANT" (ELECTRONIC VERSION?)**
    - **SHOULD BE FULLY CONSISTENT WITH THE EXISTING LEGISLATION**

EFPIA/EMEA INTERACTIONS

- **VALIDATION/PRE-SUBMISSION:**

  - TEMPLATES FOR SmPC, LABELLING AND PACKAGE LEAFLET

  - **NEW VERSION IS "FROZEN" FOR NEW APPLICATIONS (FROM SUBMISSION TO APPROVAL)**

EFPIA/EMEA INTERACTIONS

- **VALIDATION/PRE-SUBMISSION:**

  - TEMPLATES FOR SmPC, LABELLING AND PACKAGE LEAFLET

  - TO BE PUBLISHED (INCLUDING INTERNET):

  - **"USER FRIENDLY" CONVENTION**
  - **PIQ DECISIONS ON STYLISTIC MATTERS**
  - **QRD DECISIONS ON THE USE OF TERMS**

EFPIA/EMEA INTERACTIONS

- **FROM OPINION TO DECISION**

  - PRODUCT INFORMATION DOCUMENTS (SmPC - Labelling - Package Leaflet)

    - **DO IT CORRECTLY FROM THE BEGINNING!**

    - **THE MOST RECENT RESULTS OF THE JOINT EFPIA/EMEA SURVEY INDICATE THET IN 1998 +/- 10% OF THE TRANSLATIONS ARE STILL "SUB-OPTIMAL"**

EFPIA/EMEA INTERACTIONS

- **FROM OPINION TO DECISION**

  - EPARs

    - **NO MAJOR COMMENTS FROM INDUSTRY**

    - **THE CPMP CONSIDERS THAT THE CONTENT OF THESE DOCUMENTS COULD BE IMPROVED AND BETTER REFLECT THE FINAL DISCUSSIONS AT CPMP AND THE EXACT REASONS FOR APPROVAL**

EFPIA/EMEA INTERACTIONS

- **SCIENTIFIC ADVICE**

  - **THE INDUSTRY WANTS TO COMPLETE THE PROCEDURE IN 60 DAYS**

  - **THE NEW CPMP AGENDA (ADVICES ON MONDAY) COULD MAKE IT FEASIBLE BY THE COMPANY) COULD BE ADOPTED THE SAME WEEK**

EFPIA/EMEA INTERACTIONS

- **SCIENTIFIC ADVICE**

  - **RECENT STATISTICS INDICATE**

    - **AN INCREASING NUMBER OF"FOLLOW-UP ADVICES" - THIS COULD CONTRIBUTE TO DECREASE "THE FAILURES" IN THE CENTRALISED PROCEDURES (WITHDRAWALS AND NEGATIVE OPINIONS)**

    - **AN INCREASING NUMBER OF CONSULTATION OF WORKING PARTIES AND EXPERT GROUPS**

Panel discussion : assessment of the year three

All speakers and

Mrs. Françoise De Cremiers
Director, Registration Advice, Europe - Worldwide Regulatory Affairs
Wyeth Lederle

First, Mrs. De Cremiers gave some views on the interactive work among industry and regulators. She noted that a lot of guidances had already been achieved and some needed to be further developed, such as the scientific advice procedure. She suggested closer interactions based on an ICH type model with an early involvement of pharmaceutical companies. She also proposed that the centralised procedure application format be improved, as well as the current CPMP press release format. Finally, she considered that it would be useful to arrange a joint EFPIA/EMEA workshop on EPARs.

Mr. Sauer remarked that the statistics given, the comparative data 1997-1998, and the suggestions made during this first session, should all be published.

Dr. Juillet asked why the situation was different from the 1997 EFPIA Info-day one, where all the actors of the centralised procedure had expressed a high level of satisfaction. He wished to know whether anything had really changed at the CPMP level.

Professor Alexandre replied that, sometimes, the products developed had not been the best candidates for putting on the market. Secondly, certain developments had not been well fulfilled in their design and this showed the need for scientific consultation with the various national agencies and also the CPMP. However, he felt sometimes that advice had been requested only to “bless” the projects rather than to ameliorate them. The following reason was the various requirements on this side of the Atlantic compared to the other side. The CPMP had got the impression that many companies have their eyes on the American system. They had wanted to take the FDA criteria but the CPMP had been more strict. The CPMP had wanted to know what the therapeutic advantages were. The situation had therefore changed fundamentally in the last two years and should be analysed.

Dr. Lyons remarked that according to his experience before the new registration system, dossiers submitted nationally at the beginning of the 90s had been better. Around 1996, there had been a decrease of the quality of the dossiers. Another element was that the system was more transparent. Nobody had been aware of the applications withdrawn very early, with the exception of the companies involved and the CPMP members. The apparent increase in withdrawals could also be the result of a wider publication.

Dr. Lyons was asked whether he had experienced re-submission of dossiers after withdrawals. He replied positively and considered that to withdraw and then ask for scientific advice for completing the dossier before submitting the application again was a good way to solve the issue of premature applications. In the event of deeper problems, some companies had been permitted to explain their views and to discuss scientific points with the CPMP, but generally companies in these cases had been in a dead end.

CONCRETE PROPOSALS FOR IMPROVING THE PROCESS

CHAIRPERSON'S INTRODUCTION

Mr. Fernand SAUER
Executive Director
European Agency for the Evaluation of Medicinal Products (EMEA)

Mr. Sauer expressed his satisfaction at again participating in the EFPIA Info day and introduced the session. He asked how the process could be improved within the current regulatory framework and about further changing the regulatory framework. First, he considered that the 1998 results of the EFPIA/EMEA survey on the centralised procedure were more realistic than the 1997 ones, and he thanked all the participants for this exercise. He underlined that this analysis was primarily in the interest of companies, which should fully participate.

Mr. Sauer detailed the EMEA's focus on improvements, and especially in the following fields : needs and workload of the EU approval system, pharmacovigilance, transparency, costs of the EMEA linked to its performance, scientific advice, support for the mutual recognition procedure, and the IT tools. He noted the satisfaction of pharmaceutical industry with the EPARs.

Between now and the change in the registration system, he advised working for a better forum among the EMEA and the national agencies. He considered that, even though the changes would occur only in a couple of years, initiatives such as “Regulation 2000” were good thing. The MINE initiative had also to be considered.

Next, Mr. Sauer presented the EU legislative agenda for the coming years.

Finally, Mr. Sauer set out what would happen under the review of the EU approval system. He acknowledged the contribution from industry, and said he was waiting for a refined proposal before discussing with regulators. During 1999, the EU institutions, Member States as well as other partners like consumers, should give their viewpoints. He told participants that the Commission intended to launch an “audit” on the system during 1999. There would be two phases : fact-finding, and then discussion/analysis. A final report should be available at the beginning of 2000. The first issue in the review would be the balance between the central and the decentralised systems. Even though the central system functioned reasonably well, it had to be streamlined. Concerning the decentralised system, opinions were very divided. Mr. Sauer suggested to think about something close to the “ex-concertation” procedure. This would need a lot of discussion. The structure and the role of the committees in the EMEA were changing de facto. Sometimes certain disciplines, or certain specialities, were lacking at the CPMP. He suggested to modify the CPMP membership so that one delegate would represent the regulatory facet of national authorities, and then these CPMP members would agree on how to appoint the other 15 CPMP members, in order to have as wide as possible coverage of all the disciplines. In the future, this would be even more necessary when the EU would encompass 26 Member States. Everybody recognised the need for a better integration of the decision making process, to make it more efficient and quicker, especially after the CPMP opinion. Mr. Sauer proposed to delegate the decision-making directly to the EMEA, unless there were serious objections from the Member State(s) or the Commission in the last round. Mr. Sauer did not think that it would be necessary to change the Treaties. He asked whether the system should provide even more and better product information. He also wondered whether the EU system should extend to other products, e.g. medical devices, or explore other tasks.

EFPIA INFO DAY

20 NOVEMBER 1998

by Fernand SAUER

IMPROVING THE PROCESS

- EMEA'S FOCUS ON IMPROVEMENTS
- PERFORMANCE PROGRAMME AT THE EMEA
- DIALOGUE, OPENNESS AND TRANSPARENCY
- CHALLENGES AHEAD FOR THE EMEA
- THE EU LEGISLATIVE AGENDA
- REVIEW OF THE EU SYSTEM IN 2001

EMEA'S FOCUS ON IMPROVEMENTS

- Re-evaluate needs and workload of EU approval system
- Measure performance and costs of EMEA
- Consolidate on experience by re-designing procedures
- Reinforce pharmacovigilance
- Additional support to mutual recognition
- Improve transparency at all levels
- Strengthen scientific advice to companies
- Optimise management of resources
- Implement an IT platform compatible with EMEA partners

EMEA PERFORMANCE PROGRAMME

- Standard of service:
  Publication of tables,
  Timely publication of EPARs and MRL assessments,
  EFPIA/EMEA questionnaire
- Efficiency and costs:
  free report, costing exercise, ActiTrak
- Improving the quality of the system:
  ATS. QMS, good financial standards, SI2

DIALOGUE, OPENNESS AND TRANSPARENCY AT THE EMEA

- Competence, integrity and neutrality of experts : public declaration of intrests.
- Audit trail of the scientific evaluation process : European public assessment report EPAR.
- Better information for professionals and users : summary of product and pack leaflet published.
- Regular meetings with health professionals, consumers, patients and industry, info-days.
- Consultation on openness, access to documents.

CHALLENGES AHEAD FOR THE EMEA

- Workload & resources: staff, budget, IT
- Forum for partnership with National Agencies
- Globalisation of drug regulation
- More openness and transparency
- “Regulation 2000” : EFPIA, AESGP & FEDESA
- EU review in 2001 and “Mine” initiative
- EEA and Enlargement

THE EU LEGISLATIVE AGENDA

- 1998 (END) : FREE REFORM
- 1999 : ICELAND + NORWAY ; IMPACT OF EURO
- 2000 : NEW EU COMMISSION & PARLIAMENT
- 2001 : ORPHAN DRUGS
- 2002 : CLINICAL TRIALS, STARTING MATERIALS
- 2003 : REVISED EMEA & MUTUAL RECOGN.
- 2004 : 6 ADDITIONAL MEMBER STATES

REVIEW OF THE EU SYSTEM IN 2001

- CONTRIBUTIONS FROM INTERESTED PARTIES
- VISION FROM EU INSTITUTIONS AND STATES
- BALANCE BETWEEN CENTRAL/DECENTRAL
- STREAMLINE CENTRAL PROCEDURE
- FROM DECENTRAL TO “CONCENTRATION” ?
- STRUCTURE & ROLE OF COMMITTEES
- BETTER INTEGRATION OF DECISION MAKING
- MORE AND BETTER PRODUCT INFORMATION
- OTHER PRODUCTS, OTHER TASKS ?

REGULATION 2000 : WHAT IS IT AND WHAT IS IT NOT ?

Mrs. Vaila MARSHALL
Vice-President Regulatory Affairs
Pfizer Central Research

Mrs. Marshall explained that “Regulation 2000” had been a very strategic proposal concerned with a long-term future and was looking to a large extent how regulatory resources should be managed within Europe and also at the necessary transition period. She stressed that this project did not cover access to the market. The key drivers for change were based on the four years' experience of the two procedures which should be simplified, and should take account of the future EU enlargement. Innovation (genomics, drug delivery systems, etc.) and the need for a competitive EU had also to be considered.

The first phase of “Regulation 2000” involving 20 companies had been completed the previous year : in addition, a consultant company had conducted a survey involving all the leading regulators, and then, further to many brainstorming session, a consensus had been reached and the discussion document had been produced. Mrs. Marshall made very clear that this was not EFPIA's final ratified position, but a document aiming to stimulate discussions and proposals. An EFPIA priority action team had been created at the start of the current phase two or “Consensus building” phase to manage that process. This second discussion and debate phase should end in June 1999, with the definition of an EFPIA policy. Finally, phase III would aim to convince all the interested parties.

Mrs. Marshall explained that the “Regulation 2000” vision was to support “a world-class regulatory system...”. This meant best practice, i.e. the best in the world in terms of delivering quality and in terms of timing. This practice should be based on the quality, the safety and the efficacy of the medicines, protecting the interest of patients and citizens, within a flexible commercial environment supporting a single market.

Mrs. Marshall outlined that there were many possible ways to achieve the “Regulation 2000” objectives, but a clear management (“one stop shop”) was necessary. Further to a single EU decision, rapid market access was essential. A self-regulation system, for aspects of variations, should be envisaged, including a system of inspections and sanctions. This new regulation system should cover new and established products.

The proposal was build on existing system and formed a strengthened centralised function. Experience in the national agencies should be kept and mutual recognition improved, in a transition phase. A change to more centralisation would depend on satisfactory performance and flexibility.

Next, Mrs. Marshall presented the “Regulation 2000” calendar. She informed participants that a short concept paper would be released at the end of the consensus period. She also mentioned that 29 answers, representing up to 60% of potential company responses, had already been received. The majority favoured an EU driven approach. The main concerns expressed had been how get through a transitional period, the need for an improved mutual recognition and business flexibility (co-marketing, co-promotion, etc.).

Finally, Mrs. Marshall presented the coming benchmarking dates for the project, and underlined that the discussion would be opened up with the Commission, the EMEA and the national agencies.

Regulation 2000

What Is It and What Is It Not?

Vaila M Marshall
EFPIA Info Day
20 November 1998

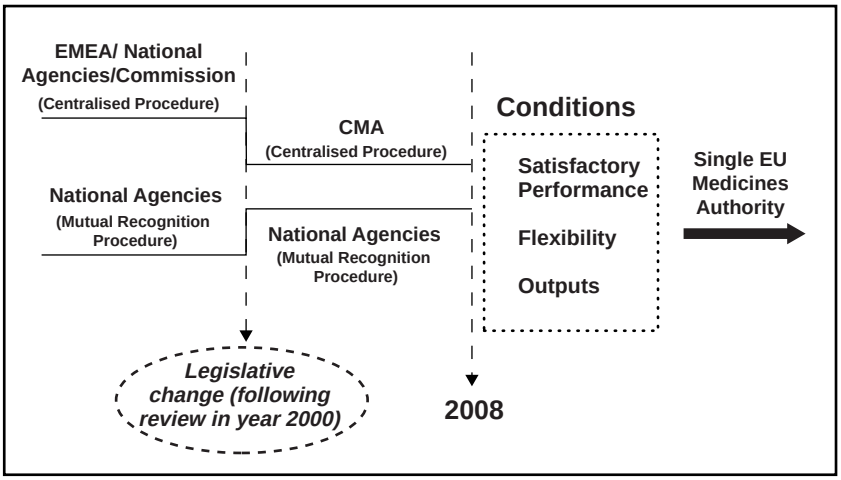
What Regulation 2000 is & what it is not?

- Regulation 2000 is concerned with:
  - defining the optimal long term future structure for regulatory resources in Europe to deliver globally competitive performance
  - the transition of activities from a national to a European level (with a smooth execution)
  - a broad overview of the relevant principles and concepts, not with detailed implementation
- Regulation 2000 is not concerned with:
  - issues other than regulatory decisions on Q, S and E (*e.g.* pricing & reimbursement), however possible impacts will be considered
  - enabling market access competitive with US
  - short term Industry efforts to improve the current regulatory procedures (*e.g.* decision making process) which are independent but complementary activities

Key drivers for change

- Experience of current systems
  - (complexity, duplication, robustness)
- Evolution and expansion of the European Union
- Innovation (in science, medicine and regulation of medicines)
- Competitiveness of EU - need for performance-driven
- European regulatory environment
- Management of healthcare
- Opportunity for reform - legislative obligation by December 2000

Regulatory 2000 proposals for the future EU regulatorysystem



Overview of Regulation 2000 project

Phase I: ***Development of Proposals***

Jan 97-Apr 98

- brainstorm
- survey of Regulators
- achieve consensus in Steering Committee
- prepare Discussion Document

Overview of Regulation 2000 project

Overview of Regulation 2000 project

Phase II: *Consensus Building*

Apr 98-Jun 99

- formation of EFPIA PAT
- communicate and debate preliminary proposals
- achieve consensus in Industry
- define EFPIA Policy

Phase III: *Promotion of Policy*

Jun 99-2001

- including specific regulatory proposals

Regulation 2000 - Priority Action Team

Chairman:	H Kummer (Schering-Plough)	
Deputy Chairmen:	E Donnelly (SmithKline-Beecham)	
	V M Marshall (Pfizer)	
Other Members:	G Disselhoff (Merck KGaA)	
	O Ernoux (Rhone-Poulenc-Rorer)	
	D Gilbert (Norvatis)	
	C Griffett (Zeneca)	
	M McDonald (Lilly)	
	J-P Osselaere (Schering-Plough)	
	Y Juillet (HMR)	/ *STRPC Chairman*
	R Jones (Glaxo Wellcome)	/ *ESPC Chairman (*)*
	B Yorke (Norvatis)	/ *IPPC Chairman (*)*
	O Amadeo-Manesme (SNIP)	
	E Baumbauer (VFA)	
	F Charlesworth (ABPI)	
	F Granata (FARMINDUSTRIA/Dompe Biotech)	
	M Lovehagen (LIF-Sw) / *alternate:* P Bonne Eriksen (LIF Dk/Novo Nordisk)	
	I Sanz de Madrid (FARMAINDUSTRIA)	
	M Van Maarschalker Weerd (NEFARMA/HMR)	

(*) may be substituted by another ESPC/IPPC representative respectively

Special advisory panels

- Support PAT in review and consideration of comments

Regulation 2000 vision

"A worldclass, scientifically robust, European regulatory system, meeting the needs of all EU citizens in a single pharmaceutical market."

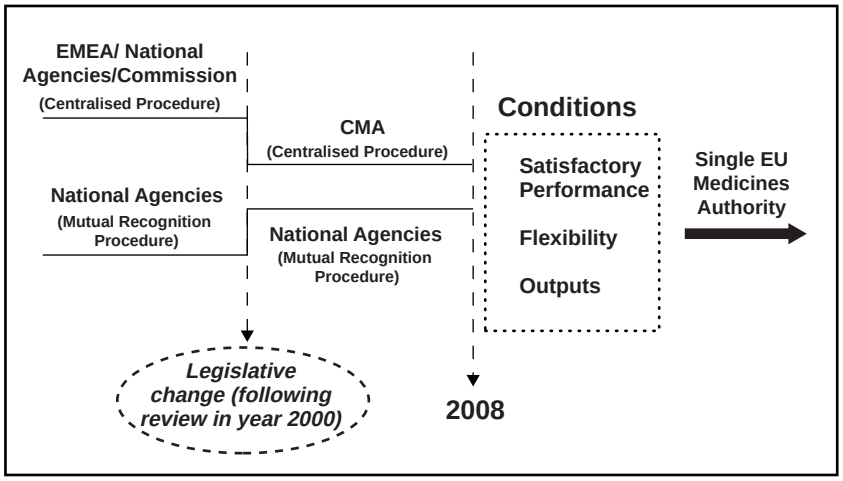
Regulation 2000 - assumptions 1/2

- The Steering Committee support one or more processes operating under clear management, each of which will provide a 'one stop shop' for the provision of scientific advice, submission and approval of MAAs (and maintenance of MAs), applicable to the EU environment
- The Steering Committee assume that a single EU decision (*i.e.* SmPC) will not compromise our ability to effectively market our products immediately in individual EU Member States (*i.e.* pricing & re-imbursement issues require resolution)

Regulation 2000 - assumptions 2/2

- Regulation should be moved increasingly towards self-regulation as far as is compatible with public health protection
- Effective and efficient regulation needs to apply equally to approval of new medicines and maintenance of established products
- EU systems will continue irrespective of EMU and other political possibilities

Regulatory 2000 proposals for the future EU regulatorysystem



Where are we in the process?

Discussion Document distributed to industry and regulators	June '98 ✓
Meeting with various Trade associations	June-Sept '98 ✓
Workshop No 1	27 July '98 ✓
Receive input from Companies and Trade Associations	15 October '98 ✓
Assess and assimilate comments	10 November "98 ✓
Produce 2-3 page summary	19 November '98 ✓
Feedback at EFPIA Info Day	20 November '98 ✓
Regular feedback to STRPC/ESPC	Ongoing

Results so far

29 Answers: 10 Associations
19 Companies

Majority favour a European driven approach

Concerns

- Caution about need for workable transitional arrangements
- Must retain business flexibility
- Mutual Recognition must keep improving

What next?

Interim report to EFPIA Board	December
Industry workshop	February '99
Obtain Regulator input	Ongoing
Final position to EFPIA Board	June '99

WHAT WOULD WE LIKE TO ACHIEVE ?

Dr. James RITCHIE
Director of Pre-clinical and Regulatory Strategy
SmithKline Beecham

Dr. Ritchie was replacing Mrs. E. Donnelly, and conveyed her apologies for not being able to attend.

First, Dr. Ritchie illustrated what had been achieved in Europe with a comparison on time for approval between national and European registration systems for 6 new chemical entities, from 1993 to 1996. This showed that the approvals in 1995 and 1996 had been very much faster. Next, he reviewed the evolution of the European Regulation system since the Treaty of Rome in 1957.

Dr. Ritchie then commented on the statement summarising the Regulation 2000 vision : "A world-class, scientifically robust, European regulatory system, meeting the needs of all EU citizens in a single pharmaceutical market". He presented one possibility for a European central medicines agency (see slides). This agency would be empowered to make decisions for the EU, would use internal and external expertise, would issue single flexible European marketing authorisations, and would be responsible for pharmacovigilance and for setting the European regulatory standards.

Next, he presented the long-term objectives as debated within the Regulation 2000 group, defining the real needs in terms of organisation and efficient use of resources : a non-complicated, streamlined, accountable predictable organisation with which industry interacts, with "State of the Art" skills, providing ongoing accessibility and a "one-stop shop" for advice. A transitional period is necessary to achieve these long-term objectives, and the Regulation 2000 Steering Committee had rejected a single step to achieve these aims. The retention of the two registration procedures had therefore been considered essential in a short/medium term.

Dr. Ritchie then explained the key concepts of the discussion document, and detailed the transition steps applying to the centralised and the mutual recognition procedures, pharmacovigilance, maintenance and IT needs. Some issues still needed to be resolved : scope, framework of the legal basis, accountability and liability, Commission structures and roles, and institutional and constitutional structures from the political, economic and social viewpoints in the future system. He remarked that attention should be paid to the potential accountability and liability issues, in the context of a move from a national to a European citizen.

Finally, he outlined the next steps of the project : the need for constructive collaboration between all stakeholders of all the actors in building the new registration system; open discussion of all perspectives within industry and with regulators; awareness of the policy implications; and protection of the successful elements of the existing system.

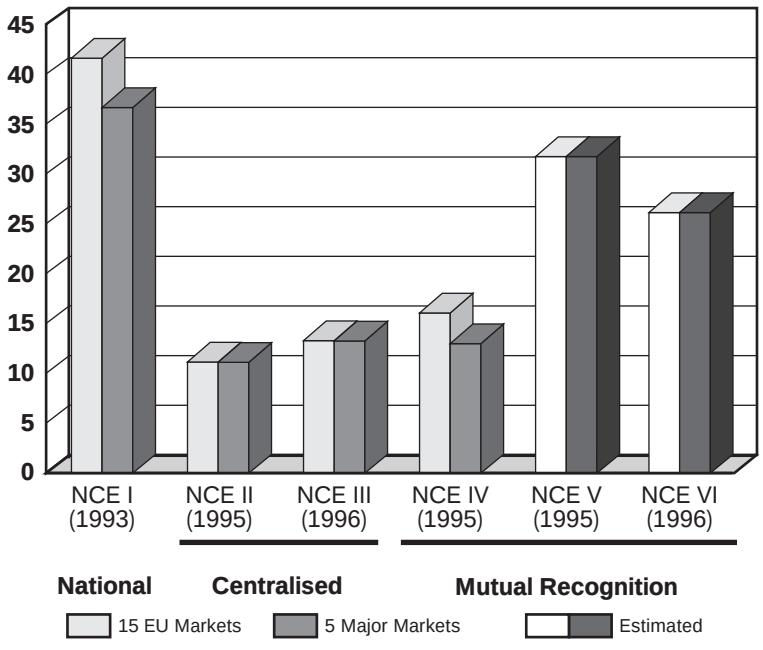
Concrete Proposals for Improving the Process

What would we like to achieve?

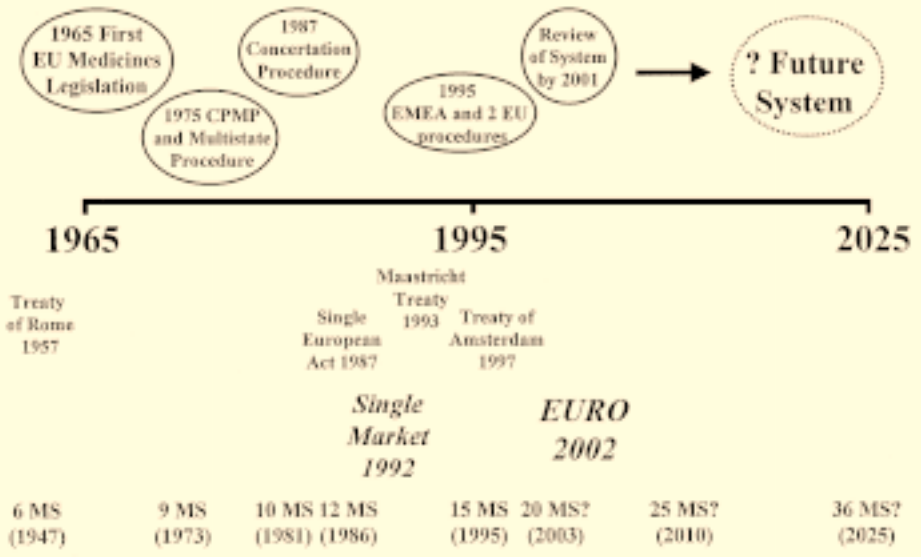
Summary

1. ***Achievements to Date***
2. Long Term Goals
3. Transition Steps
4. Other Considerations
5. Next Steps

Time to Approval
EU National vs MR/Centralised



Perspective on EU Medicines Regulation: A 60 Year Journey



Concrete Proposals for Improving the Process

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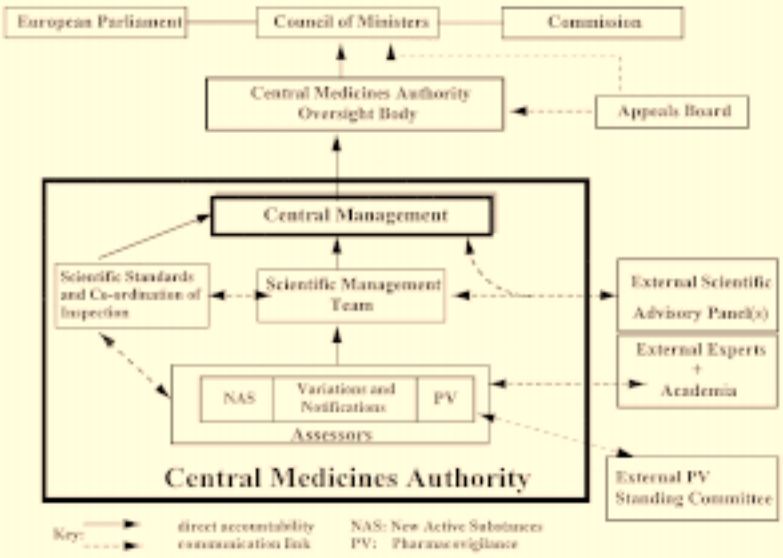
Regulation 2000 Vision

"A worldclass, scientifically robust, European regulatory system, meeting the needs of all EU citizens in a single pharmaceutical market"

Regulation 2000 Vision

- A **worldclass system** that meets best practice international standards for quality, time and cost of registration decisions, and inspires confidence both within the EU and globally.
- A **scientifically robust** system that reaches decisions on Safety Quality and Efficacy based on the highest quality contemporary scientific knowledge, thereby ensuring the respect of the global scientific and medical community.
- A **European regulatory system** that covers all aspects of the regulatory lifecycle (clinical trials, scientific advice, registration, maintenance, pharmacovigilance) and provides a single assessment and single decision resulting in a single licence for the whole of the EU. The system would accommodate medical diversity across the EU.
- A system **meeting the needs of all EU citizens** by promoting and protecting the legitimate interests of patients, consumers, taxpayers and all other interested parties, and providing full accountability for all actions.
- A system operating in a **single pharmaceutical market** that allows flexible commercialisation of products (e.g. co-marketing), market access, and the free movement of pharmaceutical products throughout the EU.

Possible Organisational Framework of Proposed European Central Medicines Agency



Key Features of the Central Medicines Authority

- a single authority empowered to make decisions for the EU
- employs professional reviewers performing EU assessments
- access to external Experts/Expert Advisory Committees
- output from authority is a single flexible European Marketing Authorisation
- responsible for Pharmacovigilance for EU
- responsible for setting EU regulatory standards

Long Term Objectives

- Non-complicated, streamlined, accountable predictable organisation
- With State of the Art competencies
- Providing ongoing accessibility
- One stop shop for advice during development, CTs registration and maintenance
- Performance targets agreed
- Capable of maximising the value of electronic technology

Concrete Proposals for Improving the Process

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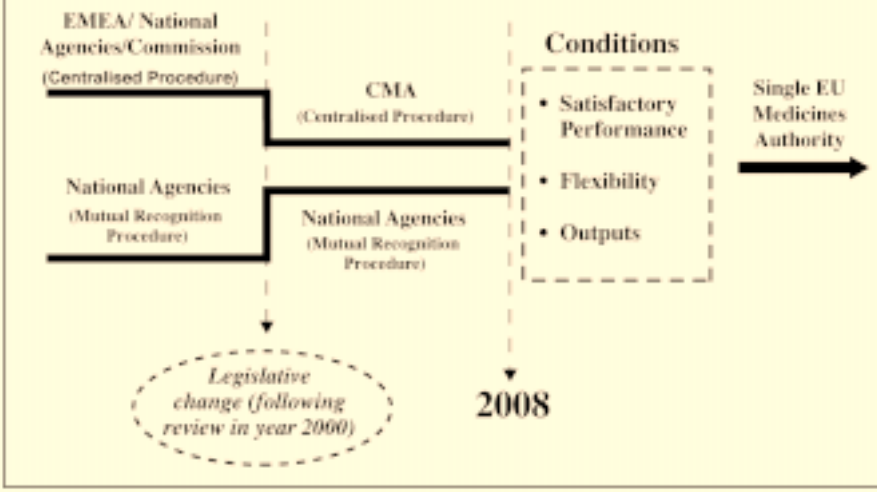
Rationale for Steering Committee Proposal

- single step to ultimate vision of a single authority rejected because:
  - **Central Authority unproven**
  - **Central Authority will need time to develop**
  - **retention of backup/choice during transition**
  - **time needed for transfer of existing products which represent bulk of regulatory workload**
- consequently, retention of national authorities and MR procedure considered essential in short/medium term

Regulatory 2000 Proposals for the future EU Regulatory System



Community Procedures for NCEs

1995 - 1997	1998-2002	2002-2010	2010-
• National			
• Mutual Recognition*	• Mutual Recognition*	• Amended Mutual Recognition*	? (performance)
• Centralised*	• Centralised*	• new Centralised**	? (performance)

* *Resources from National Authorities* ** *Dedicated Centralised resources*

Discussion Document
Key Concepts

1. The gradual evolution of the "EMEA" into a fully resourced European Community Authority

2. The retention of two registration procedures at least during transition
   - one based on National Authority resources
   - one based on a centrally resourced "EMEA"

3. The streamlining of registration support for marketed products i.e. once for Europe

4. Greater harmony on pharmacovigilance decisions

5. The establishment of an IT network across all regulatory resources in Europe.

Other Transition Steps

Centralised	• Decision Making Time • Business Flexibility • Intermittancy • Advice
Mutual Recognition	• Theory vs Practise • Arbitration time • Leadership • Single Decision
Pharmacovigilance	• Once for EU • Interaction with Sponsor
Maintenance	• Once for EU • Notification - Type A; Type B - 60; Type C - Compliance • No renewals
IT	• One IT Network and System for Europe

Concrete Proposals for Improving the Process

What would we like to achieve?

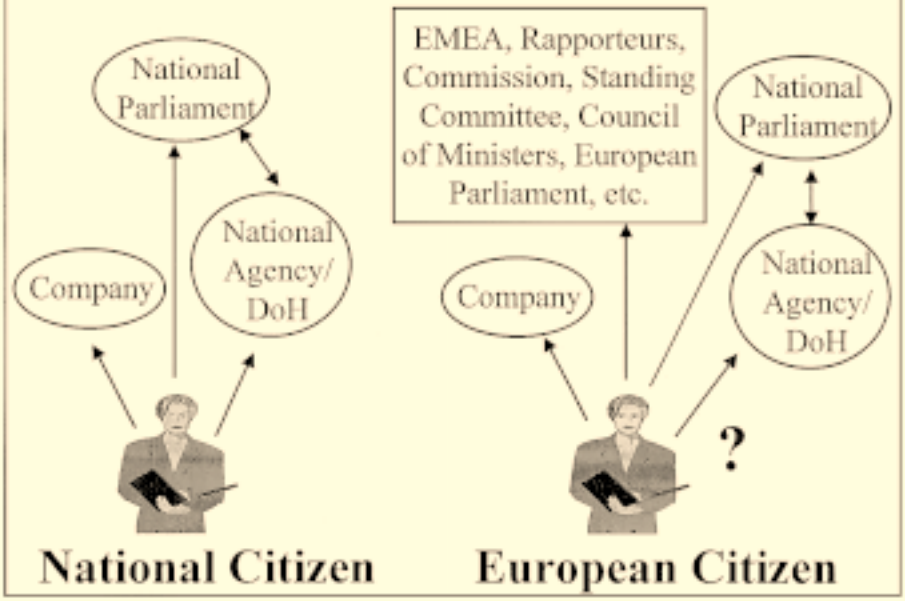
Summary

1. Achievements to Date
2. Long Term Goals
3. Transition Steps
4. ***Other Considerations***
5. Next Steps

Issues to be Resolved

- Scope
- Legal Basis
- Accountability/Liability
- Commission Structure / Roles
- Institutional/Constitutional/Structures

Accountability/Liability Issues



Concrete Proposals for Improving the Process

What would we like to achieve?

Summary

1. Achievements to Date
2. Long Term Goals
3. Transition Steps
4. Other Considerations
5. *Next Steps*

Next Steps

- Vital that all parties collaborate to build the next generation registration system
- Open discussion of perspectives
- Build on success and experience avoiding polarisation
- Be conscious of the significant political aspects
- Must protect the current successful new systems as we move forward
- Make the most of the exciting opportunity to build an EU community system for the new millennium

Panel discussion : How to be better prepared for the next century ?

All speakers and
Dr. Ib Bo LUMHOLTZ
Danish member of the Committee for Proprietary Medicinal Products (CPMP)

Prof. Hans WINKLER
Austrian member of the Committee for Proprietary Medicinal Products (CPMP)

The panel discussion was introduced by some remarks from Dr. Lumholtz and Prof. Winkler.

Dr. Lumholtz stated that the main priority of the national agencies is to focus on public health issues. 90% of resources spent in the national agencies are used to assess marketing applications and maintenance of medicinal products on the market. He evoked the possibility of having a clearly-regulated system, in which industry would control itself. However, some recent urgent safety restrictions showed a complete disagreement between companies and authorities. This clearly demonstrated that a system like that was more theoretical than perhaps a real possibility at least in the near future, because of very clear differences.

Dr. Lumholtz explained that the Danish system relies on a small agency functioning with a very broad network of clinical experts who understand the clinical situation and the benefit for the patients. He shared Professor Alexandre's view that the CPMP discussions are very useful because they look at the best practices across Europe, always bearing safety in mind. On the other hand, this consensus group from time to time takes positions in the wrong direction. Next, Dr. Lumholtz underlined that he did not really see two systems, because there was no different way of handling applications, but the same quality level for the assessment. From this perspective, he clearly welcomed the view that the EMEA, which works efficiently, should provide a secretariat for both systems.

Next, Dr. Lumholtz considered that the real problem with the mutual recognition system was the lack of a legal framework, even co-operation among national agencies was increasingly working well. He recommended a legal framework similar to that of the central system, would welcome a common secretariat for both systems. He did not expect major changes in the political scene and environment in the next ten years. He therefore did not think that the national authorities would delegate much more power to the central bodies. National competence must be maintained. Dr. Lumholtz suggested to further build on the good quality of national resources and then network together via a central secretariat. Finally, he considered that a sort of European FDA would be possible, but not in the near future.

Next, Professor Winkler underlined that regulators and pharmaceutical companies needed a partnership, even though they have different interests and obligations. However, one common obligation is scientific principle and science. Discussions were necessary, but also to really find out if something is going wrong. Concerning the 24 negative opinions or withdrawals, Professor Winkler mentioned that only 4 or 5 cases had been such that it had been 60/40 decisions. All the other decisions had been clear unanimous agreements : either the data had not been sufficient or the medicinal product had not been good. He considered that such decisions have to be very transparent.

Professor Winkler suggested that, once a year, the CPMP meet companies at an unofficial level and really discuss the problems of the previous year in a searching way, and not simple congratulate each other. He also stressed that, even it is satisfying for everyone that medicinal products be introduced very fast on the market, speed also meant that medicinal products were marketed without many safety evaluations. This had been corroborated recently with some specific cases of serious safety problems. It is therefore essential to consider that speed and safety do not always go in parallel. Development without immediate consideration of safety is not a good development.

Professor Winkler also proposed to re-emphasise critical and searching discussions. He considered that the CPMP should find more time to concentrate on the controversial and really difficult issues, in order to provide industry with the best standard decisions. He also told participants that he was personally very much in favour of assessing all innovative medicinal products under the centralised procedure as Part B products. Concerning the mutual recognition procedure, he considered that involving different people working in different agencies produced differing results.

Finally, Professor Winkler mentioned that he did not support the idea of having a huge central bureaucratic agency, and thought that it was possible to maintain the national agencies, which have important functions. It should really be a collaborative effort among all the actors in the European registration system. He recommended a continuous evolution towards the central registration of all innovative medicinal products.

Next, Dr. Lumholtz stressed that the MINE project was an effort to spread the best medical practice across Europe. He recognised that this was a huge enterprise, but a valuable effort. He reported that in Denmark, it had been decided to make SmPCs available to the public, as prices had already been.

Mr. Sauer invited the audience to ask questions.

A question was asked on Mr. Sauer's idea to try and improve the mutual recognition procedure on the basis of the principles of the ex-concertation procedure, in the light of Professor Winkler and Dr. Lumholtz's remarks.

Mr. Sauer replied that the question was whether the mutual recognition procedure could be upgraded in the same way as the so-called concertation procedure, which had been used for the biotechnology products before 1995. There had always been a discussion before the Member States made a decision but the Member States had still made a decision and granted national licences, with secretarial support for these activities.

Dr. Lumholtz observed that this would a possibility, but that it would take away the companies' option of flexibility regarding the market place.

Professor Winkler's major concern was the specific problem of major objections, which sometimes had not really been major objections. He considered that objections were sometimes raised simply to prevent the medicinal product from getting into a Member State. The possibility of withdrawing applications from two or three Member States which had raised serious objections had not been scientifically satisfying. An arbitration procedure would help to find out whether there really were major concerns, and also to move, step by step, towards the centralised procedure for new innovative medicinal products.

Mrs. Marshall felt that a move towards a concertation-type procedure would mean the end of the whole concept and philosophy of the mutual recognition. Even though it might be attractive to have one place for scientific debate, industry would lose some of the possibilities of the mutual recognition procedure, such as the flexibility to only apply in certain Member States, and the greater business flexibility. She considered that one of the reasons for which this procedure did not function very well was that companies did not want to go into arbitration because this process is very long. It the arbitration period could be shortened, then industry would use it and it would be possible to have genuinely scientific discussion and debates about serious public health issues.

Another question was asked on the reasons why the European procedures had always been lagging 10 years behind the US. Ten years ago, the FDA had asked for more and more data. It seemed that the European current practice was closed to this old FDA approach. Moreover, it was stressed that divergent medical practices had nothing to do with science. It was also pointed out that the FDA authorised significant new therapeutic entities much faster than the centralised procedure, and that the recent suspensions in Europe had not been matched by the FDA.

Professor Winkler recognised that there are differences of medical culture in Europe, which would be smoothed out in future. Evidence-based medicines had to develop slowly until all Member States accept the same scientific principles in medical practice. These principles were accepted in the medical schools, but it always took 20 to 30 years to be applied in medical practice. Professor Winkler also remarked that the CPMP did not ask for large amounts of data, but for good data. He mentioned that he had already seen a lot of dossiers with excellent data with a limited amount of patients, but representing good studies.

Mrs. Marshall shared her experience on a dossier submitted on the same day in Europe and in the US. The marketing authorisation had been granted a considerable number of months faster in the US. She was convinced that the quality of assessment had been the same. One of the reasons for these different periods was that there was no other process after the scientific evaluation in the US. The European scientific opinion delivered in Europe still took longer than the FDA could take. She would not recommend that Europe copy exactly what the FDA did, but suggested to share more the positive aspects of the both systems.

Mr. Sauer concluded these discussions by underlining that nobody wanted a transition which would be a disruption. Strong regulators were needed for the European citizens, but sometimes also for companies themselves, for example in the case of emergencies. Nobody wanted double standards. Mr. Sauer considered that the centralised procedure was reasonably speedy. He was not in favour of speed to the detriment of quality.

Mr. Sauer thought that industry and regulators had achieved a lot in making a good start for the new system. He proposed to continue this collaboration in shaping the better system of the future. The brainstorming might end in June 1999. By that time, a clear view on where industry and regulators totally agree, where they had alternative proposals to make, and when and why exactly they disagree, might be available.

AFTERNOON SESSION
THE MUTUAL RECOGNITION PROCEDURE

PERFORMANCE SINCE THE 1997 EFPIA INFO DAY

CHAIRPERSON'S INTRODUCTION

Dr. Christa WIRTHUMER-HOCHE
Chairperson of the Mutual Recognition Facilitation Group (MRFG)

Dr. Wirthumer-Hoche opened the afternoon session, stressing that, recently, the number of procedures had increased, and also that a number of strategic issues relating to the mutual recognition procedure had been resolved. However, there were still remaining concerns to examine. In the first session, the recent amelioration and the work achieved within the Mutual Recognition Facilitation Group would be presented.

FROM TRANSITION TO REALITY : THE MAIN DIFFERENCES

Dr. David JEFFERYS
Previous Chairperson of the Mutual Recognition Facilitation Group (MRFG)

First, Dr. Jefferys presented a chart showing the substantial growth of mutual recognition procedures since 1995. He remarked that in 1996, the bulk of mutual recognition procedures had been authorised during the last quarter of the year. An impressive growth had occurred in 1997 and 1998. Then he showed the range of medicinal products according to product type. From 1995 to July 1998, 102 marketing authorisations had been granted for major new medicinal products, with the mean of 11 Concerned Member States involved.

Next, Dr. Jefferys told participants what had occurred during the extended UK chairmanship of the MRFG. An important contribution to the improvement of the performance of the procedure had been the 2-day discussions during the informal MRFG meeting held in May 1998. The concepts of visibility and transparency, a deeper problem, had been discussed during a workshop held in September 1998. Dr. Jefferys welcomed the development of Eudratrack which, he said had brought considerable benefits to the procedure, and also mentioned the preparation of the Commission Communication during that period. Concerning performance, one of the main messages from the industry had been about the delays in starting the procedure. The MRFG had agreed to initiate automatic validation for new applications and all types of variations. Although concern had been expressed about the level of withdrawals, they had in fact affected no more than one Member State per procedure. Dr. Jefferys remarked that, often, companies had withdrawn rather than accepting a rather tighter SmPC. The overall level of withdrawals had been under 4%, and since January 1998, there had been around a 50% reduction in the number of withdrawals, essentially because the environment had changed after the end of the transition period, meaning that the flexibility of withdrawing and continuing with the national licence had been stopped.

Further to the debate on the reasons for withdrawals, one of the actions had been the revision of the breakout session protocol. Other ideas looked at included introducing a new document to set out clearly what were potentially serious public health issues, involving a second RMS or sharing work. Dr. Jefferys also outlined the need for earlier scientific discussion, indicating that the CPMP scientific advice procedure was available for all medicinal products, whichever route they took. Concerning delays in issuing licences, he considered that a significant part of the problem might lie within affiliate companies.

To improve visibility, the MRFG press release had been introduced since June 1997. The press release now contains considerable statistical information, and also feedback on policy matters which are elaborated with the help of the Commission. Dr. Jefferys welcomed the creation of the heads of agencies' web site in May 1998, and mentioned the future launch of the product index and the publication of the mutual recognition procedure SmPCs.

Dr. Jefferys felt that transparency was a rather deeper issue, and mentioned the possibility of publishing mutual recognition public assessment reports. The driver for this was to ensure a balance between the two procedures, and the stakeholder expectations. In doing this, the MRFG needed to be sensitive to the same issues which had been faced by the EPARS generated by the EMEA, and also had to recognise the expectations of other countries who were looking to the system to enable them to draw on information on mutual recognition procedures for their own use, particularly the Eastern European countries. Finally, Dr. Jefferys concluded by pointing out that the MRFG had handled more than 450 procedures, representing almost 600 medicinal products, and that more than 780 variations had undergone this procedure. That, he said, was a very encouraging figure.

THE MUTUAL RECOGNITION PROCEDURE

From Myth to Reality

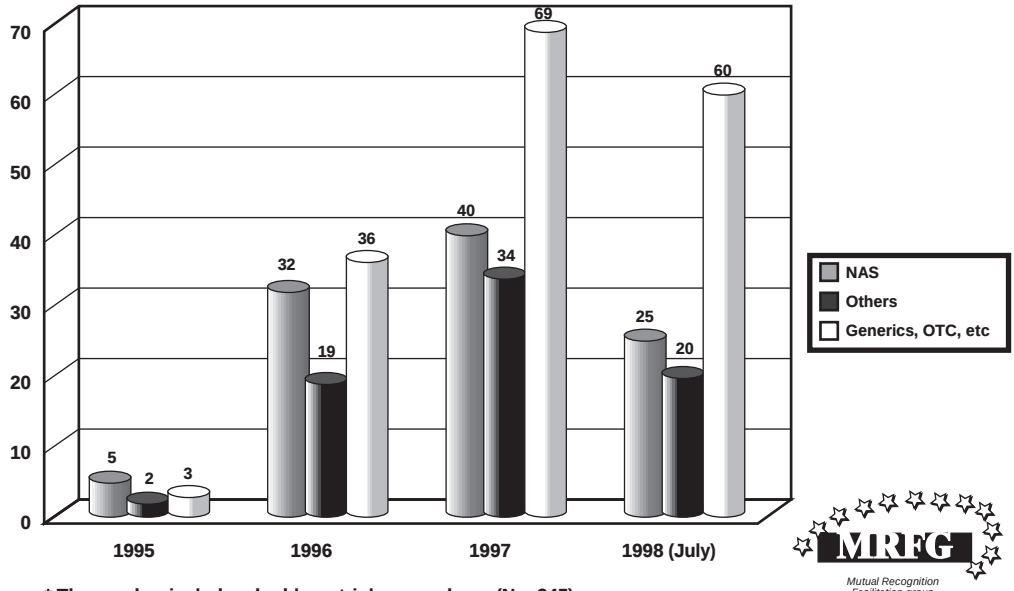
Dr. David Jefferys

MCA UK

Focus Of The Extended UK Presidency

- Improvement in performance (Informal MRFG, May 1998)
- Visibility and transparency (Workshop, September 1998)
- Development of Eudratrack
- Preparation for the Commission Communication

Total number of procedures finalised
(From 1995 up to July 1998)*



MRFG
Mutual Recognition Facilitation group

* The number includes double or triple procedures (N. =345)

TOTAL NUMBER OF FINALISED PROCEDURES BY TYPE

(From 1995 up to July 1998) *

	N.	%
NAS	102	29.6
Generics	75	21.8
Line extension	49	14.2
Fixed Combination	33	9.5
OTC	8	2.3
Herbal	3	0.8
Others	75	21.8

* The number includes double and triple procedures (N. = 345)

MRFG
Mutual Recognition Facilitation group

Improvement In Performance

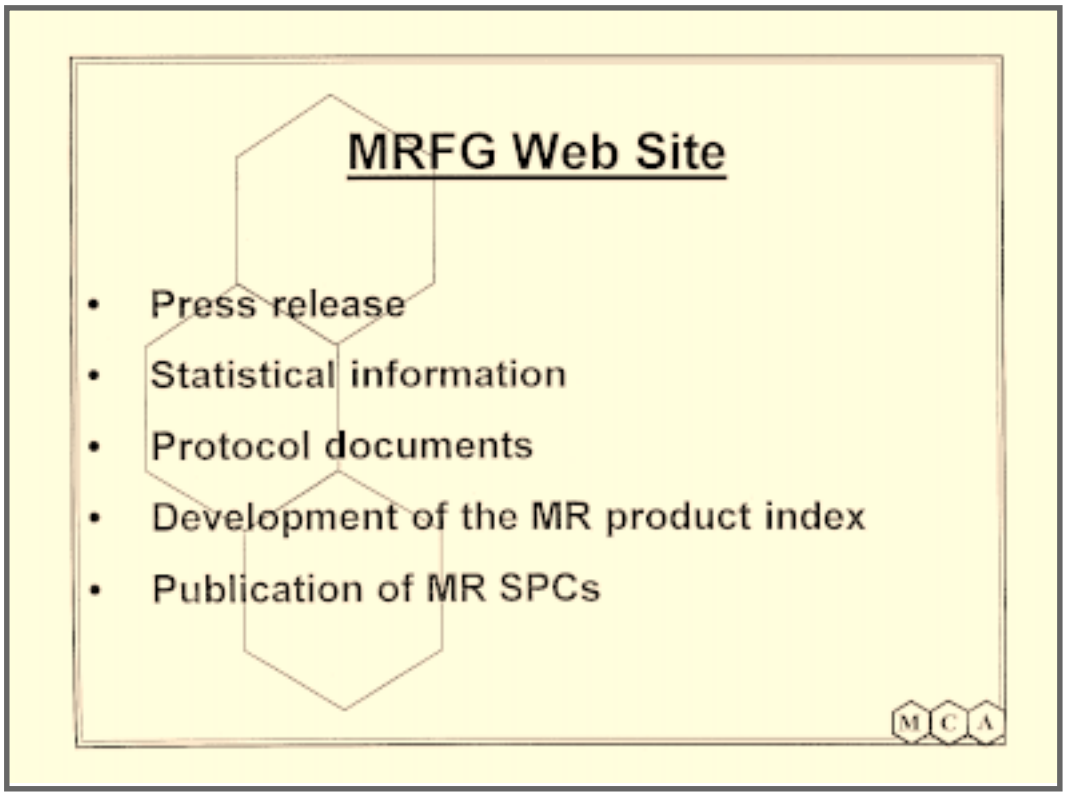
- Initiation of the procedure
  - Automatic validation - new procedures
    - variations
- Reduction in withdrawals
  - Analysis and diagnostic investigation
  - Revised breakout protocol document change from day 60 to day 55

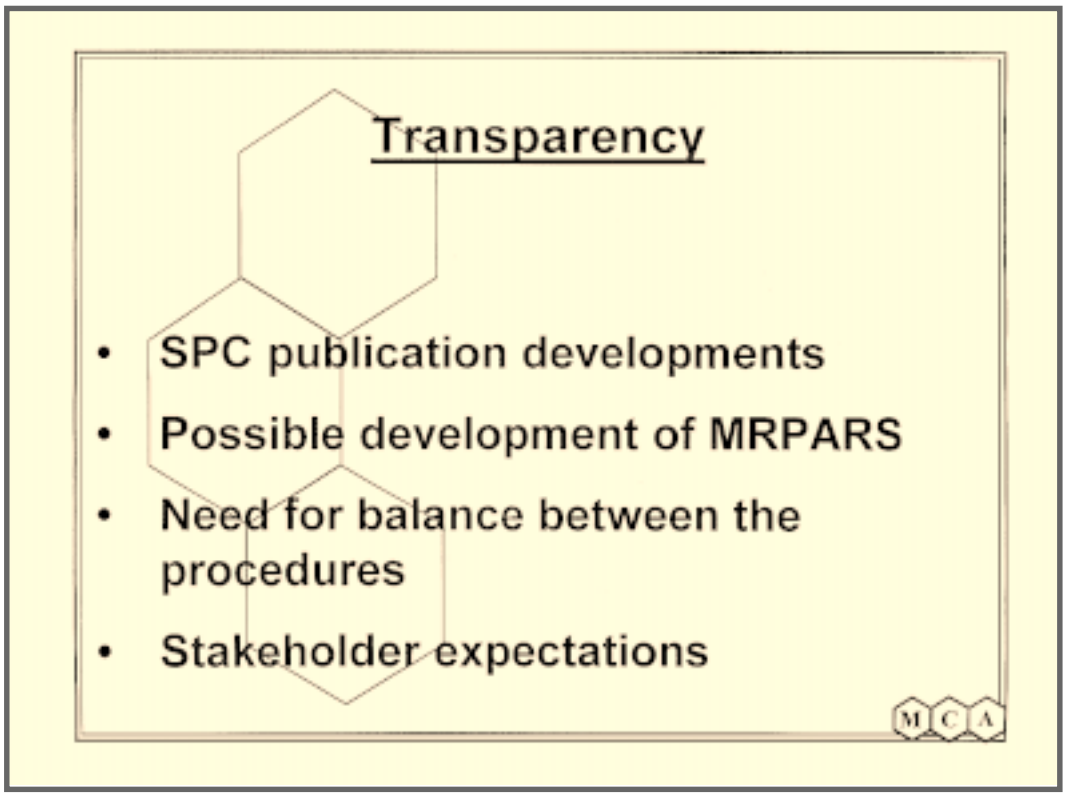
M C A

Visibility

- Introduction of the Press Release (November 1997)
  - Statistical information
  - Factual information
  - Feedback
  - MRFG logo
- Introduction of regular liaison meetings with the Trade Associations, Specialist Groups
- Introduction of Heads of Agency Web Site, May 1998 (MRFG site)

M C A


MRFG Web Site
• Press release
• Statistical information
• Protocol documents
• Development of the MR product index
• Publication of MR SPCs
M C A


Transparency
• SPC publication developments
• Possible development of MRPARS
• Need for balance between the procedures
• Stakeholder expectations
M C A

From transition to reality : the main differences

Dr. Christa WIRTHUMER-HOCHE
Chairperson of the Mutual Recognition Facilitation Group (MRFG)

Dr. Wirthumer-Hoche, who was presenting her own views and also Dr. Blandine Picon's presentation, conveyed Dr. Picon's apologies for not being able to attend.

First, Dr. Wirthumer-Hoche presented the automatic validation procedure, introduced in May 1998. This meant that within ten working days, a mutual recognition procedure could be started by the RMS, unless CMS(s) indicated that the application was not valid. After a six-month trial period and due to the positive experience, it had been decided to definitely adopt this procedure. For variation procedures, the June 1998 amendments to the variation regulations meant that type I variations no longer required a validation phase. For type II variations, there still remained the validation period, for which the automatic validation process had applied since the beginning of November 1998.

As the MRFG had found that the period between the end of the 60 days and the completion of the procedure was very important for scientific discussion, it had agreed to reduce day 60 to day 55. Even though 5 days was not very long, it was better to have 5 more days for discussion and clarification. Consequently, the best practice guide had been revised in July 1998. Further on, there had been a change of the applicants' response date, i.e. by day 65, because it was essential that the companies' responses be received in due time by the national authorities. Dr. Wirthumer-Hoche mentioned that the breakout session protocol had been revised, pointing out that the breakout sessions should not been carried out routinely, but only in the event of serious public health concerns. All CMSs should participate in these meetings to ensure that a consensus is reached. As an alternative, she proposed to use more video and audio facilities in the future. She also noted that a breakout session was not appropriate before the assessment of the companies responses. The number of break-out sessions during the previous months had decreased by about 48%. The main topics discussed had been efficacy and SmPCs, only minor questions had focused on quality and safety.

In the event that problems could not be solved during breakout sessions, companies might choose to risk an arbitration or else to withdraw the application. She deplored withdrawals to avoid arbitration, because questions of Community interest should not be avoided. However, she welcomed the reduction in withdrawals in 1998, and showed statistics on partial withdrawals.

Next, Dr. Wirthumer-Hoche underlined that there was still a problem with the delay for national licensing. The main reasons were the late submission of translated SmPCs and PILs, were the quality of translations and also the workload of the national authorities. However, the quality of translations really was improving, and this issue would be analysed in more depth with the help of the future joint Industry-MRFG survey.

Dr. Wirthumer-Hoche welcomed the Eudratrack system, which was now fully operational. She explained that Eudratrack was a system for tracking applications within the mutual recognition procedure, managing all administrative data. It was not intended for written procedures, and comments would still be exchanged via fax or via e-mail. She also presented the Eudranet system, a secure database for exchanging information among the authorities.

Next, she looked at questions from industry and authorities. Industry wondered whether the mutual recognition procedure was flexible enough, fast enough and whether it was at risk. The authorities wondered whether the procedure genuinely minimised the risk to public health and whether scientific exchanges were fruitful and sufficient. She remarked that, even though not all the problems were solved, the mutual recognition procedure was improving.

One procedure that had worked very successfully was the fast track procedure for 6 influenza vaccines, with the support from the Commission. All RMSs and CMSs involved had stuck to the timetable, and the annual Type II variations had been licensed in all Member States in good time. This example might perhaps function as a model for other procedures.

Next Dr. Wirthumer-Hoche noticed that the July 1998 publication of the Commission Communication (98/C 229/03) had triggered in-depth MRFG discussions. She stressed the need for Member States to have the same interpretation on all the topics. The MRFG was therefore elaborating standard operating procedures (SOPs) in order to determine how to deal with the different problems. The first SOP, on article 7a, had just been adopted. This document opened a further step not foreseen in the legislation, which would give companies the flexibility to introduce a mutual recognition procedure from their side, in the event of parallel applications. She indicated that the MRFG was elaborating a SOP on the informed consent application. She also mentioned that the MRFG had received many questions from companies concerning duplicate applications. According to the Commission, the only possibility was one marketing authorisation in a CMS for each mutual recognition procedure. The MRFG had also identified the need for more information on renewals, and was working on a discussion paper to be forwarded to the Commission Notice to Applicants group.

Further MRFG projects included the MRP index, the publication of the SmPCs and the publication of the assessment reports for medicinal products authorised via the mutual recognition procedure, and especially for new chemical entities.

Dr. Wirthumer-Hoche concluded by stressing that the move from the mutual recognition procedure to the centralised procedure was not the best solution. She mentioned that the MRFG would like to improve the attractiveness of the mutual recognition procedure and to further harmonise the assessment criteria within the national authorities. Perhaps it would be possible to have more guidelines, more scientific exchanges and to create core SmPCs, as the experience with the influenza vaccines had been a great success.

Mutual Recognition Procedure

recent experience

Christa Wirthumer-Hoche

Federal Ministry of Labour, Health and Social Affairs
Vienna

Validation phase (1)

- New applications:
  - automatic validation procedure - validation within 10 working days, unless informed by a CMS that the application is not valid
  - Started in May 1998 - for a 6-months initial period
  - due to the positive experience - definitely adopted
- between 1995-1997 : mean : 50 days
- experience since the 1.5.1998
  - significant decrease:

Validation phase (2)

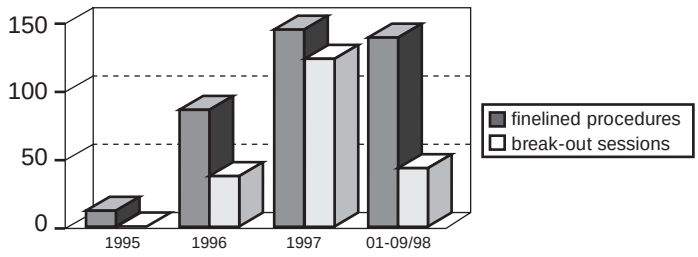
- Type I variations:
  - no validation phase - according to the amended EC Rep. 541/95 of 2 June 1998
  - RMS informs the CMS of the start date of the procedure
- Type II variations:
  - extension of the automatic validation procedure to all Type II variations from the 2 November 1998 (MRPG Oct.90)

MRP: 90-day procedure phase

- Comments to be provided by the CMS until day 55
  - *Change in the Bael practice guide adopted by the Heads of agencies in July 1998*
- Response document provided by the companies to the CMS at day 65
  - *10 days before the break-out session*
- Break-out sessions around day 75
  - *break-out session protocol (revised June 1998)*

Break-out sessions

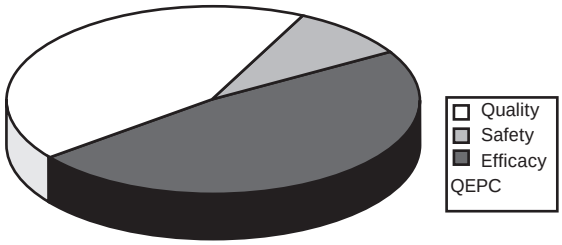
New applications



- 1995-1997: 67% break-out sessions for new applications
- 01-09/98: 32% break-out sessions for new applications
  - decrease of 48%

Break-out sessions

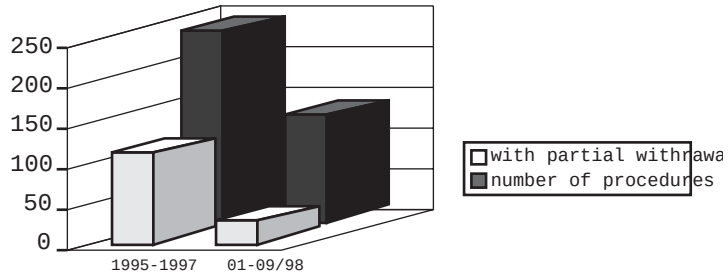
Items discussed



MRP - day 85 - 90

- Still remaining major objections raised by one or several MS's:
- For Industry - 2 main issues
  - right of arbitration
  - withdrawal

MRP - partial withdrawals



- 1995-1997: partial withdrawals in 16% of proc
- 01-09/98: partial withdrawals in 26% of proce
  - decrease of 40%

Post 90-days MRP marketing authorisation

- Compilance with the Best Practice Guide?
- Still a delay in licensing - but decreasing
  - date of submission of the translated SmPC and PIL
  - good quality translation
  - workload in the national authorities
- Joint Industry - MRFG Survey

Eudra Track

- IT Tracking System for applications of medicinal products within the MR-Procedure
- Manages all MRP administrative data
- Increases efficiency of work
- Secure database via EudraNet
- Data source for the public MRP-Index
- Member States act as the Project Managers

Projects of the MRFG

- MS-SOP on Art. 7a of Dr 68/65/EEC: adopted at the Nov. 98 MRFG-meeting and put on the MRFG web site for information
- MS-SOP on informed censont applications (in progress)
- MS-SOP on suspension ref. to Art. 7 (2) of Dir 65/86/EEC (in progress)
- MS-SOP on 5-year renewals (in progress)

Factors of attractiveness

Industry:

- **is it flexible enough ?**
- **is it a fast procedure ?**
- **is it a risk ?**

Health Authorities:

- **Does the MRP minimise the risk to public health ?**
- **Are the scientific exchanges fruitful ?**

All:

- **Is it improving ?**

Factors of attractiveness for Health Authorities

Does the MRP minimises the risk to public health ?

- ➔ **transitional period with national reviews to ensure consistency with national evaluation**

- ➔ **in the future: recognition of a single assessment**

Are the scientific exchanges fruitful ? **Yes**

1. Example of Influenza vaccines

very successful fast track procedure for 6 influenza vaccines due to:

- **support from the Commission**
- **existing core SPCs**
- **core dossiers**
- **agreed timetable**

➔ **positive outcome for the new decision and annual type II variation in all CMS**

Projects of the MRFG (2):

- **MFRG internal guide for using the MRP after 1st January 98**
- **Index for products authorised in the MRP in the common web site**

Next steps:

- **public database on SPCs ?**
- **central secretariat ?**
- **MPARs ?**
- **core SPCs ?**

How to improve the attractiveness of Mutual Recognition ?
3.To develop the MRP further (1998-2000)

- **To harmonise further the assessment criteria within national Authorities**
  - **more guidelines**
  - **more scientific exchanges**
  - **core SPCs**

- **To improve national times and transparency**
  - **tracking system of national authorisation times**
  - **harmonised SPCs database and MPARs**

EFPIA AND MRFG INITIATIVES TO ACHIEVE A "REAL MUTUAL RECOGNITION SPIRIT"

Dr. Ekkerhard BAADER
Head of European Strategic Regulatory Development
Hoechst Marion Roussel

First, Dr. Baader remarked that the mutual recognition procedure had significantly progressed, and had been much more successful than many had predicted. Nevertheless, there were problems to address and several issues to be satisfactorily resolved. After a slow start to the procedure in 1995, which had been necessary to gather experience to guide practices and adjustments, the total number of marketing authorisation applications approved through the mutual recognition procedure had increased each year. This was a good sign that the procedure had gained acceptance in industry and among authorities. The main challenge in 1998 and beyond was to achieve a truer mutual recognition, which would require changes in the national decision-making process as well as in the behaviour of applicants in situations where no agreement existed.

Dr. Baader considered that the Heads of Agencies' best practice guide and the industry best practice guide had set out how a procedure must be run. He also stressed that the revision of the MRFG breakout session protocol would help further reduce the number of withdrawals and cumbersome operational procedures. He indicated that industry was working jointly with the MRFG on a prospective survey designed to monitor the performance of the procedure. The objectives of this exercise was to collect relevant information from the users of the procedure, RMS, CMSs, and companies, with a view to identifying elements of concern which could be addressed to both industrial and regulatory users in order to improve the performance of the procedure. In order to obtain complete and relevant information from Member States, the MRFG had agreed to provide industry with data from Eudratrack on dates and periods. As an experimental phase, this survey would apply to a sample of applications. The second draft was now under discussion and was expected to be adopted soon.

Dr. Baader then presented the preliminary results of a short EFPIA survey initiated in September 1998, which had included questions on companies' experience with the automatic validation procedure, the new break-out session protocol, specific unjustified national requests and abnormal delays in granting the national marketing authorisation. EFPIA had received 27 responses, each of which covered one or more applications. On automatic validation, companies had reported a positive experience in 18 procedures, aside from a number of companies having no experience with this new procedure. Only minor critical comments had been received. The automatic validation procedure had therefore proven to be efficient and the continuation of the validation process, including type II variations, was a logical consequence of this positive effect. The response relating to the revised break-out session protocol was difficult to analyse, because 24 companies had answered that they had no experience with it. He felt that the number of break-out sessions had decreased in 1998 mainly because not all CMSs raising major concerns attended the meetings, and because industry and authority participants were not always decision-makers. The responses on the abnormal delays had been very clear, as in 23 out of 27 cases, companies reported delays in licensing ranging from one month to 12 months or more. Overall all CMSs had been affected, and a comparison with the 1997 data did not point out any improvement.

Finally, Dr. Baader shared his experience with an arbitration procedure, which was necessary for conflict resolution. However, he felt it did not need to be so complex and lengthy, for either companies or the authorities. It was essential to improve the decision making process, and to increase transparency. In conclusion, the initial framework had benefited from the recent initiatives. The mutual recognition procedure is a competitive alternative to the centralised procedure for the registration of new active substances in the EU, said Dr. Baader.

Hoechst Marion Roussel

EFPIA and MRFG Initiatives to Achieve a "Real Mutual Recognition Spirit"

EFPIA Info Day
London, November 1998

Dr. Ekkehard Baader
Hoechst Marion Roussel

Hoechst Marion Roussel

Mutual Recognition Procedure

Initiatives

- Best practice guides
- Break-out session protocol
- Automatic validation process
- Fast track procedure

- Increase of mutual recognition procedures in 1998

Hoechst Marion Roussel

Mutual Recognition Procedure

Mutual Recognition Procedure Survey

- Joint EFPIA and MRFG survey
- Experimental phase January 1st and May 1st,1999
- Eudratrack use on dates and time periods

- Short EFPIA questionnaire initiated in September 1998

Hoechst Marion Roussel

Mutual Recognition Procedure

Mutual Recognition Procedure Survey Questions:

- Experience with the automatic validation procedure
- Experience with the new break-out session protocol
- Unjustified national requests
- Abnormal delays in obtaining the national marketing

- 27 responses received

Hoechst Marion Roussel

Mutual Recognition Procedure

Mutual Recognition Procedure Survey
Automatic validation procedure

- Positive experience : 18 procedures
- Automatic validation process had proved to be efficient
- Continuation, and to use it for all type II variations

Dr E.Bander, 20.11.1998, EFPIA, London

Hoechst Marion Roussel

Mutual Recognition Procedure

Mutual Recognition Procedure Survey
Break-out session protocol

- Positive experience : 1 procedure
- No experience: 24 companies

Effective and efficient break-out sessions reduce the need for subsequent arbitration
Why the decrease in break-out sessions in 1998 ?

Dr E.Bander, 20.11.1998, EFPIA, London

Hoechst Marion Roussel

Mutual Recognition Procedure

Break-out session

Difficulties:

- Not all CMSs who raised "serious health concerns" attended
- Absence of CMSs having positive opinion
- Ensuring that decision makers are present
- Issues "resolved" at MRFG later raised again

Dr E.Bander, 20.11.1998, EFPIA, London

Hoechst Marion Roussel

Mutual Recognition Procedure

Mutual Recognition Procedure Survey
Abnormal delays in obtaining the national marketing authorisation

- Delay in licencing in 23 out of 27 cases
  - Range between 1 month and 12 months
  - All CMS affected
- No improving trend

Dr E.Bander, 20.11.1998, EFPIA, London

Hoechst Marion Roussel

Mutual Recognition Procedure

Arbitration

- Arbitration is necessary for conflict resolution
- If arbitration required, this part of procedure must not so complex and lengthy (decision making process)
- Transparency during the process

Hoechst Marion Roussel

Mutual Recognition Procedure

Conclusions

- All stakeholders in MR recognised the usefulness and importance of the MRP
- Initial framework of MR benefited from recent initiatives
- Initiatives helped to tackle some of the procedural problems and delays
- A number of administrative and procedural issues still need resolution

Panel discussion : assessment of the year three

All speakers and
Mrs. Agnete KJAERVIG
Manager - Regulatory Affairs
Novo-Nordisk

Mrs. Kjaervig supplemented Dr. Baader's presentation on the recent EFPIA survey by commenting on the companies' responses about specific unjustified national requests. Since these results had been almost the same as for the previous, they showed that the majority of the EU authorities still tend to assess the whole EU file rather than the position of the RMS. A lot of administrative and pharmaceutical questions were still not uniform, as well as what were “major” and “minor” concerns. She stressed that improvements were necessary regarding specific national requests and delays in national marketing authorisations.

It was asked how the authorities intend to enforce the 30-day limit for giving national approvals either in the variations procedure or in the complete mutual recognition procedure.

Dr. Jefferys replied that first it was necessary to diagnose the problem. He observed that long delays were now rare. It was essential to work together to solve this issue. Eudratrack would help to monitor this. National agencies had committed themselves to the authorities' best practice guide. The authorities needed to gather information in order to find out where the problems lie. He suggested that some reasons had been the issue of translation and also the adequacy of leaflets.

Dr. Wirthumer-Hoche stressed that the MRFG had noted this issue about delays, especially relating to Type II variations not affecting SmPCs. The MRFG and every Member State were aware that within 30 days of the end of the mutual recognition, some sort of notification should be sent to companies, because no further implementing measures was necessary for the national authorities. To avoid confusion over Type II variations, the MRFG would propose that companies first contact the RMS in order to receive the corresponding variation number and then mark all the dossiers and afterwards submit it simultaneously to the CMSs. Concerning the translations issue, she stressed that, where for example, an English company had no local person in a German-speaking country, it was very difficult to talk in English with an English native speaker about German changes in the text.

A question was asked about the Euro-SmPC, and especially the difficulties encountered in Member States which had a national SmPC/information policy. How do the authorities plan to improve this situation and how is progressive harmonisation of the SmPCs to be achieved ?

Dr. Jefferys replied that this was a very difficult issue, because of the widely-differing views of national advisory committees and behind them the medical professions. Some differences in medical practice and expectations had influenced policy. The MRFG was in helping to manage this change. One of the problems was that when compromise was reached, authorities then had to think through what the change would mean in the national markets. Next, the industry interest came back because the Euro-SmPC triggered disadvantages compared to other national products. Dr. Jefferys noted that companies wanted the harmonisation at one level but did not like the consequences for their products on national markets. He felt that there was a greater spirit of willingness to change, but there were also some difficult consequences not only for Member States but also for companies. He thought that a higher level of arbitration, if the arbitration phase could be shortened, might actually reset the balance point in Europe.

A question was asked about the risk of confusion for the public if the SmPCs were published, because of the differences between SmPCs approved via the mutual recognition procedure and those approved via national routes. Which type of SmPCs was planned to be published on the web site ?

Dr. Wirthumer-Hoche replied that the MRFG was aware that European harmonisation of the SmPCs could trigger national disharmony of SmPCs. The MRFG had decided that it would first start to publish the SmPCs resulting from the mutual recognition procedure. She considered that hopefully there would be soon harmonisation throughout the European market.

It was asked whether there was any experience with second round of the mutual recognition procedures, i.e. further to withdrawals in one or a few Member States. Due to the facts that there was no possibility for a clock-stop during the mutual recognition procedure, and that some Member States had asked for additional data, e.g. from clinical trials, there had been cases of withdrawals in some Member States. Afterwards, companies had provided the requested data, those Member States had been involved in a second round of the mutual recognition, and the outcomes had been positive.

Dr. Jefferys replied that there had been 9 instances where companies had reapplied and those had gone through

successfully. The MRFG had also increasingly seen that the smaller companies in the OTC sectors or in others, applied for a limited indication in perhaps 3 markets, and then asked for a second and even a third round. They had worked with their RMS on the 3 initial approvals, and had then successfully added 2 further markets, and were coming back to add a further 2 markets. This confirmed the flexibility of the system : it could be used in a variety of different ways depending on what products you have and how you want to access the European market.

A question was asked on the number of difficulties relating to break-out sessions, their organisation and what the MRFG would recommend to remedy them.

Dr. Wirthumer-Hoche replied that it was not always possible for CMSs to send its expert to the breakout session, because of the national workload and the travel costs overhead. There should be more use of audio and video facilities in order to facilitate the involvement of all CMSs in the breakout sessions, whether their views were positive or negative, in order to clarify their problems and find a consensus.

Dr. Jefferys commented that this issue had been discussed during the May 1998 meetings. It had been agreed to arrange breakout sessions only when it would be useful, so as to avoid an intolerable burden on resources. It was necessary to try to identify when a breakout session would be useful, and on those occasions the breakout needs to be as long as it needs to be. The idea of restricting it to one hour was not practical, as some breakouts need to go into considerable depth, whilst others frankly served no purpose. One positive development had been the shift in the CPMP week. The fact that each Monday of CPMP weeks was devoted for MRFG and the break-out sessions had resolved some of the tensions for those who had to travel.

It was asked whether the decrease in the number of withdrawals pointed to an increase in mutual trust.

Dr. Wirthumer-Hoche replied that she would like to say yes, but that the MRFG had in fact to deal with very few cases of arbitration, and the decrease in withdrawals was partly due to the end of the transition period, i.e. it had not been possible for a company to come back again using national way. The MRFG had tried to define a “public health concern” but this had been impossible. This really was a case-by-case decision. Nevertheless, the trust among the different Member States i.e. in the recognition of assessment reports, was genuinely increasing, as well as the willingness of those working together.

Dr. Jeffreys said that he would also be optimistic, considering that both the centralised and mutual recognition procedures functioned in a collegial spirit. He noted that increasingly the assessors across Europe were establishing their own network. That was how this procedure was ultimately going to work, and that was how problems were solved, by people getting together.

CONCRETE PROPOSALS FOR IMPROVING THE PROCESS

Chairman's introduction

Dr. Roger BOLTON
International Group Manager Worldwide Regulatory Strategy
Zeneca Pharmaceuticals

Dr. Bolton introduced the last session by underlining that the MRFG itself had been a solution to potential problems. He mentioned that the previous session had helped to identify initiatives coming from the MRFG and Member States, some of them arising from proposals and ideas from the industry associations. Even though there had been a lot of progress, it was clear that the situation was not satisfactory, and there still were some serious issues and problems to overcome before the European regulatory system for human medicines would run smoothly in practice.

Dr. Bolton wondered what was going to happen when in addition to the new applications, an ever increasing down-stream volume of activity, namely the maintenance, the variations, the renewals of Community based authorisations began to take effect. He also highlighted the need to consider how to resolve some of the remaining difficulties, e.g. the concept of serious public health objections, the problem of national delays, and the extra-national requirements.

Accelerated arbitration : is it a solution ?

Dr. Brenton JAMES
Pharmaceutical Regulatory Policy
GlaxoWellcome, R&D

on behalf of **Dr. Gabriele DISSELHOFF - Head of Regulatory Affairs** - Merck KGaA

First, Dr. James stressed the need to address the question of whether a withdrawal is a dereliction of the companies' duty with regard to public health. He started by talking about arbitration and withdrawals, and highlighted that withdrawals for national applications had been possible before 1st January 1998. To date, there had been a very few arbitrations : three for marketing authorisation applications and two for variations' applications. This presentation would suggest some improvements further to the debates within the Regulation 2000 team on the current mutual recognition procedure issues.

Dr. James then turned to the inadequate recognition by Member States of each other's assessments. This was linked to the problem of “public health issues”, for which the European rules refer to quality, safety and efficacy, but that did not seem adequate. There was also the question of inadequate resources for administrative management, co-ordination and assessment, and there was in addition no clear ownership of the process. Dr. James considered that the Heads of Agency had control of the arbitration process. He explained that arbitration was lengthy and complex and that this was why any prudent regulatory person would have withdrawn and not gone to arbitration during the transition period. In the best case, it would take around 150 days and in the worst case more than 240 days.

A second wave of mutual recognition could be envisaged, but it meant 100 additional days in the best case. This was not a good solution, as there was a delay, but this was surely also a technique for isolating the CMS that had major concerns on public health. Further to Dr. Jefferys' presentation, it appeared that all the 9 second waves had been successful. Dr. James wondered why those CMSs, in the 90-day bilateral phase, had been minded to say no on public health grounds but had authorised the product in the second wave. Additional data might have been provided, but Dr. James understood that those CMSs had approved the original SmPCs.

Next, Dr. James explained the Regulation 2000 proposal for a faster arbitration procedure. The idea was to have the “significant public health concerns” validated by the Standing Committee, i.e. it would make the decision as to whether the issues were indeed of major public health concern. If, however, some CMSs did not approve the product, there would be a 30-day arbitration period. Three possible binding decisions would be : approval in all Member States, approval in all Member States with amended labelling, or withdrawal.

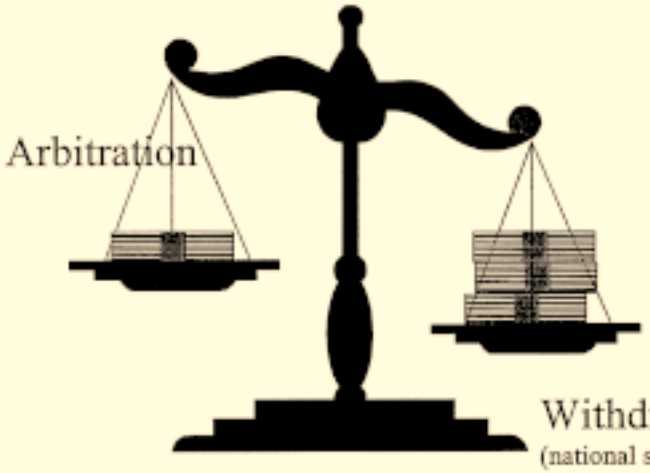
Then Dr. James presented the key features for amending the procedure : assessment really performed by one Member State, project management and oversight of the standards by a central authority, shortened and simplified arbitration, and scientific opinion and binding decision delivered by a Standing Committee. The single binding decision would result in national marketing authorisations with flexibility on patient information. He stressed that industry would use arbitration if true mutual recognition were practised, if the arbitration was in 90 days, if serious risk to public health was exactly defined (not extra chemistry and pharmaceutical questions), and if the marketing authorisation in CMS were granted within 90 days. Perhaps it would be useful to implement a mechanism to allow public health issues to be addressed on a more formal basis, before potential arbitration. A co-RMS might help quality assurance for the RMS, with a parallel assessment. A true mutual recognition, meaning automatic recognition, was essential, since all regulatory agencies in Europe work with the same scientific standards.

Accelerated Arbitration
Is it a Solution?

EFPIA Info Day
London, November 20, 1998

Dr. Gabriele Disselhoff
Head of Regulatory Affairs
Merck KGaA, Darmstadt, Germany
disselho@merck.de

Arbitration - Status 1997



Withdrawals
(national submissions possible before 1.01.1998)

Regulation 2000

Issues with Current Mutual Recognition Process

- **inadequate recognition of each others assessments by MS (e.g. too many/inappropriate questions during MR)**
- **insufficient resources for administrative management, co-ordination & assessments**
- **no clear ownership of process**
- **arbitration is lengthy and complex**

Regulatory Affairs MERCK KGaA Darmstadt, Germany

Arbitration

65/65 EEC Article 7 / 75/319 EEC Articles 10-14

Duration

Best Case	150 days
Worst Case	> 240 days

Consequence

- no access to up to 14 markets during that time
- withdrawals and national submissions no longer possible

Regulatory Affairs MERCK KGaA Darmstadt, Germany

2nd Wave MRP - Is it the Solution?

Duration

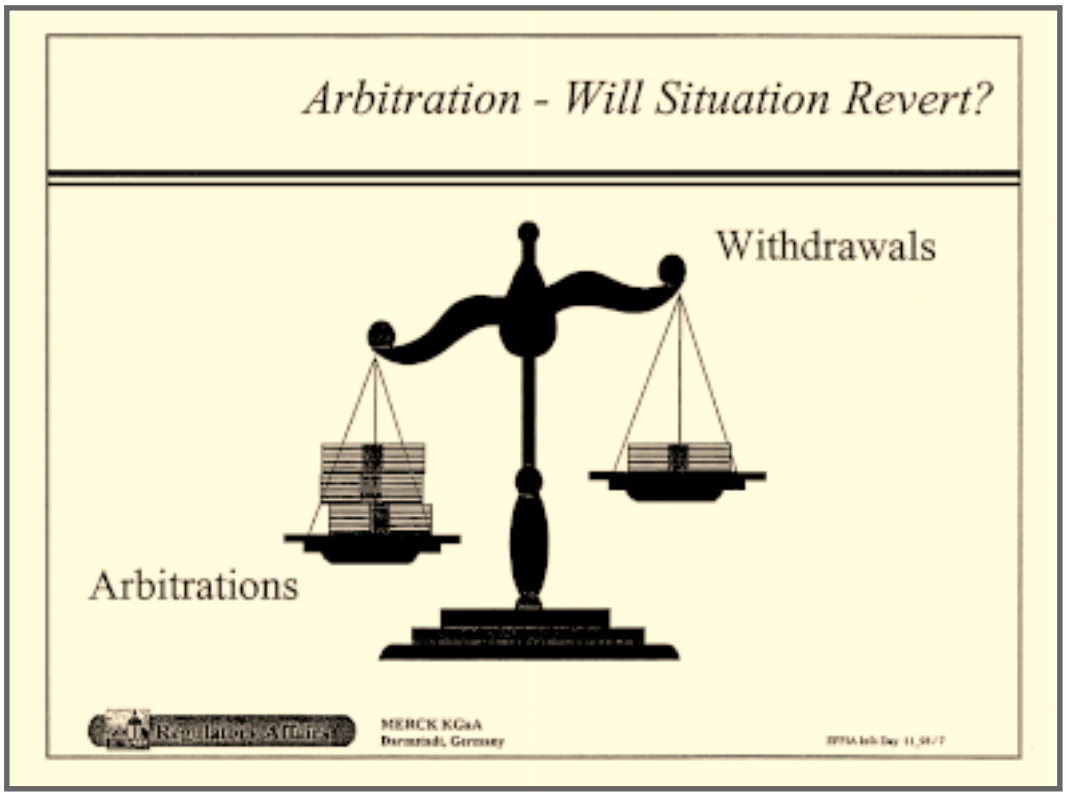
Best Case ~ 100 additional days

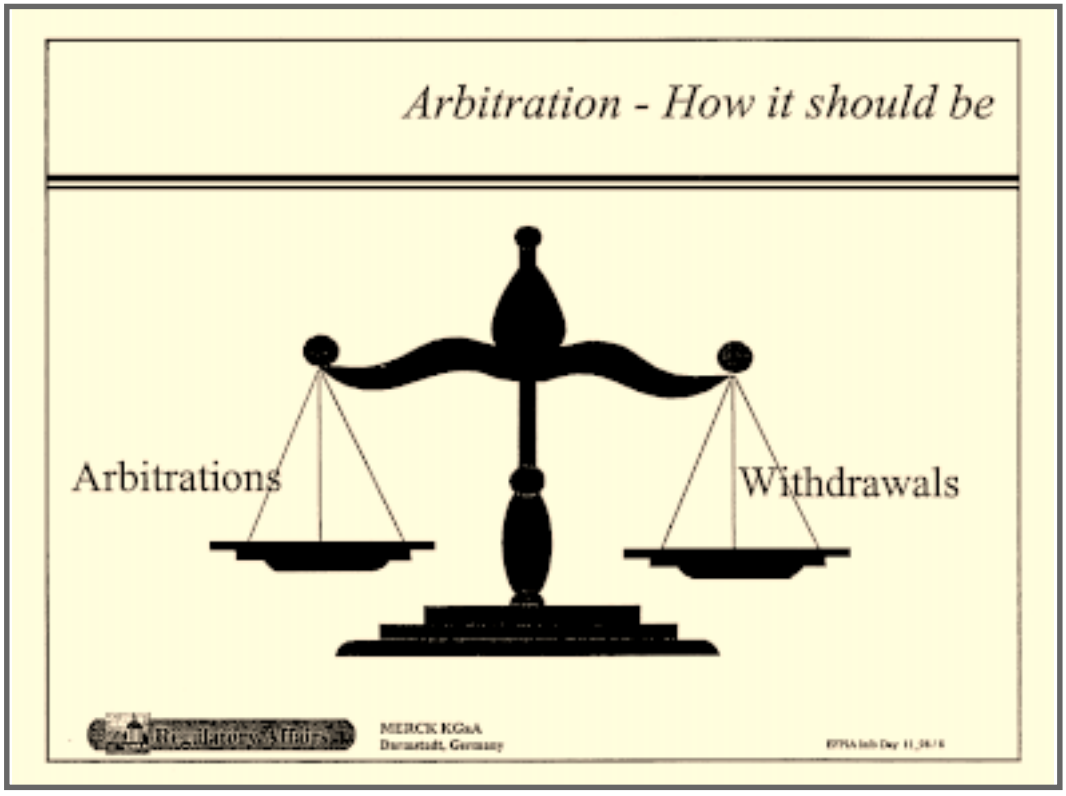
for one to many markets

This is not a good solution!

Commission Communication

... encourages greater use of arbitration for generic applications


Arbitration - Will Situation Revert?
Withdrawals
Arbitrations
Regulatory Affairs
MERCK KGaA
Darmstadt, Germany


Arbitration - How it should be
Arbitrations
Withdrawals
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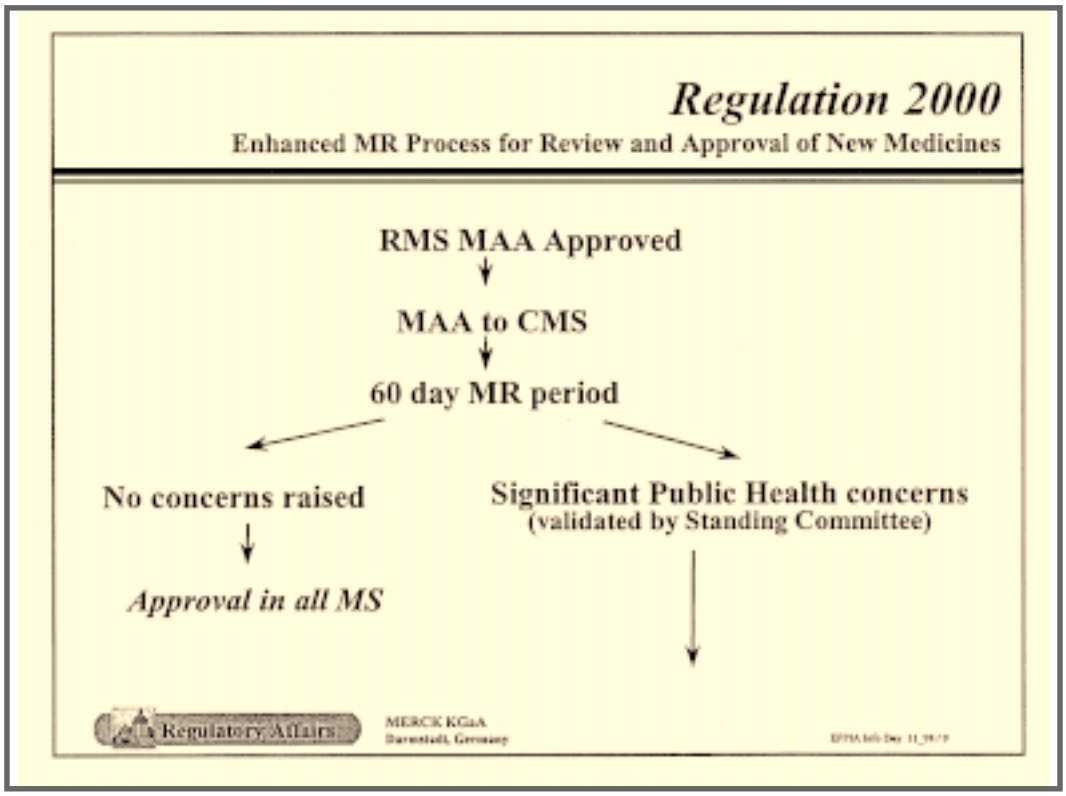
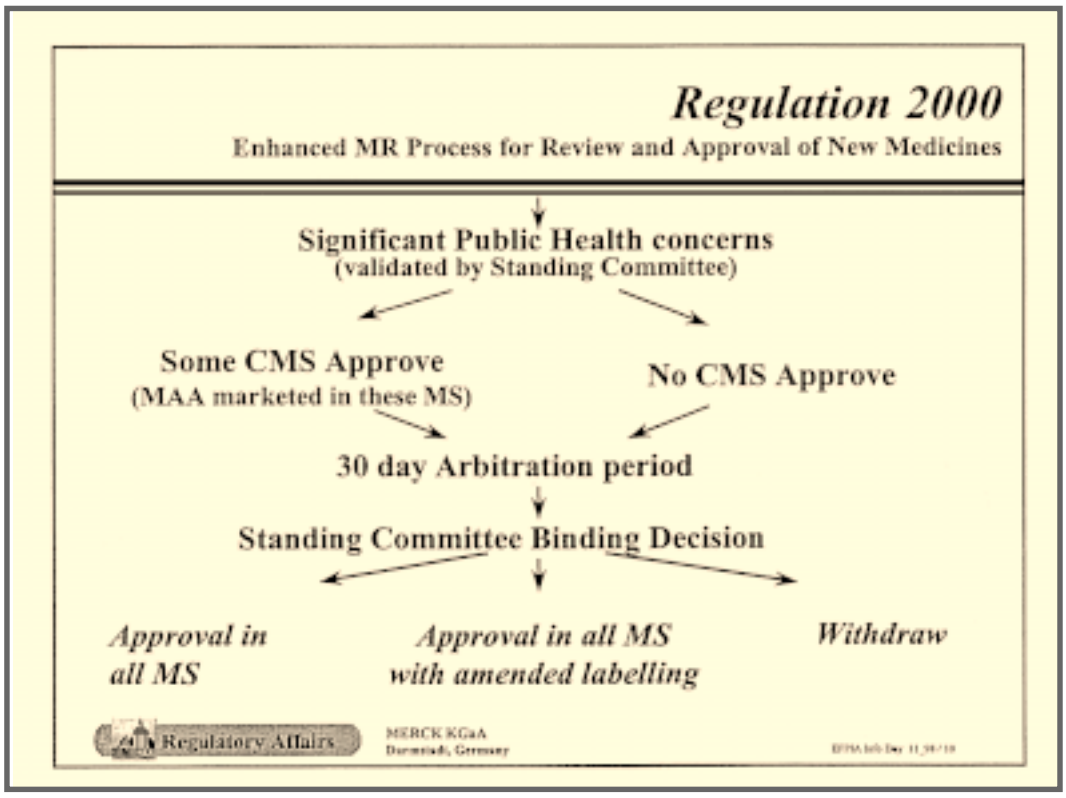

Regulation 2000
Enhanced MR Process for Review and Approval of New Medicines
RMS MAA Approved
MAA to CMS
60 day MR period
No concerns raised
Approval in all MS
Significant Public Health concerns
(validated by Standing Committee)
Regulatory Affairs
MERCK KGaA
Darmstadt, Germany


Regulation 2000
Enhanced MR Process for Review and Approval of New Medicines
Significant Public Health concerns
(validated by Standing Committee)
Some CMS Approve
(MAA marketed in these MS)
No CMS Approve
30 day Arbitration period
Standing Committee Binding Decision
Approval in all MS
Approval in all MS with amended labelling
Withdraw
Regulatory Affairs
MERCK KGaA
Darmstadt, Germany

Regulation 2000

Key Features of Amended MRP

- assessment performed by a single MS (RMS) on behalf of EU
- project management of procedure and oversight of standards by Central Medicines Authority
- **shortened and simplified arbitration period (30 days)**
- **scientific opinion and binding decision following arbitration delivered by a Standing Committee**
- single binding decision results in national marketing authorisations and national flexibility on PIL's and Packs

Food for Thoughts

Industry would accept arbitration - if

... true Mutual Recognition was practized

... arbitration was dealt with within the 90 days MR period

... "serious risk to public health" was exactly defined

... CMS without public health issues would grant MA within the 90 days MR period

More Food for Thoughts ...

... from Regulation 2000 Comments

- could a mechanism be implemented to allow public health issues to be addressed on a more formal scientific basis before potential arbitration is reached?
- could the product be moved into the CP for a scientific opinion if concerns are raised by one or more CMS within the 60 days period?
- could a Co-RMS help quality assuring the RMS, thereby avoiding arbitrations?

The common efforts of Member States to improve the process of mutual recognition

Dr. Thomas LöNNGREN
Swedish member of the Mutual Recognition Facilitation Group (MRFG)

First, Dr. Lönngren presented the current management structure of the mutual recognition procedure, with the different actors involved : the Commission, responsible for the legal framework and the interpretation of the legislation, the Heads of Agencies, an informal group aiming to facilitate the procedure (policy and resources discussions), the MRFG, the Member States acting as RMSs and/or CMSs, the EMEA, providing a limited support, and the CPMP, where the standards and norms were created and scientific advice given. A lot of tools had been developed : Eudratrack, Eudranet and soon the product index. He stressed that no actor was standing over the other, and concluded that this management was without formalised duties and responsibilities, and without financing. Considering the resources allocated, in comparison with the EMEA -which had nearly 200 people managing only 40 products per year - the results of the common effort by the Member States were satisfying.

Dr. Lönngren considered that up to 2003, it would be necessary to tackle the operational problems. From the management perspective, he recommended that some Member States speed up and allocate resources and competence in order to participate in the procedure. He thought that, even though the secretariat received help from the EMEA, the MRFG needed more than secretarial support, in order to monitor, follow up and make in-depth studies of the system (5-6 skilled pharmacists). The Commission had to take responsibility for financing the system, and had recently announced it would have no money after 1999 with which to finance the Eudranet and Eudratrack systems. Dr. Lönngren stressed the need for more flexibility, referring to the July 1998 Commission Communication. At the heads of agencies level, one of the challenges was to come up with a common approach on how to deal with the “public health” issue. He mentioned that the video conference facilities were absolutely necessary considering the workloads coming up in the near future. He felt that it was too early to set up the new system after 2003, and that it would be better to make a proper evaluation of the current one. For this evaluation, he questioned whether the legal framework was enough to ensure that only safe and effective medicines would be authorised. For example, maybe comparative studies should be introduced into the legislation.

Dr. Lönngren next noted that all the information about the MRFG was published on the Heads of Agencies web site : standard operation procedures, calendar of the meeting dates, different kinds of reports, statistics, contact points and press releases. He indicated that a product index was being developed. One important thing was that the content of the information would be in the hands of the national agencies, which would be responsible for the quality of the information used in updating Eudratrack. He remarked that the information would be automatically transferred from Eudratrack into the index and published on the web site. The product index would indicate who was the RMS, who were the CMSs, the procedure number, the trade name in the RMS and CMSs, the strength, the form, the active ingredients, the type of application, the marketing authorisation holder and the date of day 90. It was being tested among the national competent authorities and was expected to be launched in January or February 1999. Further developments of this index were being discussed. It could be based on the concept that national agencies publish product information on their own web sites. For example, Sweden publishes the SmPC for all products authorised. The idea was that from this index, a simple link could be made from the product to the national agencies' web sites when the SmPCs were published. The publication of the leaflets, the national public assessment reports and the mutual recognition public assessment reports was being discussed, and this would be a very powerful driver for transparency and visibility when it came to the next mutual recognition procedure.

MEDICAL PRODUCTS AGENCY

“2000 minus 2”

EFPIA info day November 1998

The common efforts of Member States to improve the process of Mutual Recognition

Thomas Lönngren
Medical Products Agency
Sweden

MEDICAL PRODUCTS AGENCY

“2000 minus 2”

- The management of the Mutual Recognition procedure today
- The management up to - tear 2003
- The new system from - tear 2003 ?
- Presentation of a concrete activity
  - The heads of Agencies Web-site
  - The product index

MEDICAL PRODUCTS AGENCY

The management of the Mutual Recognition procedure today

Commision

Heads of Agencies

EMEA

MRFG and Sub-groups

Break-out sessions

CPMP(V) Working parties

Member States Authorities

Supported by some common tools as: Eudranet, Eudratrack, Web-Site, Product index

MEDICAL PRODUCTS AGENCY

The management of the Mutual Recognition procedure today

- A management without formalised duties and responsibilities
- A management without proper financing
- Despite these deficiencies
  - The system produces marketing authorisations
  - It is extremely cost effective
  - A result of common efforts by the member states

MEDICAL PRODUCTS AGENCY

The management up to - year 2003

- Up to - year 2003 the procedure should handle a majority of MAH;s in Europe
- The operational problems are well known
  - Several activities on-going in order to improve the procedure
- What to do from a management perspective

MEDICAL PRODUCTS AGENCY

The management up to - 2003

- Member state authorities
  - Some MS need to allocate resources and competence
- MRFG needs a secretariat
- EMEA support with meeting facilities

MEDICAL PRODUCTS AGENCY

The management up to - 2003

- Commission
  - Financial support
  - Flexibility in interpretation and adjustments
- Heads of agencies
  - a common approach how to deal with risk to public health
- Video conference facilities

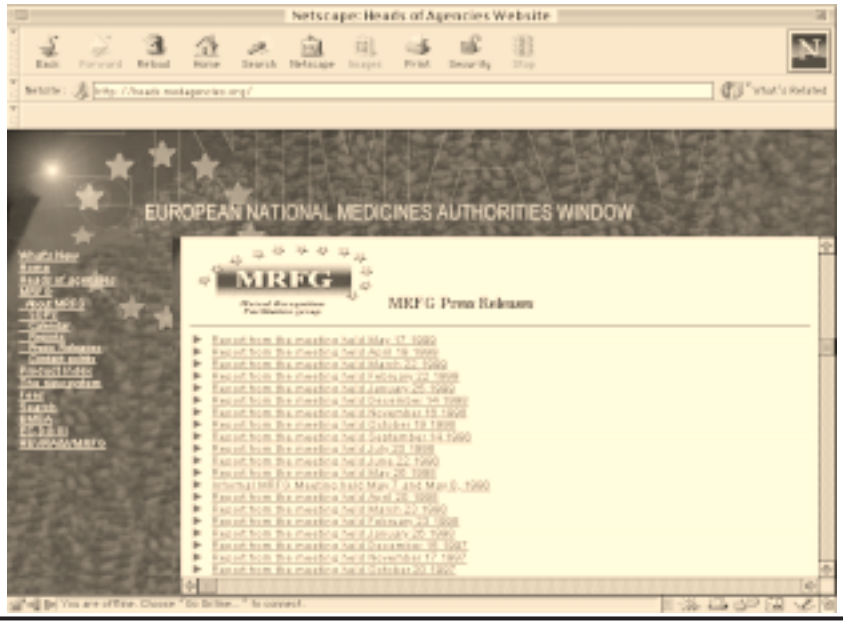
MEDICAL PRODUCTS AGENCY

The new system from - year 2003 ?

- A proper evaluation of the present system
- From the perspective of public health and single market
- Legislative base for marketing authorisations
- The quality of scientific decisions
- The operational performance

MEDICAL PRODUCTS AGENCY

MEDICAL PRODUCTS AGENCY



MEDICAL PRODUCTS AGENCY

European Product Index for Products Authorised in the Mutual Recognition Procedure

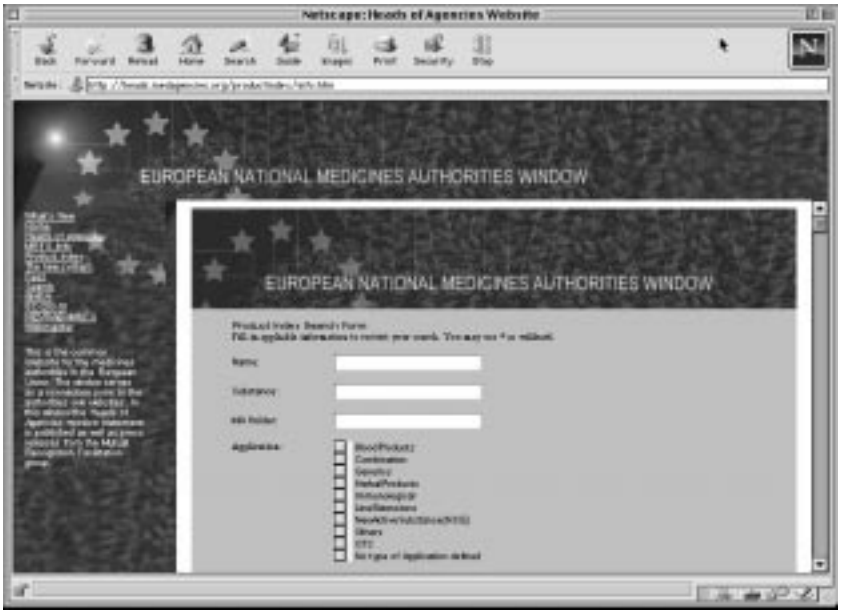
- Initiative taken by the MRFG
- Decided by the Heads of Agencies
- Purpose : to make a simple product index available to the public through the world wide web
- Located on the Heads of Agencies web-site
- The content of the Product Index is in the hands of MS agencies
- To be launched in January 1999

MEDICAL PRODUCTS AGENCY

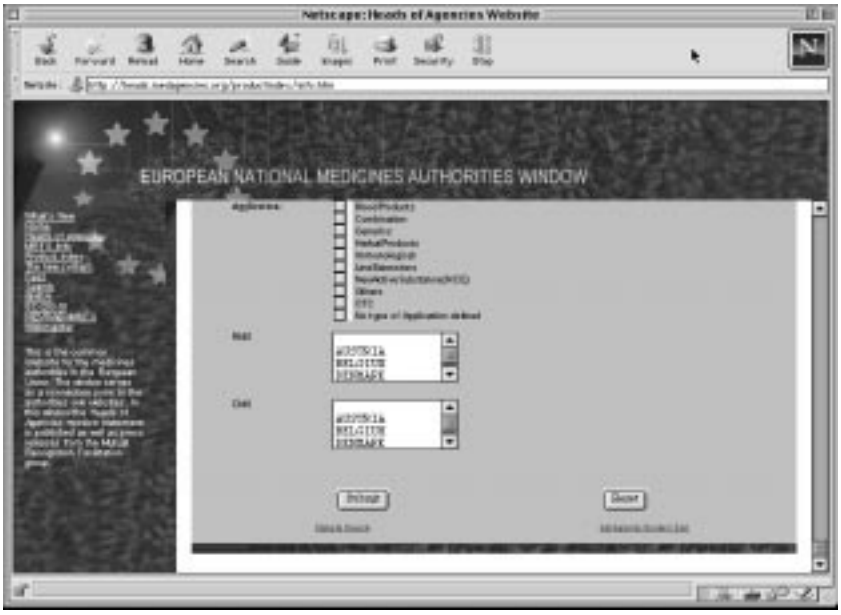
Information in the Product Index

- Automatic transfer of data from Eudratrack
- RMS and CMS
- MR number
- Name in RMS and CMS, strength and form
- Active ingredient
- Type of application
  - NCE, line extension, fixed combinations, generics, herbal, OTC, others
- Marketing authorisation holder
- Date of day 90 in the procedure

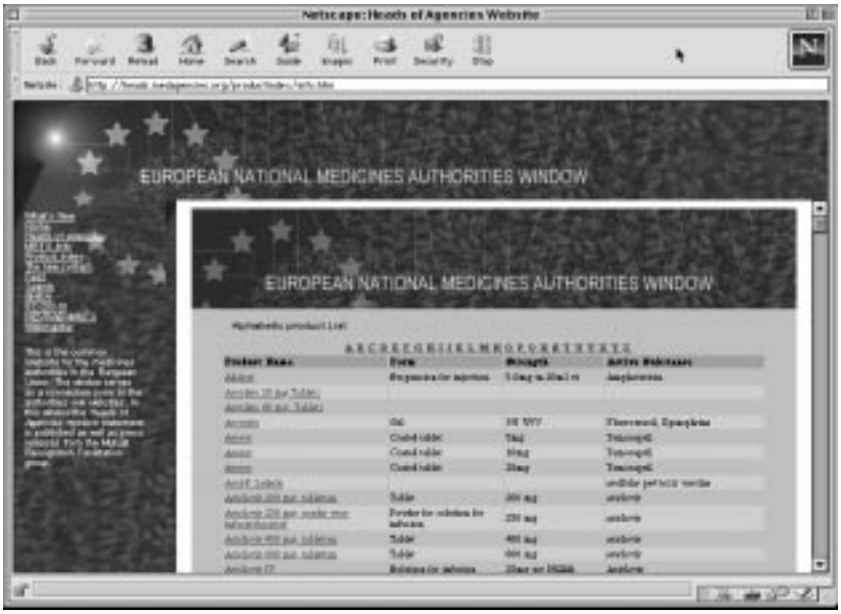
MEDICAL PRODUCTS AGENCY



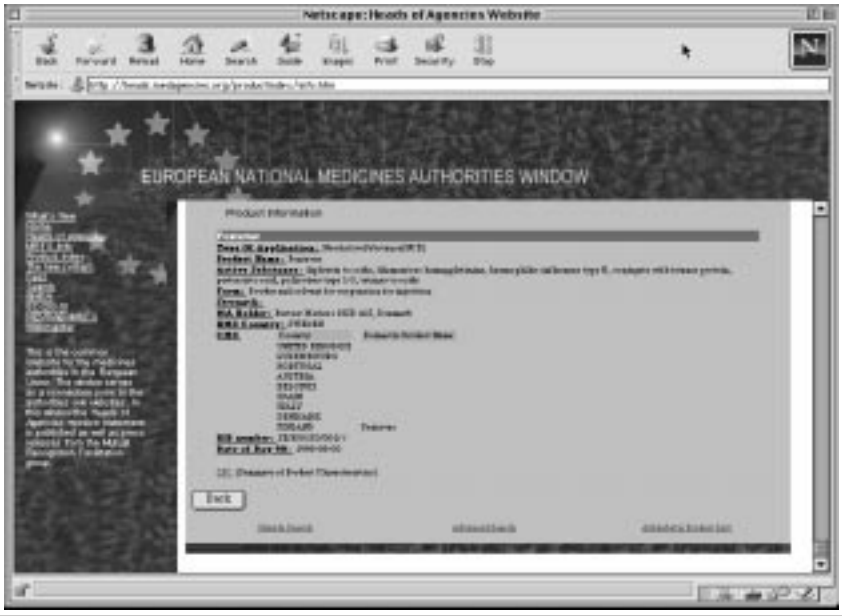
MEDICAL PRODUCTS AGENCY



MEDICAL PRODUCTS AGENCY



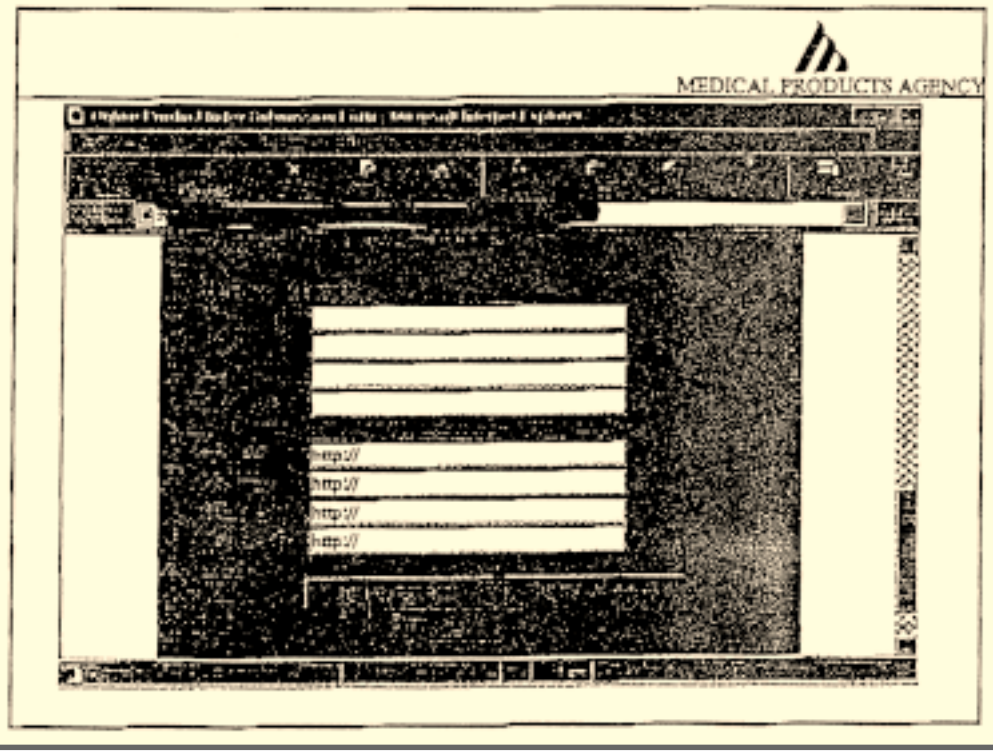
MEDICAL PRODUCTS AGENCY



MEDICAL PRODUCTS AGENCY

Further development of the index

- Under discussion (no decision taken)
- Based on the concept that MS agencies publish product information on their own web-sites
- Links should be set up from the product index to MS web-sites on:
  - SPC:s (local language and in English)
  - Packaging leaflets
  - Mutual Public Assessment Reports



Panel discussion : How to be better prepared for the next century ?

All speakers and
Dr. Olivier AMEDEE-MANESME
Medical Director
Syndicat national de l'Industrie Pharmaceutique (SNIP)

Dr. Birka LEHMANN
Next Chairperson of the Mutual Recognition Facilitation Group (MRFG)

Dr. David ROBERTS
Director of Scientific and Regulatory Affairs
Almirall Prodesfarma

Dr. Bolton opened the discussion by asking each of the participants if they had any thoughts to share, and first he asked Dr. Lehmann to comment on whether the Commission Communication had made a positive contribution to the mutual recognition procedure.

Dr. Lehmann replied that positive side was clearly that it was out, although she thought that some clarification might be needed. She explained that the MRFG had asked some open questions to the Commission in respect of “informed consent” applications (called “copies” or “clones” previously). It had to ask the Commission again whether it was possible for generics to have so-called “line extensions”, or must they be fixed under the line extension exception as mentioned in the Commission communication. The MRFG needed more clarification on what the Commission meant by “line extension”. Even though the MRFG had had a long-lasting discussion with the Commission, which had given some hints and information on how the Communication should be interpreted, the MRFG needed more detailed information. Next, the Commission or the MRFG would compile all this information so that everybody would be aware of the rules of the game. Concerning the definition of “public health concern”, she considered that if this was so easy to do, all the trade associations would have already defined it.

Dr. Bolton agreed that to define a “public health issue” was very difficult, and asked Dr. Roberts what particular issues he had to face. Dr. Roberts replied that he was as much concerned about preserving certain aspects of the regulatory present as about changing the regulatory future. Since his Spanish research-based company only had subsidiaries in Portugal and Belgium, it needed licensees simply to get marketing access for its products to the rest of Europe. This could involve having different licensees in different Member States. This in turn resulted in a corresponding need for more than one trademark, a situation not permitted under the centralised procedure and potentially under threat under the mutual recognition procedure. Dr. Robert's company products also operated inversely as licencee to co-market multinational medicinal products under its own trademark in Spain, and this was facilitated by the approval of a “clone” dossier presented nationally for a product already approved by mutual recognition. Recently, the Spanish authorities had indicated that that was no longer permitted by the Commission.

Next, Dr. Amedee-Manesme stressed that the main concern was patients, and that industry was working for people with diseases and to solve public health problems. Secondly, he welcomed the suggestion of using more video conferences. Next, he gave a summary of the day : a lot of advantages and disadvantages of the centralised procedure, and the industry's willingness to increase the harmonisation of the two procedures. He explained that industry did not want a “European FDA” in two years, but wanted to keep the national agencies, whilst reducing the administrative workload and enhancing transparency.

A remark was made on the mutual recognition system, which did not seem to be designed for more arbitration because this meant sequence of three different procedures : 210 days to get the first marketing authorisation, 90 days to complete the first mutual recognition and 150 days or more to complete the arbitration, i.e. around 2 years to complete the process. A question was asked on the need for mutual recognition, and why a marketing authorisation granted by one Member State is not automatically valid in the rest of Europe.

Dr. Lehmann replied that until now, the national agencies had borne the responsibility laid down in national laws and in EU legislation, to check on risks to public health. Member States had therefore to check all incoming applications.

Dr. Lönngren commented that the two procedures aimed to harmonise medicines in Europe. Medicines were part of the healthcare profession, and the EU had not harmonised medical practice throughout Europe. Member States still had differing medical cultures and practices.

Next there were some comments on Dr. James' presentation. For the time being, it was not so bad to use the so-called second wave applications and it was important to try to avoid arbitration. The proposal regarding a Standing Committee

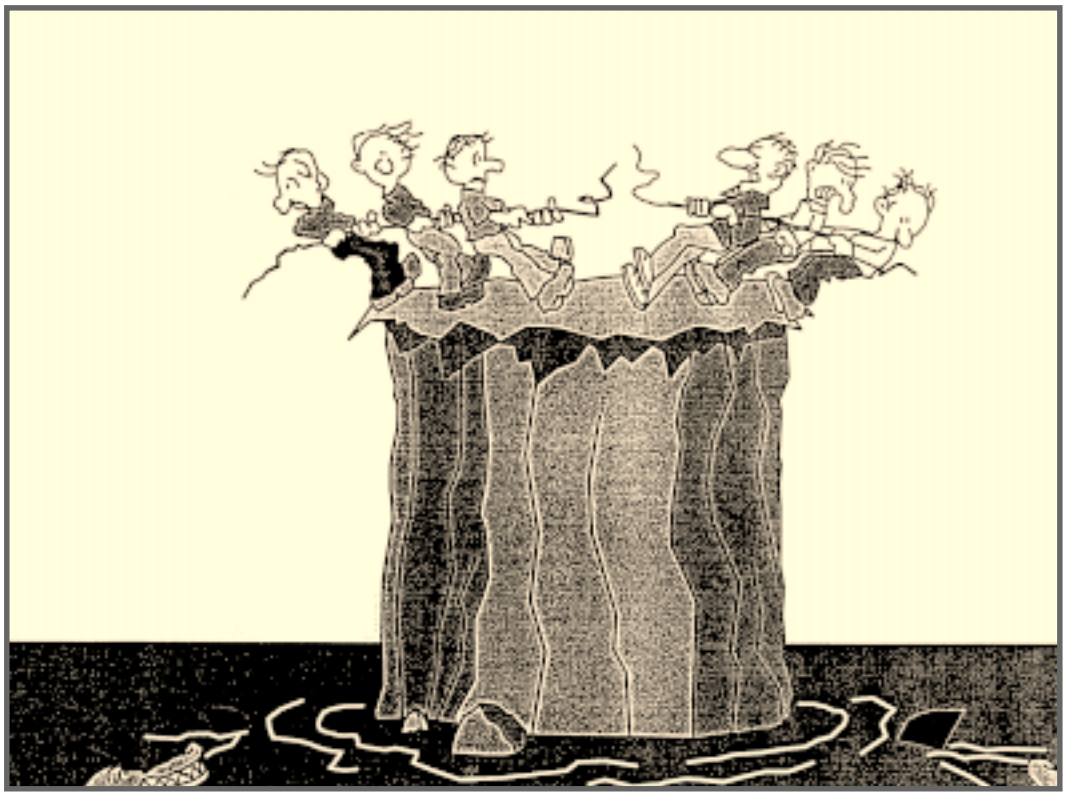
to assess whether a certain problem was a real public health issue was not so clear, i.e. the membership of this Committee, or the real benefit in terms of time. The MRFG dealt only with procedural aspects, but not scientific ones. This group identified scientific issues that were then discussed in the breakout sessions. The results of the breakout sessions had not always been as expected because many Member States had been very reluctant to send their senior experts who were empowered to take decisions. It was therefore suggested to explore the possibilities and the feasibility of having a legal framework for such a group. A scientific body with a legal framework could kick in before day 90 to avoid arbitration, without any clock stop, which would change the principles of the mutual recognition.

Dr. James welcomed this idea and remarked that while he was giving his presentation, he had wondered about the respective resource implications of going through arbitration or using a "second wave" for the national authorities.

Dr. Lehmann replied that the experience was limited with only 5 arbitrations and 9 "second wave applications". She thought that in a second wave, Member State concerns had not melted away but the Members States had been convinced by new data or new information. It was difficult to say that if you had one scientist opinion, everybody had to agree with this opinion.

Mr. Sauer remarked that it might be possible to combine the mutual recognition procedure and the ex-concertation procedure and that this should be explored. He did not affirm that this was the solution, but at this stage, this could be easily done without new legislation. If the rate of arbitration was going up, the CPMP would anyway spend a lot of resources on it. RMSs would assess the dossiers, but instead of doing it at national levels, they would share some parts of their thoughts with other colleagues, and the EMEA could provide some support. This had the virtue of creating the necessary confidence, really brining down all the anxieties which would not be very serious health concerns, and providing a mechanism for validation. Then, when the RMSs had delivered their authorisations, the 90 days could still be useful to make sure it would have been an effective process, leading to rapid decision. Member States would keep all the cards in their hands. This was worth consideration, if arbitration entails investing massive resources in scientific discussion.

Dr. Bolton concluded by stressing the importance of freer and more frequent discussions in the dialogue between industry , associations, MRFG, the Commission, and the EMEA. It was essential to keep these initiatives moving toward a better position for patients receiving new medicines whilst ensuring that this was done in accordance with the best public health protection standards.



	CENTRALISED PROCEDURE	DECENTRALIZED PROCEDURE
ADVANTAGES	X	1
	Y	2
	Z	3
	...	...
DISADVANTAGES	X	1
	Y	2
	Z	3
	...	...

Dr. AMEDEE-MANESME

REGULATION 2000

IN FACT KEEP AND INCREASE THE EFFICIENCY AND HARMONIZATION OF THE 2 PROCEDURES.

EMEA IN 2OOO ?

File door

WE PREFER A HUMAN FACE FOR OUR ADMINISTRATION

DECREASE THE ADMINISTRATIVE FLOW

INCREASE THE TRANSPARENCY

CLOSING REMARKS

Mr. Strachan HEPPELL
Chairman of the Management Board
European Agency for the Evaluation of Medicinal Products (EMEA)

Mr. Heppell offered some conclusions, stressing that progress in Europe had been incremental, and that this was the right way to go, as had been widely agreed during the day. People together were better than the best individual alone. The value of learning from experience was essential. EFPIA and EMEA would need to talk about how to achieve better responses both from companies and regulators. He finally shared three thoughts about that background : working together, choice and self-regulation. He agreed that good regulation was no more regulation than necessary, but added that there were risks in self-regulation and that a single company could damage the industry a great deal. Public confidence matters. He thought that the pharmaceutical industry should remember what had happened to the UK financial services industry, which had been very badly damaged by poor self-regulation in selling to personal pensions : it had lost a good reputation, and would take many years to recover it fully.

Mr. Brian AGER
Director General
European Federation of Pharmaceutical Industries and Associations (EFPIA)

Mr. Ager concluded by expressing his satisfaction with the very positive, constructive, and high-quality level of discussion. He summarised the main outcomes, stressing the proposals for short-term improvements and construction. Concerning the performance of the centralised procedure, more criticisms had come from both sides. That always indicated that the system was healthy system, that it worked, and that real issues had been spotted. Good ideas would immediately be transformed into actions, and especially Mr. Sauer's suggestion of publication of the performance results in an even more transparent way on the web site. That would give a rolling system in which trends could be identified at more points in the curve and not just once a year. Prof. Winkler's suggestion, of a case study between the EMEA, the CPMP, EFPIA and the companies involved going into more depth for specific areas about specific problems rather then putting them into the pie-chart, was also well worth pursuing. Concerning the long term, Mr. Sauer had presented what would happen between now and 2005/2008, and the Regulation 2000 discussion document was not a set of EFPIA proposals, but just a trigger for debate. It was essential to think collectively about the future and this had been why EFPIA introduced that project. Over and above all the details discussed, Mr. Ager highlighted that the discussion between the regulators and the regulative was really impressive and that this had to be the only way to achieve improvements. Everybody wanted Europe to have the best world-class system for public health, R&D and innovation, including a strong competitive industry and patients. This was a worthwhile vision we must keep in mind.

4. SUMMARY OF THE 1998 JOINT EFPIA / EMEA SURVEY ON THE CENTRALISED PROCEDURE

4. SUMMARY OF THE 1998 JOINT EFPIA-EMEA SURVEY ON THE CENTRALISED PROCEDURE

At the initiative of the EMEA Management Board chairman, a joint industry/regulatory survey on performance indicators was initiated in 1996 to collect relevant information from the users of the centralised procedure. The objective was to identify areas of concern that could be addressed to improve the overall performance of the EMEA. For this purpose a detailed EMEA/EFPIA questionnaire has been developed. A joint industry/regulatory review panel, with members taken from CPMP, EMEA staff and EFPIA representatives discusses the results of the survey twice a year. The results are presented annually to a public meeting consisting of some 200 industry representatives and officials, most recently at the EFPIA Info day on 20 November 1998.

This latest survey included 26 completed centralised procedures (leading to a positive Commission Decision) covering the period from 18 June 1996 to 17 October 1998 . Replies were received from 100% of EMEA project managers, 73% of rapporteurs, 50% of co-rapporteurs and 77% of the applicants. The written report of the results are annexed to this paper.

As a result of the previous survey presented in 1997 covering the period between 21 May 1995 and 28 September 1997[1], several joint EMEA/ EFPIA workshops have been organised at the EMEA concerning pre-submission, validation, translations, variations and pharmacovigilance.

In addition, specific action has been taken on the following key issues :

- The scientific advice procedure has been improved and more support is given by the CPMP members and EMEA staff in managing this procedure. This will particularly facilitate the review of the application dossier, as already shown in certain cases.
- The opportunities for pre-submission meetings have been increased. The organisation of the meetings has been streamlined and a pre-submission request form together with an interactive and user-friendly guidance document have been made available on the EMEA web site.
- There has been an increased emphasis on providing a higher quality of public documents and translations from the start of the procedure. A Product Information Quality (PIQ) initiative involving some 40 project managers and secretaries of the EMEA was introduced in October 1997 to check documents at EMEA level. Furthermore, the activities of the Quality Review of Documents working group (QRD-members consist of EMEA staff and representatives of Member States) have been improved particularly by finding the right balance between meetings and usage of e-mail. Templates have been updated and are frozen for a defined period during an application and in addition, a format convention and summary of QRD terminology have been provided to applicants.

Analysis of the responses from the 1998 survey showed that since the 1997 results, overall timelines have been better respected and oral explanation meetings were more productive. The quality of translations has notably improved, although there is some indication of a division into two groups of applicants, one providing poorer translations and the other even better translations. This could indicate a differential level of experience and effort being made between different applicants.

The current survey also revealed more criticism of the quality of the initial dossier and the expert reports received from the applicants. During the procedure itself, there were more outstanding objections raised by CPMP members to the approvability of an application, with a consequent increase in the number of hearings and a significant increase in the number of withdrawals by applicants. These withdrawals are possibly due to an increase in the number of premature applications being filed by companies and the strict time-frame imposed by the CPMP obliging applicants to provide responses to the questions raised by the CPMP within 6 months. The scientific causes of the withdrawals are in the process of being further investigated and the main outcome will be made public later this year.

During the 1998 survey, 9 applications for the centralised procedure were withdrawn and analysed separately (a separate written report is attached). Replies were received from 100% of the project managers, 30 % of rapporteurs, 22 % co-rapporteurs and one-third of the applicants. The applications related to 2 part A (biotech) and 7 part B (new chemical substances) products. It should be noted that CPMP scientific advice had not been requested for any of these procedures. The reasons for withdrawal were lack of efficacy in 8 cases and one safety concern. In all cases, it was clearly stated at day 120 that the products were non-approvable. The applications were withdrawn, as the applicants were not able to provide additional information, data and responses. Oral explanations did not take place. In the meantime, one application was subsequently updated and re-submitted and a positive opinion has been adopted by the CPMP.

For the 26 centrally-approved medicinal products, it should be noted that in 7 out of 18 cases reported, a “non-approvable” letter was issued at day 120, although ultimately all these products were approved. This shows the importance of the second evaluation round and the additional opportunities provided by hearings. This also indicates the ability of the CPMP to reconsider its position once presented with additional data and convincing arguments by the applicants.

Some concerns remain regarding the quality and the clarity of the issues raised in the assessment reports, as well as

[1]Time period covering date of start of first included procedure and date of last Commission Decision

the clarity of the list of questions. These issues will be explored in more depth in a workshop to be organised involving concerned applicants, CPMP members and EMEA staff in early 1999.

In conclusion, applicants are encouraged to continue to seek a continued dialogue with the EMEA and accept guidance at an early stage of development to avoid problems later on. A continued interaction between applicants and the EMEA before submission and throughout the procedure is recommended, especially for applicants choosing the centralised procedure for the first time. Procedures and tools are available to support the product and the dossier development like scientific advice and pre-submission meetings. The EMEA will continue to help applicants to improve the quality of documents and translations. The survey on the centralised procedure will continue, based on a revised questionnaire focusing on major steps of the procedure (impact of scientific advice) and will include negative opinions and withdrawals. The accuracy of the survey will depend on increasing the response rate, especially from industry and co-rapporteurs.

5. FULL EMEA REPORT ON THE COMPLETED CENTRALISED PROCEDURES SURVEY 1998

GENERAL INFORMATION

DESCRIPTION OF THE COVERED PROCEDURES

Inclusion criteria: completed centralised procedures (Commission Decision) since last phase of the Survey

Covered time period: June 1996 (start of the first included procedure) - October 1998 (Commission Decision of last included procedure)

Questionnaires sent out for: 57 procedures

Procedures Withdrawn: 9

Number of included centralised procedures(Commission Decision taken): 26

Date of last response: 10 November 1998

Number of responses from project manager:26

rapporteur:19

co-rapporteur:13

Rapporteur and Co-rapporteurship for the enrolled procedures:

Delegation	Number of times designated	Participation in questionnaire
France	5	4
Germany	3	2
Portugal	3	0
UK	5	4
Italy	1	0
Spain	3	2
Belgium	4	1
Greece	2	2
Ireland	3	3
Sweden	5	4
Finland	4	4
Austria	4	4
The Netherlands	5	0
Luxembourg	2	0
Denmark	3	2

PRODUCT INFORMATION

Number of Part A products: 6

Number of Part B products: 20

13. *Basis of Part A status:*

- recombinant DNA technology (number of products): 3
- hybridoma and monoclonal antibody methods (number of products):3

14. *Basis of Part B status:*

- based on radio-isotope which is of significant therapeutic interest (number of products): 1
- derived from human blood/plasma (number of products): 1
- manufacturing process which demonstrates a significant technical advance (number of products): 1
- new active substance (number of products): 18
- others (number of products): 2

ANALYSIS OF PROCEDURE

PRELIMINARY SCIENTIFIC ADVICE (BEFORE SUBMISSION TO EMEA)

15.a) *Was scientific advice sought from the CPMP during the development process before submission to the EMEA? (PM)*

YES	NO
1	25

15.b) *Was scientific advice sought from National Authorities during the development process before submission to the EMEA? (PM)*

YES	NO
7	19

If yes, specify which National Authorities:

Sweden (2), UK (1), Netherland (1), France (1), Finland (1) and non-specified (1).

16. *If yes, how useful was the scientific advice from CPMP? (R)*

1	2	3	4
0	1	0	0

Comments:

- Development in knowledge leads to a different current opinion.
- In the case of advice from National Authorities, it was appraised as useful in four cases and very useful in the other three cases.
- Comments on methodology used for clinical trials, the wording of SPC.

17. *Do you think this advice would influence the following steps of the procedure? (R)*

YES	NO
1	0

Comments:

- The clinical study design was agreed upon the advice.
- Comments on advice from National Authorities: It helped the Applicant to quickly provide answers to the list of questions which helped in reaching a consensus among the CPMP members.

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
R= Both Rapporteurs and Co-rapporteurs requested to answered
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

CHOICE OF RAPPORTEUR AND CO-RAPPORTEUR

20. *Comments on company proposal (PM):*

- Proposal accepted.
- Proposal not rejected. UK was rapporteur, IRL appointed the co-rapporteur.
- Company granted both, preferred Netherland and France.
- UK appointed rapporteur and Portugal co-rapporteur.
- UK was proposed by the Applicant and was accepted as co-rapporteur.

DRAFT SMPC

21. *General appraisal of the draft (PM):*

1	2	3	4	NA
1	7	9	0	9

Comments:

- The product information had been changed until the opinion phase. The grade was given in terms of template compliance, clarity, user friendly terminology (PIL) etc.
- Very poor understanding of requirements on the part of the company.
- Still very preliminary, a lot of pre-clinical and clinical information missing.
- Translation, combined SPC.
- Not according to template.
- No attention to templates.
- Template not followed.
- Was amended for scientific content, but was submitted in line with template.
- More or less OK.
- No major problems.

APPRAISAL OF PRE-SUBMISSION MEETINGS

Number of pre-submission meetings: 30

With EMEA only: 11

With EMEA, Rapporteur and Co-rapporteur: 2

With Rapporteur and Co-rapporteur: 5

With Rapporteur only: 10

With Co-rapporteur only: 2

26. *Date of the pre-submission meeting (R)*

No of days	More than 4 months before the start of the procedure	4 months or less before the start of the procedure
No of products	9	10

Note: n=19/30

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
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27. Organisation (R)

-With EMEA

1	2	3	4	NA
1	0	4	0	17

-With rapporteur and co-rapporteur

1	2	3	4	NA
0	1	3	1	5

-With rapporteur only

1	2	3	4	NA
0	0	6	2	12

-With co-rapporteur only

1	2	3	4	NA
0	0	4	0	0

28. Quality of discussion (R):

-With EMEA

1	2	3	4	NA
0	0	3	1	18

-With rapporteur and co-rapporteur

1	2	3	4	NA
0	1	3	2	4

-With rapporteur only

1	2	3	4	NA
0	0	4	1	15

-With co-rapporteur only

1	2	3	4	NA
0	0	2	1	2

Comments on the quality of the meeting:

- This was an explanatory meeting in which the Applicant outlined the clinical programme and summarised the virology data.
- There was not really any opportunity to discuss because the Applicant really wanted only to 'present'. Questions were 'fended' rather than answered.

29. *Outcome of the meeting, specify (PM, R):*

- Points for clarification, some of those were resolved before the submission of the applications. Additional work could be started at an early phase.
- Pre-submission: information was provided to the company on dossier requirements, inspection issues, samples and translations. Discussion on eligibility for fast-track assessment. Many procedural problems. Tradename problems. 'Anti-competition' problems concerning methods of analysis.
- Clarification of procedural issues.
- Timelines for application, content, inspection, release sites, fees, number of applications and labelling.
- Discussion on possibility of electronic submission and on clinical aspects of the application.
- The aim of these meetings was to present the product to the rapporteur and co-rapporteur.
- Key issues discussed included, accelerated evaluation, access to CPMP Assessment Report by 3rd parties, • o n - going licensing negotiations.
- Satisfactory.
- On first meeting, a lot of procedural/administrative questions clarified, inspections discussed, advice on the presentation of clinical results. On a later meeting, only scientific issues discussed.
- Manufacturing and batch release issue clarified, timelines discussed.
- Preclinical and clinical issues needing special emphasis in the Expert Reports were identified.
- Double application issue was advised to the company. Good meeting.
- Positive.
- Satisfactory.

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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- Useful exchange of views and information.
- Satisfactory from EMEA point of view.

30. Need to provide further information? (R, PM)

YES	NO	NA
15	2	12

-Comments on Administrative data (14):

- Amendment of Part 1A GMP certificates.
- Validation problems numerous: incomplete Part 1 A
- CV of Phr. Person.
- Copy of mock-ups, CV's, good copy of signature pages for expert reports, copy of certificate of change of company name.
- Clarification on packaging sites.
- SPC (separation/strengths) and translated labelling. Person responsible for pharmacovigilance.
- Minor issues.
- Manufacturers authorisation.
- Incomplete administration. Expert reports incomplete.
- Minor issues only.
- SPC's UPL's in MS 6 word documents.
- Person responsible for pharmacovigilance.
- Manufacturing authorisation from FDA for one of the manufacturing sites, revision of the SPC.
- MA's clarifications regarding batch release.
- Manufacturing authorisations

-Comments on Quality (4):

- Manufacturing licences.
- In relation to c-IEF test for release of the product and manufacturing sites.
- Incomplete expert reports.
- Clarification on composition statement.

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

-Comments on Non-clinical safety(1)

- Incomplete expert reports.

-Comments on Clinical Safety (1)

- Incomplete data.

-Comments on Efficacy (1):

- Incomplete expert reports.

Quality of Assessment Report

34. Date of receipt of the Assessment Reports from Rapporteur and Co-Rapporteur:

No of days	70 days or less after the start of the procedure	More than 70 days after the start of the procedure
No of products	29	23

35.Appraisal of the quality of the rapporteur's Assessment Report (PM):

-Quality part

1	2	3	4	NA
0	0	12	11	3

-Safety part

1	2	3	4	NA
0	0	11	11	4

-Efficacy part

1	2	3	4	NA
0	0	10	12	4

35bis. Appraisal of the quality of the co- rapporteur's Assessment Report (PM):

-Quality part

1	2	3	4	NA
0	0	16	6	4

-Safety part

1	2	3	4	NA
0	0	7	4	5

-Efficacy part

1	2	3	4	NA
0	0	17	5	4

36. Clarity of the issues raised in the Assessment Report (PM):

1	2	3	4	NA
0	0	14	10	2

Comments:

- Due to large number of indications sought, it is difficult to give an overview.
- One delegation produced two assessment reports one for each dosage form which had to be combined.
- No major issues.
- Satisfactory in general.
- OK

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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37. Quality of the dossier (R):

-Quality part

1	2	3	4	NA
1	9	15	4	3

-Safety part

1	2	3	4	NA
0	5	22	1	4

-Efficacy part

1	2	3	4	NA
0	6	18	3	2

-Comments:

- Many minor faults, badly arranged, sometimes contradictory.
- Orphan disease product, good dossier on limited information.
- Might have been newcomer problems in Parts II and III.
- Three major objections on Part II.
- This answer represents a Clinical Assessors judgement of the dossier.
- The technical quality only. The scientific quality was expressed in the assessment report.
- Indexes and data were problematic to the assessment process.
- Index of volumes was missing.
- Generally well organised and presented but piecemeal additions and corrections to the dossier

38. Quality of the expert reports provided by the Applicant (R):

-Quality part

1	2	3	4	NA
1	6	19	2	4

-Safety part

1	2	3	4	NA
0	6	23	2	1

-Efficacy part

1	2	3	4	NA
0	6	22	3	1

-Comments:

- Part III dossier left a number of unresolved issues; additional data submitted to support responses to CPMP questions were satisfactory.
- Very short and not critical.
- This answer represents a Clinical Assessors judgement of the Clinical Expert Report.
- The table form of expert report was partly missing.
- As usual, the Clinical Expert Report could not be described as a critical comment on the clinical data.

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
R= Both Rapporteurs and Co-rapporteurs requested to answered
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

APPRAISAL OF THE CPMP MEMBERS COMMENTS TO RAPPORTEURS AND CO-RAPPORTEURS

39.Number of CPMP members commenting (PM):

No. of members commenting	4	5	6	7	8	9	10
Regarding no. of procedures	1	5	7	4	5	1	1

Mean number of CPMP members who commented in each procedure: 7 members

40. Punctuality of CPMP, were all the comments received within the deadline?(PM)

Yes	No	NA
15	7	4

40bis. How many CPMP members replied late?(PM)

No. of members replying late	1	2
Regarding no. of procedures	5	2

41.Were major comments distinguished from minor comments?(R)

Yes	No	NA
19	9	4

42.Relevance of their comments as judged by rapporteurs (R).

1	2	3	4	NA
0	2	21	4	5

-Comments:

- Comments on Part II not relevant.
- Only minor comments from CPMP members.
- Sometimes repetition of questions already stated by rapporteur or co-rapporteur.
- Very few additional matters were raised; most were in agreement with conclusions of Assessment Report and draft LOQ.
- Comments related to the wording of the indication for fixed combination products used in hypertension.

Evaluation of the EMEA list of questions to the Applicant

45.Were the conclusions an indication of the product being approvable?(R)

Answers from:	No indication	Approvable	Non approvable
Rapporteur	1	11	9
Co-rapporteur	1	8	5

45bis.If the product was approvable, in which areas were there questions to be answered? (R)

Answer from:	Quality	Clinical Safety	Pre-clinical safety	Efficacy
Rapporteur	10	10	8	8
Co-rapporteur	7	6	4	7

45ter.If the product was not approvable, in which areas were there major objections to be addressed? (R)

Answer from:	Quality	Clinical Safety	Pre-clinical safety	Efficacy
Rapporteur	4	6	4	8
Co-rapporteur	3	2	3	5

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
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46. Number of questions removed from the draft list following CPMP discussion (PM):

No. of questions removed	1	4	34	NA
No. of times	1	1	1	23

47. Was it necessary to stop the clock?(PM)

Yes	No
20	2

48. Duration of the clock stop(PM)

No of days	Less than100 days	More than 100 days	NA
No of products	13	11	2

Mean duration of clock-stop for Part A: 169

Mean duration of clock-stop for Part B: 103

Meeting of the Applicant with rapporteurs and project managers to prepare answers

49.Was there a meeting?(R)

Yes	NA
13	13

50. Was the meeting useful to prepare the answers? (R)

Yes	No
9	4

If it was not, comments:

- Quality part of the answers inadequately documented. Major objections to Part II, III and IV.
- Discussion took place between rapporteur and Applicant extensively over the telephone, not a face to face meeting.
- Meeting with US Applicant was supplanted by several conference calls between assessor and Applicant. Preclinical follow up questions put to Applicant.
- Preparation of the answers was successfully discussed with the Applicant over the telephone.
- Useful exchange of views and information.

Quality of responses by Applicant

53.1 Quality(R)

1	2	3	4	NA
1	6	18	4	5

Comments:

- Questions were not answered.
- Quality: many contacts with the Applicant were needed to clarify the quality aspects.
- Substantial changes were undertaken in comparison to the original dossier, new questions occurred, again sometimes contradictory, badly arranged, confusing.

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
R= Both Rapporteurs and Co-rapporteurs requested to answered
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

53.2 Pre-clinical Safety (R)

1	2	3	4	NA
0	2	22	2	6

Comments:

- Responses to Part III questions were of good quality and led to resolution of all preclinical issues.

53.3 Clinical Safety (R)

1	2	3	4	NA
1	6	22	3	2

Comments:

- Extra time allowed because important information was to come from soon-to-be completed trials.

53.4 Efficacy (R)

1	2	3	4	NA
1	3	22	3	3

Appraisal of clarity and format of the Assessment Report on the responses

57. Format and clarity of the Assessment Report on the responses (PM)

1	2	3	4	NA
0	0	12	9	5

Comments:

- OK.
- Good.
- Very good.
- Excellent. Joint Assessment Report was followed by a summary draft EPAR proposals and a list of residual questions.

Deadline of comments of CPMP members back to rapporteurs

59. Respect of the deadline for comments by CPMP members (R, PM):

Yes	No	NA
15	10	33

-If not, please specify:

- One delegation was one day late.
- Sweden and Denmark sent important objections one day late. France had important objections which were never sent, they were only revealed at the table of CPMP.
- Problems with deadline.
- French comments arrived late.
- Sweden and Spain were late.
- Some comments came late because rapporteurs joint report was not received on time.
- One delegation provided comments one day late.

60. Number of CPMP members who provided comments and objections (PM)

No. of members who provided comments	3	4	5	6	8	NA
Regarding no. of procedures	2	5	6	7	1	5

60bis.Number of CPMP members with outstanding major objections (PM)

No. of members with objections	1	2	3	10	NA
Regarding no. of procedures	3	4	2	1	16

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

Restart of the clock and oral explanation

64. Did the company request a clock stop from CPMP? (PM)

Yes	No
0	17

66. Was a preparatory meeting with the rapporteurs and project manager organised?(R)

Yes	No
12	7

67. If yes, how useful was the meeting?(R)

1	2	3	4	NA
0	0	7	5	20

Comments:

- Preparatory meetings with the rapporteur only, without project manager.
- Meeting with co-rapporteur only.
- The oral explanation for the quality was not at the CPMP meeting, but a telephone meeting between rapporteur and Applicant.
- Briefing of company on which questions to address during hearing.
- The meeting helped to resolve the questions and allowed the hearing to be cancelled.
- Resulting from the meetings, the oral explanation was very well prepared by the Applicant, i.e. written responses to the pending issues which the rapporteur assessed and circulated before the formal CPMP meetings.

69. Were you satisfied with the oral explanation (R)

1) with regard to the scientific discussion of outstanding major objections?

1	2	3	4	NA
0	1	10	6	15

2) with regard to the organisation/ facilities/ timing?

1	2	3	4	NA
0	0	7	8	17

Comments:

- Very good indeed, perhaps due to the advice given by the rapporteur.
- Quality issues resolved prior to oral explanation.
- Discussion between the Applicant and the rapporteur took place outside the CPMP plenary meeting.
- Applicant was well-prepared, focused answers on questions put and brought the key personnel to the meeting.
- Because the written response was considered sufficient, an oral presentation was not necessary.

71. Appraisal of the responses given by the Applicant during the oral explanation (R)

1	2	3	4	NA
0	1	11	5	15

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
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PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

Comments:

- All the questions were not answered.

72. Do you think the oral explanation was useful? (R)

Yes	No	NA
15	2	15

Final draft of the English SmPC, package leaflet and labelling

74. Please indicate any changes requested in the SmPC, leaflet and labelling (R)

Changes requested	Number of times
• Several changes in different sections: indications, contra-indications, interactions, special warnings, undesirable effects, pharmacodynamics...	7
• Numerous changes to give more detailed information	1
• Minor changes (special warning, typing errors...)	6
• Major changes in most parts of the document.	3
• Other	3

Translations sent by the company to CPMP Members and EMEA for comments before day 120

77. EMEA appraisal of the quality of translations provided by the Applicant before adoption of the Opinion (PM)

	1	2	3	4	NA
Linguistic	2	3	11	5	5
Format	2	4	9	5	6

-Comments:

- Very bad in all languages.
- Very bad indeed.
- QRD group revised the documents, many translations were of bad quality.
- SPC labels very bad. Pack insert not so bad.
- French comments unusual, received late in procedure and subsequently revised during Standing Committee.
- Not according to the template PIQ review.
- Only one problem with labelling texts/mock ups.
- Company provided excellent quality translations.

CPMP Opinion and CPMP draft Assessment Report

79. Date of the CPMP opinion(R)

No of days	Less than 210	More than or 210
No of products	25	1

Mean:182

Standard Deviation:25

81. Please indicate any changes between the SmPC applied for and the SmPC approved: (R)

Changes regarding:	No of procedures
• Indication	11
• Dosage	2
• Contra-indications	6
• Shelf- life	3
• Special warnings	11
• Preclinical toxicology	4
• Pharmacodynamics	3
• Undesirable effects	3
• Precautions	7
• Others	2

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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82. Assessment of changes made by the Applicant in the SmPC, Patient Package Leaflet and Labelling (R)

1	2	3	4	NA
0	0	12	5	15

Finalisation of CPMP Assessment Report and transmission of Opinion

84. Overall Assessment of translations (PM):

1	2	3	4	NA
0	2	15	5	4

Comments:

- Very poor.
- Poor.
- Still problems with labelling text for combination languages.
- Problems with the Portuguese version.
- Slight improvement on last time.
- Not bad.
- Reasonable.
- As assessed by QRD.
- Reflecting positive QRD review.
- Improved following QRD review.

85. Was the deadline respected for receiving the final translations?(PM)

Yes	No	NA
15	6	4

85bis. If no, specify delay involved: (PM)

- Greece was delayed.
- Nine languages on time, two delays.
- Six days late.
- Seven days late.
- Nine calendar days delay.
- Company was six weeks late.
- Delayed comments from members.

85ter. Time period from receipt of final translations to transfer to the European Comission (calendar days) (PM):

No. of days	2	3	5	6	7	8	10	16*
No. of procedures	2	3	3	2	5	1	3	1

Mean number of days: 6

*Delay due to massive problems with several languages

- linguistic problems
- template
- internal technical problems (transfer from Mac to PC)

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

Overall Overview

92. Were the Rapporteurs/ Co-rapporteurs satisfied with the general consistency between assessment of the dossier, issues raised and responses given? (R)

1	2	3	4	NA
1	4	11	5	3

93. Were the Rapporteurs/ Co-rapporteurs satisfied with the transparency in relationships between all partners?(R)

1	2	3	4	NA
1	1	13	6	3

94. Other comments (PM, R)

- The Applicant was 'pressing' the rapporteur/co-rapporteur at the stage before the response to the list of questions. This created discomfort.
- The transparency between the Applicant and the rapporteur and co-rapporteur was very satisfactory. But, in contrast to that, some CPMP delegations held meetings with the Applicant without giving any notice to the rapporteur. The final opinion was unduly postponed by the CPMP.
- The rapporteur had to be changed during the application procedure. This caused some minor inconsistencies, but did not cause real problems.
- There was a disagreement between rapporteur and co-rapporteur, which only came out during the oral explanation.
- The procedure for this product was highly unusual in that there was a request from the standing committee/ PGIII for a supplementary opinion of the CPMP on the issue of anti-bacterial resistance. This lengthened the decision making procedure dramatically, resulting in a Commission Decision after more than 8 months as opposed to the more normal 4 months.
- The "accelerated" review process and the ongoing nature of the data meant that the data kept "growing" during the assessment time. This sometimes became rather confusing and potentially irritating. However, Applicant was completely open regarding status and provision of data on an ongoing basis.
- There was a major quality problem with the MAA as submitted. A substantial number of errors were made in compiling the dossier. As a result the company were obliged by the EMEA to re-file a complete corrected version of the application during the evaluation procedure. There was also a licence transfer/ Applicant transfer during the procedure from one company to another effected just before the opinion was adopted at the CPMP meeting.
- BWP was involved (1) at the initial phase before list of questions and (2) before the final opinion to assess the viral safety issues.
- BWP meetings to assess the viral validation questions as post-authorisation follow-up. Ad hoc meeting on immunosuppression of the product which was discussed.
- Questions 50, 74, 82, 92 and 93 of the questionnaire are unclear
- This was a satisfactory procedure. Good product, good communication between rapporteur, co-rapporteur, EMEA and Applicant. The product was given an accelerated review on the basis that it was a replacement for a product derived from human placenta.

6. FULL EMEA REPORT ON WITHDRAWN APPLICATIONS SURVEY 1998

GENERAL INFORMATION

DESCRIPTION OF THE COVERED PROCEDURES

Number of included centralised procedures: 9

Covered time period: 21 May 1996 (date of start of first included procedure)-14 Sept 1998 (date of last withdrawal)

Date of last response: 16 November 1998

Number of responses from *Rapporteur:* 3
Co-Rapporteur: 2
Project Manager: 9
Applicant: 3

Rapporteur and Co-Rapporteurship:

Delegation	Number of times designated	Participation in questionnaire
France	2	0
Germany	2	0
Portugal	0	0
UK	2	2
Italy	4	1
Spain	1	0
Belgium	1	0
Greece	0	0
Ireland	1	0
Sweden	1	0
Finland	1	1
Austria	0	0
The Netherlands	2	0
Luxembourg	0	0
Denmark	1	1

PRODUCT INFORMATION

Number of Part A products: 2

Number of Part B products: 7

13. Basis of Part A status:

recombinant DNA technology (number of products): 2

14. Basis of Part B status:

-derived from human blood/plasma (number of products): 1
-new active substance (number of products): 5
-others (number of products): 1

Reasons for withdrawal

Lack of efficacy: 8 procedures

Safety concerns: 1 procedure

ANALYSIS OF PROCEDURE

Preliminary scientific advice (before submission to EMEA)

15.a) Was scientific advice sought from the CPMP during the development process before submission to the EMEA? (PM)

Yes	No
0	5

15.b) Was scientific advice sought from National Authorities during the development process before submission to the EMEA? (PM)

Yes	No
0	1

18. Date of pre-submission (C)

-143 days before start of procedure
-109 days before start of procedure

19. Proposed Rapporteurs (C)

France	3
Germany	1
Portugal	0
UK	1
Italy	0
Spain	0
Belgium	0
Greece	0
Ireland	1
Sweden	0
Finland	0
Austria	0
The Netherlands	2
Luxembourg	0
Denmark	1

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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R= Both Rapporteurs and Co-rapporteurs requested to answered
C= Companies
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

Choice of Rapporteur and Co-Rapporteur

20. Comments on Applicant proposal, if rejected (PM):

NL, UK (without comments)

DRAFT SPC

21. General appraisal of the draft (PM):

1	2	3	4	NA
0	1	5	0	3

22. Possible problems identified (C)

Two applications were made: handling of the two dossiers was explained. Handling of the DMF resolved. Site inspections explained for US manufacturing site.

23. Date of notification of the names of Rapporteurs and Project Manager (C)

-127 days before start of procedure
-94 days before start of procedure

24. Date of confirmation of Part A or B status (C, PM)

-127 days before start of procedure
-94 days before start of procedure

25. Are you satisfied with the choice of Rapporteur/Co-Rapporteur? (C)

Yes	No
3	0

APPRAISAL OF PRE-SUBMISSION MEETINGS

Number of pre-submission meetings: 11

With EMEA only: 5
With Rapporteur and Co-Rapporteur: 2
With Rapporteur only: 2
With Co-Rapporteur only: 2

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
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26. Date of the pre-submission meeting (C, PM)

No. of days	More than 4 months before the start of the procedure	Less than 4 months before the start of the procedure	NA
No. of products	4	3	4

27. Organisation (C)

-With EMEA

1	2	3	4	NA
0	0	0	1	2

-With Rapporteur and Co-Rapporteur

1	2	3	4	NA
0	0	0	1	2

-With Rapporteur only

1	2	3	4	NA
0	0	2	0	1

-With Co-Rapporteur only

1	2	3	4	NA
0	0	2	0	1

27. Organisation (R)

-With EMEA

1	2	3	4	NA
0	0	0	0	5

-With Rapporteur and Co-Rapporteur

1	2	3	4	NA
0	0	1	0	4

-With Rapporteur only

1	2	3	4	NA
0	0	0	0	5

-With Co-Rapporteur only

1	2	3	4	NA
0	0	3	0	2

28. Quality of discussion (C):

-With EMEA

1	2	3	4	NA
0	0	0	1	2

-With Rapporteur and Co-Rapporteur

1	2	3	4	NA
0	0	1	0	2

-With Rapporteur only

1	2	3	4	NA
0	0	1	1	1

-With Co-Rapporteur only

1	2	3	4	NA
0	0	2	0	1

28. Quality of discussion (R):

-With EMEA

1	2	3	4	NA
0	0	0	0	5

-With Rapporteur and Co-Rapporteur

1	2	3	4	NA
0	0	1	0	4

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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C= Companies
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

-With Rapporteur only

1	2	3	4	NA
0	0	0	0	5

-With Co-Rapporteur only

1	2	3	4	NA
0	0	1	0	4

29. Outcome of the meeting, specify (C, PM, R):

- Confirmation was obtained that the approach to 2 applications was satisfactory and that the Applicant would be able to submit its application on schedule.
- Clarification of all aspects of the submission
- It was clarified that the challenge was to evaluate the usefulness of a drug with poor clinical documentation for a rare disease for which only limited remedies are available.
- Unknown.
- Minutes.
- Major areas of concern with respect to preclinical safety, clinical safety and efficacy were identified.
- The meeting was well structured and organised. The Applicant had a good presentation with active interaction from Rapporteur and Co-Rapporteur.
- It was clarified that the challenge was to evaluate the usefulness of a drug with poor clinical documentation for a rare disease for which only limited remedies are available.
- Major areas of concern with respect to preclinical safety, clinical safety and efficacy were identified.

30. Need of providing further information? (C)

Yes	No	NA
2	1	0

31. Details (C)

- Comments on Administrative data (2):
- Carton and blister text in all EU languages (only English version was provided in the dossier)
- Amendment of application form to change person responsible for release of product.

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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C= Companies
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

30. Need of providing further information? (PM)

Yes	No	NA
2	1	6

31. Details (PM)

-Comments on Administrative data (2):

- Person Ph.vig/ Scientific service; mock ups in en; manufacturing authority; amended PL; BSE statement

32. Date of submission of application (C)

-28 days before start of procedure
-21 days before start of procedure

32. Why this date (C)

- To meet the July CPMP meeting date - otherwise (no August CPMP meeting) additional 2 month delay in starting review process.
- Availability of supporting technical data.

33. Start of the procedure (C)

Quality of Assessment Report

34. Date of receipt of the Assessment Reports from Rapporteur and Co-Rapporteur (C):

34.1 from Rapporteur

No. of days	Less than or 70 days after the start of the procedure	More than 70 days after the start of the procedure	NA
No. of products	2	1	0

34.2 from Co-Rapporteur

No. of days	Less than or 70 days after the start of the procedure	More than 70 days after the start of the procedure	NA
No. of products	2	1	0

34. Date of receipt of the Assessment Reports from Rapporteur and Co-Rapporteur (PM):

34.1 from Rapporteur

No. of days	Less than or 70 days after the start of the procedure	More than 70 days after the start of the procedure	NA
No. of products	3	1	5

34.2 from Co-Rapporteur

No. of days	Less than or 70 days after the start of the procedure	More than 70 days after the start of the procedure	NA
No. of products	3	1	5

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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35. Appraisal of the quality of the Rapporteurís Assessment Report (C):

-Quality part

1	2	3	4	NA
0	0	1	2	0

-Safety part

1	2	3	4	NA
0	0	1	2	0

-Efficacy part

1	2	3	4	NA
0	0	1	2	0

35. Appraisal of the quality of the Rapporteurís Assessment Report (PM):

-Quality part

1	2	3	4	NA
0	0	5	4	0

-Safety part

1	2	3	4	NA
0	0	3	4	2

-Efficacy part

1	2	3	4	NA
0	0	4	4	1

35bis. Appraisal of the quality of the Co-Rapporteurís Assessment Report (C):

-Quality part

1	2	3	4	NA
0	0	3	0	0

-Safety part

1	2	3	4	NA
0	0	3	0	0

-Efficacy part

1	2	3	4	NA
0	0	2	0	1

35bis. Appraisal of the quality of the Co-Rapporteurís Assessment Report (PM):

-Quality part

1	2	3	4	NA
0	0	5	3	1

-Safety part

1	2	3	4	NA
0	0	4	3	2

-Efficacy part

1	2	3	4	NA
0	0	4	3	2

36. Clarity of the issues raised in the Assessment Report (C):

1	2	3	4	NA
0	0	2	0	1

36. Clarity of the issues raised in the Assessment Report (PM):

1	2	3	4	NA
0	0	7	2	0

Comments:

- The dossier received had a draft negative conclusion. Sections III and IV.
- Major clinical issue identified.

37. Quality of the dossier (R):

-Quality part

1	2	3	4	NA
2	0	1	1	1

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
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C= Companies
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-Safety part

1	2	3	4	NA
0	2	2	0	1

-Efficacy part

1	2	3	4	NA
0	4	1	0	0

-Comments:

- Studies generally old and non- GLP. Part IV not completed in line with NTA.

38. Quality of the expert reports provided by the Applicant (R):

-Quality part

1	2	3	4	NA
0	2	1	1	1

-Safety part

1	2	3	4	NA
0	0	4	0	1

-Efficacy part

1	2	3	4	NA
0	3	1	0	1

-Comments:

- Safety: expert did a reasonable assessment of incomplete and inadequate data set. Efficacy: not prepared in line with NTA. No critical risk/ benefit discussion.

Appraisal of the CPMP Members comments to Rapporteurs and Co-Rapporteurs

39. Number of CPMP Members commenting (PM):

No. of Members commenting	4	5	6	7	8	9
Regarding no. of procedures	1	1	1	3	2	1

Mean number of CPMP Members who commented in each procedure: 4 Members

40. Punctuality of CPMP, were all the comments received within the deadline? (PM)

Yes	No	NA
4	5	0

40bis. How many CPMP Members replied late? (PM)

No. of Members replying late	1	3	4
Regarding no. of procedures	2	2	1

41. Were major comments distinguished from minor comments? (R)

Yes	No	NA
3	0	2

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
R= Both Rapporteurs and Co-rapporteurs requested to answered
C= Companies
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

42. Relevance of their comments as judged by Rapporteurs (R)

1	2	3	4	NA
0	0	2	1	2

-Comments:

Not all comments were of course deemed relevant, but the bulk were very relevant.

Evaluation of the EMEA list of questions to the Applicant

43. Date of receipt of list of questions (C)

Day 272 after start of procedure
Day 115 after start of procedure

44. Clarity of list of questions, overall conclusions and executive summary (C)

1	2	3	4	NA
0	0	2	1	0

45. Were the conclusions an indication of the product being approvable? (C, R)

Answers from:	No indication	Approvable	Non approvable
Rapporteur			3
Co-Rapporteur			2
Applicant			3

45ter. If the product was not approvable, in which areas were there major objections to be addressed? (C, R)

Answer from	Quality	Clinical Safety	Pre-clinical safety	Efficacy
Rapporteur	2	3	2	3
Co-Rapporteur	1	0	0	2
Applicant	0	2	0	2

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
R= Both Rapporteurs and Co-rapporteurs requested to answered
C= Companies
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

46. Number of questions removed from the draft list following CPMP discussion (PM):

No. of questions removed	1	3	NA
No. of times	1	1	7

47. Was it necessary to stop the clock? (PM)

Yes	No
9	0

48. Duration of the clock stop (PM)

No. of days	Less than 100 days	More than 100 days
No. of products	0	9

Mean duration of clock stop: 210 days

Meeting of the Applicant with Rapporteurs and Project Managers to prepare answers

49. Was there a meeting? (C)

Yes	NA
2	1

50. Was the meeting useful to prepare the answers? (C)

Yes	No	NA
2	0	1

50. Was the meeting useful to prepare the answers? (R)

Yes	No	NA
3	0	2

Quality of responses by Applicant

52. Date of submission of responses (C)

280 days after start of procedure

52bis. Were earlier responses provided to Rapporteurs (C)

Yes	No	NA
0	2	1

53. Quality of the responses (R)

53.1 Quality (R)

1	2	3	4	NA
0	0	2	0	3

53.2 Pre-clinical Safety (R)

1	2	3	4	NA
0	0	2	0	3

53.3 Clinical Safety (R)

1	2	3	4	NA
0	0	2	0	3

53.4 Efficacy (R)

1	2	3	4	NA
0	0	2	0	3

54. Date of restart of the clock (C, PM)

286 Days after start of procedure
294 Days after start of procedure

55. Delays in the restart of the clock relative to the submission of the responses (C)

Yes	No	NA
1	1	1

Appraisal of clarity and format of the Assessment Report on the responses

57. *Format and clarity of the Assessment Report on the responses (PM)*

1	2	3	4	NA
0	0	4	1	4

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
R= Both Rapporteurs and Co-rapporteurs requested to answered
C= Companies
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

Deadline of comments of CPMP Members back to Rapporteurs

58. Deadline for comments on (PM. R)

168 Days after start of procedure
209 Days after start of procedure
321 Days after start of procedure

59. Respect of the deadline for comments by CPMP Members (PM, R):

Yes	No	NA
3	2	9

-If not, please specify:

- Some Members do not comment, some are late.
- The Netherlands Member was late.

60. Number of CPMP Members who provided comments and objections (PM)

No. of Members who provided comments	4	5	7	8	NA
Regarding no. of procedures	1	1	1	1	5

60bis. Number of CPMP Members with outstanding major objections (PM)

No. of Members with objections	4	8	7	NA
Regarding no. of procedures	1	1	1	6

61. Advice from Rapporteurs on need to present an oral explanation (C)

Yes	No	NA
0	0	3

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
R= Both Rapporteurs and Co-rapporteurs requested to answered
C= Companies
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

62. Oral explanation (C)

Yes	No	NA
0	0	3

Restart of the clock and oral explanation

64. Did the Applicant request a clock stop from CPMP? (C, PM)

	Yes	No	NA
Applicant	0	0	3
EMEA	2	1	6

66. Was a preparatory meeting with the Rapporteurs and Project Manager organised? (C, R)

	Yes	No	NA
Applicant	0	0	3
Rapporteur	2	1	2

67. If yes, how useful was the meeting? (R)

1	2	3	4	NA
0	0	0	1	4

Comments:

Withdrawal without a hearing

68. Date of restart of clock (C, R)

Comments:

All applications were withdrawn before an oral explanation could take place

77. EMEA appraisal of the quality of translations provided by the Applicant before adoption of the Opinion (PM)

	1	2	3	4	NA
Linguistic	0	0	1	0	8
Format	0	0	1	0	8

OVERALL OVERVIEW

92. Were the Rapporteurs/Co-Rapporteurs satisfied with the general consistency between assessment of the dossier, issues raised and responses given? (C, R)

	1	2	3	4	NA
Applicant	0	0	2	0	1
Rapporteur	0	1	1	1	2

93. Were the Rapporteurs/Co-Rapporteurs satisfied with the transparency in relation between all partners? (C, R)

	1	2	3	4	NA
Applicant	0	0	1	1	1
Rapporteur	0	0	2	1	2

94. Other comments (C, PM, R)

Comment received from one Applicant:

- Question 34. A major concern arose, raised by the Rapporteur which gave rise to a pre-day 70 clock stop. The Co-Rapporteur was unavailable/uncontactable to attend a meeting with the Rapporteur and the Applicant. This, it was felt by the Applicant, was the reason for the delay in obtaining the Co-Rapporteur's assessment report - the clinical safety section being revised to match that of the Rapporteur's. The conclusion of the Applicant was that the Co-Rapporteur's assessment has not been independent.

Please note that NA means not available
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied
The note in brackets after each question means:
PM= Only Project Managers (EMEA) requested to answered
R= Both Rapporteurs and Co-rapporteurs requested to answered
C= Companies
PM,R= All Three Project Managers, Rapporteurs and Co-rapporteurs requested to answered

7. FULL EFPIA REPORT ON THE COMPLETED CENTRALISED PROCEDURES (updated) SURVEY 1998

ANALYSIS REPORT OF THE JOINT EMEA/EFPIA SURVEY ON THE NEW EUROPEAN REGISTRATION SYSTEM - CENTRALISED PROCEDURE -

GENERAL INFORMATION

20 responses

PRODUCT INFORMATION

5. Rapporteurs

Member States	Times designated
Austria	1
Belgium	0
Denmark	1
Finland	2
France	2
Germany	0
Greece	0
Ireland	0
Italy	1
Luxembourg	0
Portugal	1
Spain	1
Sweden	2
The Netherlands	4
United Kingdom	4
Not available	1

6. Co-rapporteurs

Member States	Times designated
Austria	1
Belgium	0
Denmark	1
Finland	2
France	2
Germany	0
Greece	0
Ireland	0
Italy	1
Luxembourg	0
Portugal	1
Spain	1
Sweden	2
The Netherlands	4
United Kingdom	4
Not available	1

13. Status of the product

Part A 4 Part B 16

14. Basis for Part A status :

- recombinant DNA technology	3
- controlled expression of genes coding for biologically active proteins	0
- hybridoma and monoclonal antibody methods	1

15. Basis of Part B status :

- other innovative biotech process	0
- innovative new delivery system	0
- novel indication	0
- based on radio-isotope which is of significant therapeutic interest	2
- derived from human blood/plasma	0
- manufacturing process which demonstrates a significant technical advance	0
- new active substance	13
- others	1

SCIENTIFIC ADVICE

16. During the development process before submission to the EMEA, was scientific advice sought from the CPMP ?

Yes 2 (10%) No 18 (90%)

16.1 If yes, in which area was scientific advice sought ?

Quality1 Not available 1 NA 18

16.2 If yes, how useful was this scientific advice ?

Dissatisfied 1 Not available 1 NA 18

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

Comments :

• Scientific advice was refused.

17. Did the advice influence the following steps ?

17.1 Development of the product

Yes 1 No 1 NA 18

17.2 Subsequent assessment of the dossier

Yes 1 No 1 NA 18

18. Did you seek scientific advice from national authorities prior to this request ?

Yes 11 (55%) No 9 (45%)

18.1 If yes, in which country(ies) ?

Member States	Times chosen
Austria	0
Belgium	0
Denmark	1
Finland	0
France	6
Germany	3
Greece	0
Ireland	0
Italy	1
Luxembourg	0
Portugal	0
Spain	0
Sweden	6
The Netherlands	7
United Kingdom	6

18.2 If yes, was this advice of additional help ?

Yes 9 No 3 Not available 8

Comments:

- The advice was sought late in development. It impacted on strategy for pre-submission and submission.
- Conflicting advice was provided by national authorities.
- Discussion on the need for active comparatordata (finally not fully accepted by the CPMP).
- It highlighted the scientific aspects of potential concern to CPMP members.
- Advice identified likely areas of difference among Member States. In the case of German advice, additional pre-clinical evaluation.

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

NOT LATER THAN 120 DAYS

19. Proposed rapporteurs (nationally)

Member States	Times chosen
Austria	0
Belgium	0
Denmark	4
Finland	4
France	10
Germany	5
Greece	0
Ireland	3
Italy	1
Luxembourg	0
Portugal	1
Spain	1
Sweden	8
The Netherlands	5
United Kingdom	8

20. Identification of “possible problems” by the EMEA

- Trademarks (4 applications).
- Part II (proposed BIRD format).
- Adequate control of emulsion particule size, variability of active substance, use of a novel excipient
- Dual application (4 applications)
- Need to identify alternative rapporteurs.
- Sufficient data from clinical trials, lack of clinical endpoint data.
- Drug Master File.

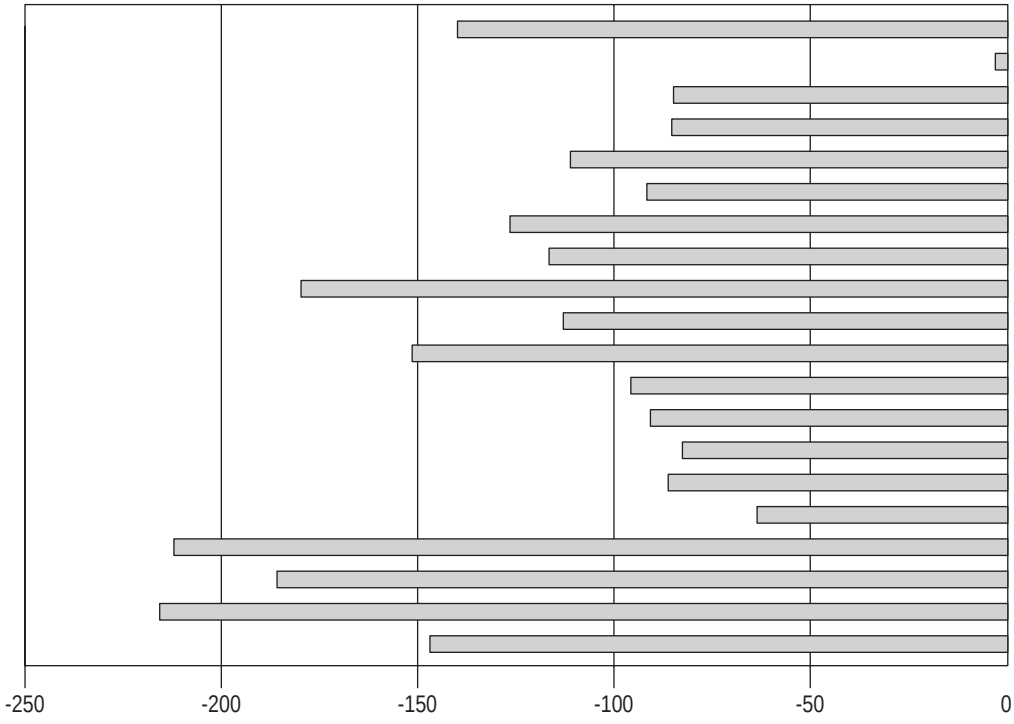
20.1 If yes, date of notification to the company

4 medicinal products < 100 days before the start of procedure
101 days < 5 medicinal products < 200 days before the start of procedure
4 medicinal products > 199 days before the start of procedure
Not available 7

- 90 DAYS APPROXIMATELY

21. Date of receipt of notification of the names of rapporteur, co-rapporteur and project manager and identification of fee to be paid

6 medicinal products < 90 days before the start of procedure
14 medicinal products > 90 days before the start of procedure



Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

22. Are you satisfied with the choice of the rapporteur/co-rapporteur ?

Yes 15 (75%) No 5 (25%)

22.1 If no, please give comments

- Information and instructions received from the rapporteur were in conflict with instructions and information received from the EMEA (administrative desk).
- We found the rapporteur to be scientifically competent but practically unable to provide any help. There were clear differences of opinion between rapporteur and co-rapporteur, which resulted in unexpected difficulties at the time of the hearing. These difficulties should have been addressed prior to this time.

- Yes for the rapporteur, but no for the co-rapporteur : difficult to gain access, inflexibilty (not prepared to enter into meaningful discussions, tendancy to not meet timelines during the registration process.
- The rapporteur and the co-rapporteur turned out to have rather little influence within the CPMP. The project manager was assigned after filing when which made the communication with the EMEA somewhat complicated.

NOT LATER THAN - 15 DAYS

23. Did a pre-submission meeting take place

23.1 with the EMEA only (administrative/regulatory issues) ?

Yes 15 No 5

If yes, when ?

9 medicinal products < 100 days before the start of procedure
101 days < 3 medicinal products < 150 days before the start of procedure
3 medicinal products > 149 days before the start of procedure
NA 5

23.2 with rapporteur and co-rapporteur and the EMEA (scientific issues) ?

Yes 6 No 14

If yes, when ?

6 medicinal products < 100 days before the start of procedure
NA 14

23.3 with rapporteur only at national level ?

Yes 11 No 9

If yes, when ?

6 medicinal products < 100 days before the start of procedure
101 days < 2 medicinal products < 150 days before the start of procedure
3 medicinal products >149 days before the start of procedure
NA 9

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

23.4 with co-rapporteur only at national level ?

Yes 12 No 8

If yes, when ?

8 medicinal products < 100 days before the start of procedure
101 days < 4 medicinal products < 150 days before the start of procedure
NA 8

23.5 with rapporteur and co-rapporteur jointly at national level ?

Yes 0 No 20

24. Quality of the meeting with regard to organisation, facilities and timing

24.1 with the EMEA ?

1	2	3	4	NA
0	1	10	4	5

24.2 with rapporteur and co-rapporteur and the EMEA ?

1	2	3	4	NA
1	1	2	2	14

24.3 with rapporteur only at national level ?

1	2	3	4	NA
0	0	6	5	9

24.4 with co-rapporteur only at national level ?

1	2	3	4	NA
1	1	6	4	8

24.5 with rapporteur and co-rapporteur jointly at national level ?

NA 20

Comments :

- The rapporteur was available for less than 10 minutes and proposed a process outside of the CPMP SOPs/ guidelines without time for discussion.
- The applicant would have preferred not to have had both meetings on the same day, but timescale was too short to organise this (not the fault of rapporteur and co-rapporteur).
- The meeting with the rapporteur and the co-rapporteur was of limited value. It took place during the CPMP week and it was clear that the rapporteur had other more pressing issues to resolve.

25. Please qualify the usefulness of the meeting(s)

25.1 with the EMEA only ?

1	2	3	4	NA
1	3	8	3	5

25.2 with rapporteur and co-rapporteur and the EMEA ?

1	2	3	4	NA
1	1	2	2	14

25.3 with rapporteur only at national level ?

1	2	3	4	NA	Not available
0	0	5	5	9	1

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

25.4 with co-rapporteur only at national level ?

1	2	3	4	NA
0	2	5	5	8

25.5 with rapporteur and co-rapporteur jointly at national level ?

NA 20

Comments :

- EMEA reversed decision on legal status in the week before the submission. The objections to the trademark were discussed. It was decided to wait for new data. Legal status of UK offices. Proposal for accelerated review.
- Applicant was provided with misleading information by the EMEA. The EMEA meeting led to confusion and conflict with rapporteur's opinion. Scientific meetings with rapporteur and co-rapporteur were very helpful.
- Overview of the dossier. Identification of probable scientific issues. Agreement on submission practicalities.
- No specific outcomes. The meetings were used more as an introduction to the medicinal product. Some general comments were useful.
- Very little information was obtained from the co-rapporteur.
- Even though rapporteur and co-rapporteur were satisfied with the dossier, the EMEA made very significant comments one week prior to submission and this had a great impact on the dossier, which had already been printed. The EMEA advised that the application might not be validated unless the alterations were made.

26.Were any problems identified during the meetings which could have led to major objections during the assessment of the file ?

Yes 2 (10%) No 12 (60%) NA/not available 6 (30%)

26.1 If yes, please give comments

- To the contrary, no problems were identified then, but they surfaced later in the CPMP procedure.
- Choice of the reference standard for potency assay. Decrease of the response.

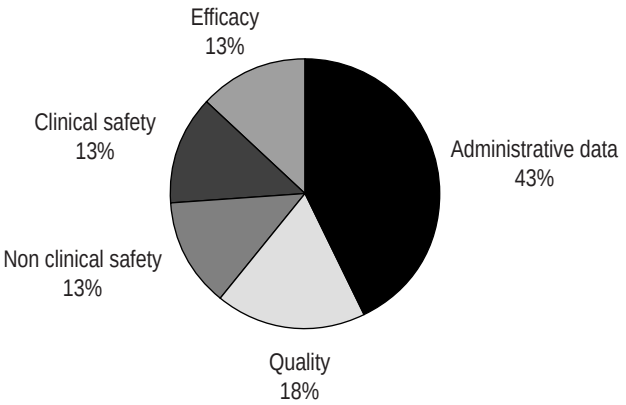
27. Have you been requested by the EMEA to provide further information ?

Yes 10 (50%) No 9 (45%) Not available 1 (5%)

28. If yes, in what category and give brief details

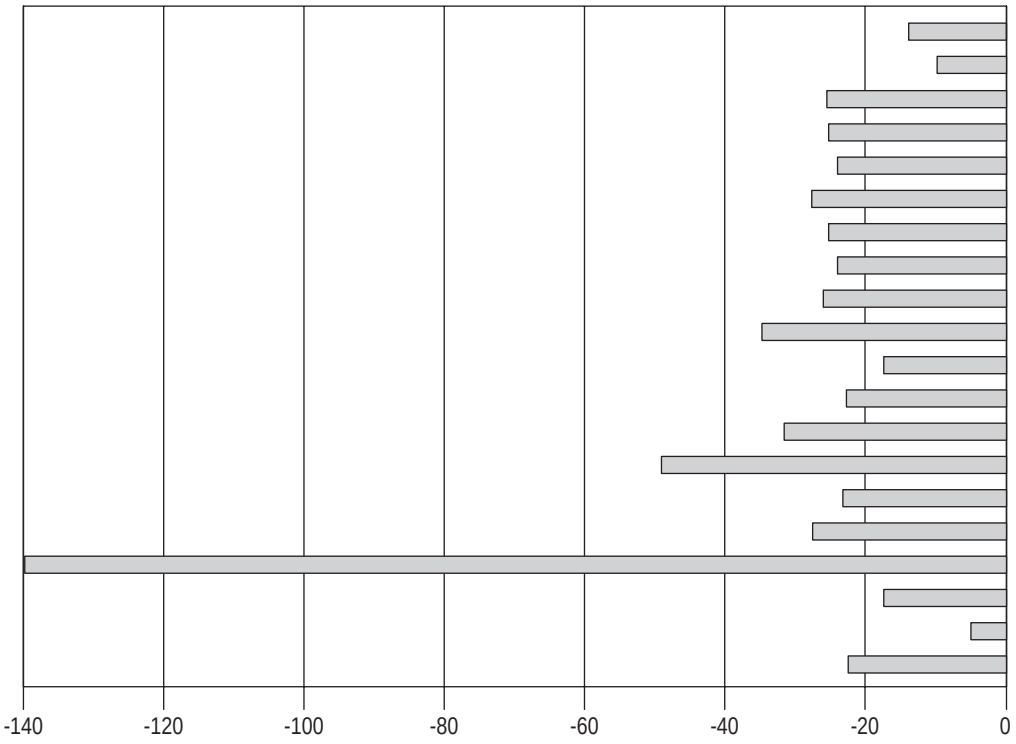
Administrative data	7	• Change applicant's legal status and clarify importer for quality control and batch release. • Mock-ups. Discussion on the number of strengths and corresponding fees. • Confirmation of qualified person for manufacturing. Letter to Commission about dual applications. • Proof of establishment of the applicant in the European Union. • With respect to the number of applications when applying for different strengths. • Expert statements on both active ingredients in the expert reports
Quality	3	• Additional information requested for manufacturing, quality and stability data. • Statement of compliance with TSE guideline.
Non clinical safety	2	• Bibliographical references. • Full part III dossier comprising previously submitted and approved on both individual active ingredients.
Clinical Safety	2	• Updated paediatric safety data. ISS filed to FDA, safety data experienced from 24 week reports of pivotal trials. • Expert reports requested separately rather than in combination with clinical summary.
Efficacy	2	• App. II statistical methods. DSMB organisation. • Clinical study report for a key clinical end point study. This study had already been submitted for a previous application. We did not plan to submit it again, as both the rapporteur and co-rapporteur did not think this necessary.

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable



29. Date of submission of the application

3 medicinal products < 15 days before the start of procedure
17 medicinal products > 14 days before the start of procedure



31. Were any problems identified during the validation phase ?

Yes 7 No 6 Not available 7

31.1 If yes, please give comments

- There was no official note confirming the receipt of the dossier.
- Manufacturing authorisations had inadvertently been left out.
- Minor problems related to administrative data which could be resolved by clarification. More than 3 weeks for the completion of the check-in procedure.
- Administrative request for various items, all of which are now clearly detailed in the new edition of the latest Notice to Applicants (proof of company registration, identification of responsible people in the company, etc.)
- Replacement pages to be provided.
- Relationship between the applicants (duplicate applications).

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

DAY 1

32. Date of start of the procedure

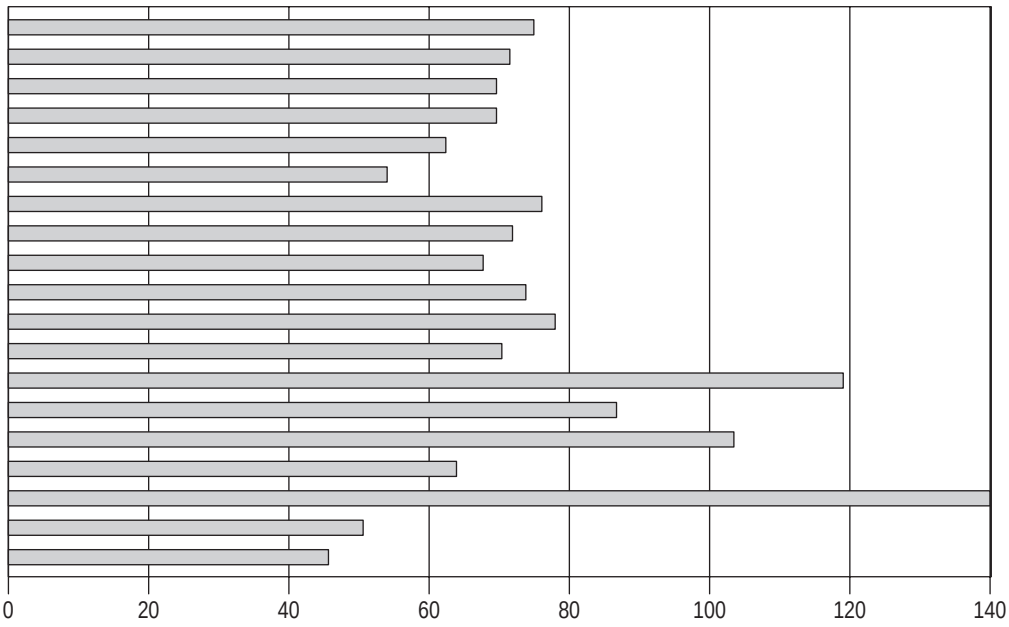
Number of products	Dates
1	June 1996
1	July 1996
3	December1996
3	January 1997
3	February 1997
1	March 1997
1	April 1997
1	May 1997
2	June 1997
2	July 1997
1	October 1997
1	December 1997

DAY 70

33. Date of receipt of the assessment report

33.1 from rapporteur

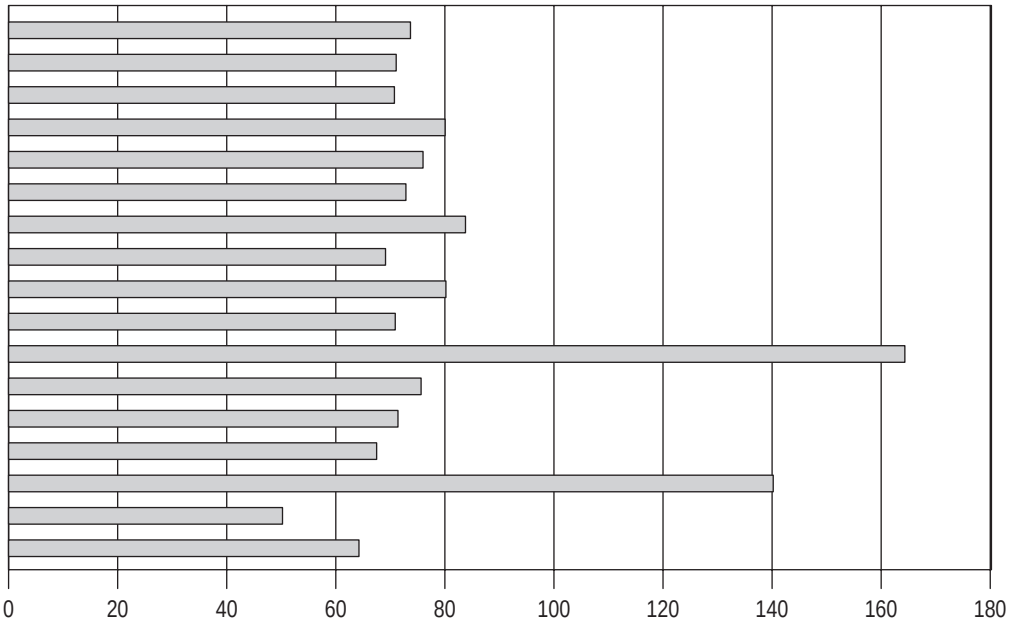
5 medicinal products < 70 days
71 days < 11 medicinal products < 100 days
3 medicinal products > 99 days
Not available 1



33.2 from co-rapporteur

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

3 medicinal products < 70 days
71 days < 12 medicinal products < 100 days
2 medicinal products > 99 days
Not available 3



34. Quality of the rapporteur's assessment report

34.1 Quality part

1	2	3	4
1	0	13	6

34.2 Safety part

1	2	3	4
0	1	14	5

34.3 Efficacy Part

1	2	3	4
1	0	13	6

35. Quality of the co-rapporteur's assessment report

35.1 Quality part

1	2	3	4
0	3	15	2

35.2 Safety part

1	2	3	4
0	5	11	4

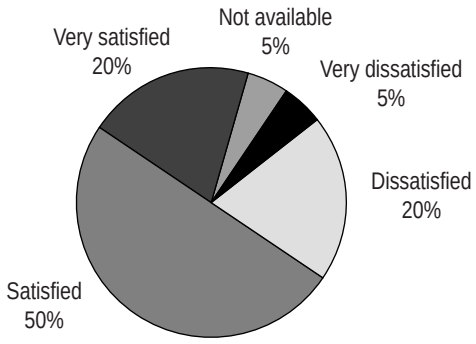
35.3 Efficacy part

1	2	3	4
1	4	12	3

36. Clarity of the issues raised in the assessment report

1	2	3	4	NA
1	4	10	4	1

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable



Comments :

- Some questions needed further clarification.
- The clinical part did not clearly anticipate the critical issues raised in the CPMP discussions.
- It was often unclear why certain issues had been raised. Some of the key issues raised by the clinical results were not addressed in the assessment report.
- Issues were raised that were repetitive from a previous application, but overall quality was very good.

39. In the case of scientific advice being given by the CPMP, to what extent was it followed in the development of the product and preparation of the file ?

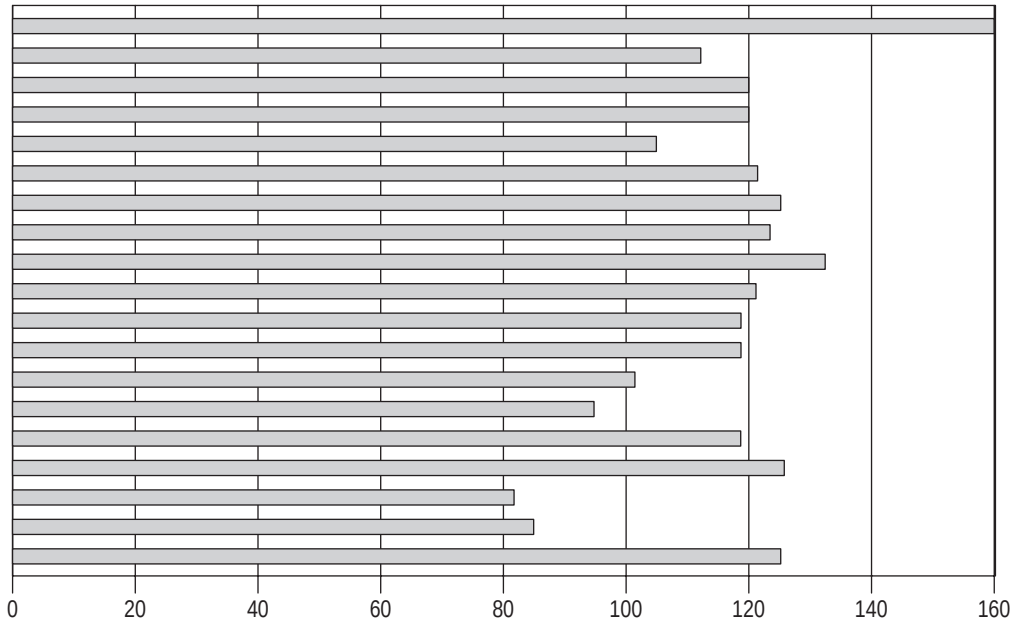
39.2 To what extent did the scientific advice facilitate the assessment of the dossier ?

No experience on CPMP scientific advice (please see question 16) :
NA 20

DAY 120

49. Date of receipt of list of questions

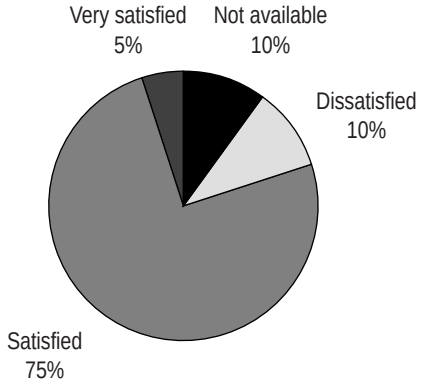
9 medicinal products < 120 days
10 medicinal products > 119 days
Not available 1



Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

50. Clarity of list of questions, overall conclusions and executive summary

1	2	3	4	NA
0	2	15	1	2



Comments :

- Some repetitions in questions.
- Some questions needed further clarification.
- Some of the questions were unclear due to the English. The majority of questions were minor and should have been resolved before this stage.
- Overall conclusions were vague, saying risk/benefit ratio cannot be fully assessed.
- Clinical section : many unclear and poorly translated points.
- The rapporteur and the co-rapporteur requested that the company clarify a limited number of issues during the assessment phase. The assessment reports contained several minor and some major objections, together with numerous amendments to the proposed SmPC.

51. Please specify if overall conclusions indicated whether the product was approvable or non approvable

No indication 2 (10%) Approvable 11 (55%) Non approvable 7 (35%)

52. If the product was approvable, in which areas were there questions to be answered ?

Quality	Pre-clinical safety	Clinical safety	Efficacy
11	9	10	10

53. If the product was not approvable, in which areas were there major objections to be addressed ?

Quality	Pre-clinical safety	Clinical safety	Efficacy
4	2	4	6

Comments on “No indication” (2) :

- Questions on each part of the dossier.
- Questions on the quality and the efficacy parts of the dossier.

53.1 Were any questions related to an issue for which scientific advice had been requested ?

54. Did the CPMP reconsider their initial scientific advice ?

55. If the CPMP reconsidered their scientific advice, do you think it was justified ?

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

No experience on CPMP scientific advice (please see question 16) :
NA 20

56. Date of the clock stop (if applicable)

9 medicinal products < 120 days
8 medicinal products >119 days
NA 2

57. Was a meeting needed for preparing answers

57.1 with the EMEA only ?

Yes 4 No 14 NA 2

If yes, when did it take place ?
1 medicinal product >119 days
Not available 3
NA 16

57.2 with rapporteur and co-rapporteur and the EMEA ?

Yes 7 No 11 NA 2

If yes, when did it take place ?

2 medicinal products < 120 days
2 medicinal products > 119 days
Not available 3
NA 13

57.3 with rapporteur only at national level ?

Yes 7 No 11 NA 2

If yes, when did it take place ?

1 medicinal product < 120 days
3 medicinal products > 119 days
Not available 3
NA 13

57.4 with co-rapporteur only at national level ?

Yes 0 No 18 NA 2

57.5 with rapporteur and co-rapporteur jointly at national level ?

Yes 1 No 17 NA 2

If yes, when did it take place ?
1 medicinal product > 119 days
NA 19

58. Quality of the meeting with regard to organisation, facilities and timing

58.1 with the EMEA only ?

1	2	3	4	NA	Not available
0	1	0	0	16	3

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

58.2 with the EMEA, rapporteur and co-rapporteur ?

1	2	3	4	NA	Not available
0	1	1	3	13	2

58.3 with rapporteur only at national level ?

1	2	3	4	NA	Not available
0	1	2	3	13	1

58.4 with co-rapporteur only at national level ?

NA 20

58.5 with rapporteur and co-rapporteur jointly at national level ?

1	2	3	4	NA
0	0	0	1	19

Comments :

- Discussed issues over the phone. Schedules would not permit a meeting.
- We wanted a meeting with the rapporteur alone, but it proved extremely difficult to arrange one, and this proved to be an insurmountable problem.
- Meetings : timing poor, facilities not good, much time wasted waiting for start of meetings.
- The co-rapporteur refused to attend any meeting, either alone or with others.
- The meeting took place in a small room which was insufficient for the number of participants.
- We would have preferred an earlier meeting date.

59. Please qualify the usefulness of the meeting(s) with respect to scientific discussion and added value

59.1 with the EMEA only ?

1	2	3	4	NA	Not available
0	0	1	0	16	3

59.2 with the EMEA, rapporteur and co-rapporteur ?

1	2	3	4	NA	Not available
0	0	3	2	13	3

59.3 with rapporteur only at national level ?

1	2	3	4	NA	Not available
1	0	2	3	13	3

59.4 with co-rapporteur only at national level ?

NA 20

59.5 with rapporteur and co-rapporteur jointly at national level ?

1	2	3	4	NA
0	0	1	0	19

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

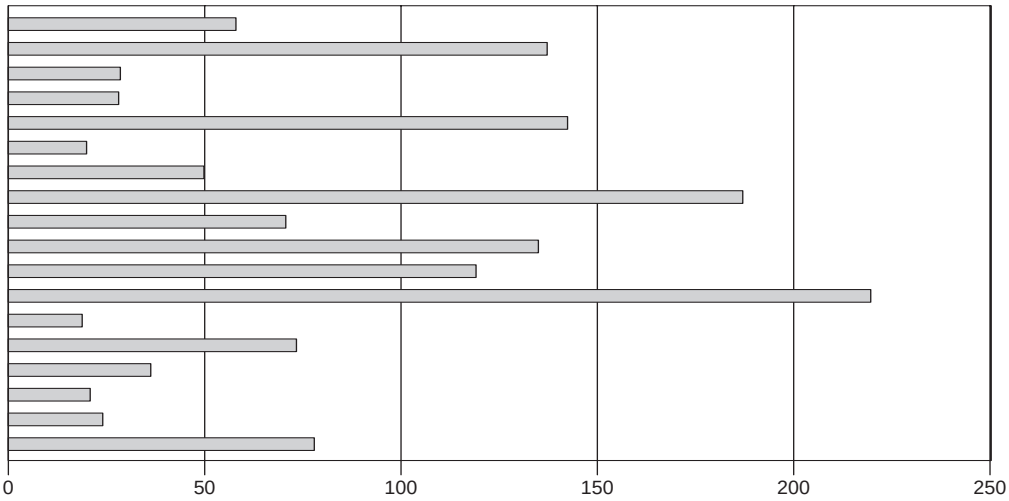
Comments :

- Phone calls sufficient to clarify any issue.
- Meetings were useful.
- Meeting useful, providing valuable clarification.
- Support by the rapporteur was very helpful, however, the proposed argumentation was not fully accepted by the CPMP.
- There was no added value as the rapporteur clearly did not have the necessary experience in the field to discuss the issues with the company experts. In addition, all the major issues had been raised by other members of the CPMP.

DAY 121

60. Date of submission of the responses - Length of the clock stop (question 60 - question 56)

12 medicinal products < 90 days
89 days < 4 medicinal products < 150 days
2 medicinal products > 149 days
Not available 1
NA 1



61.Did the applicant have any difficulties in providing responses within the time frame proposed by the CPMP ?

Yes 1 No 19 NA 1

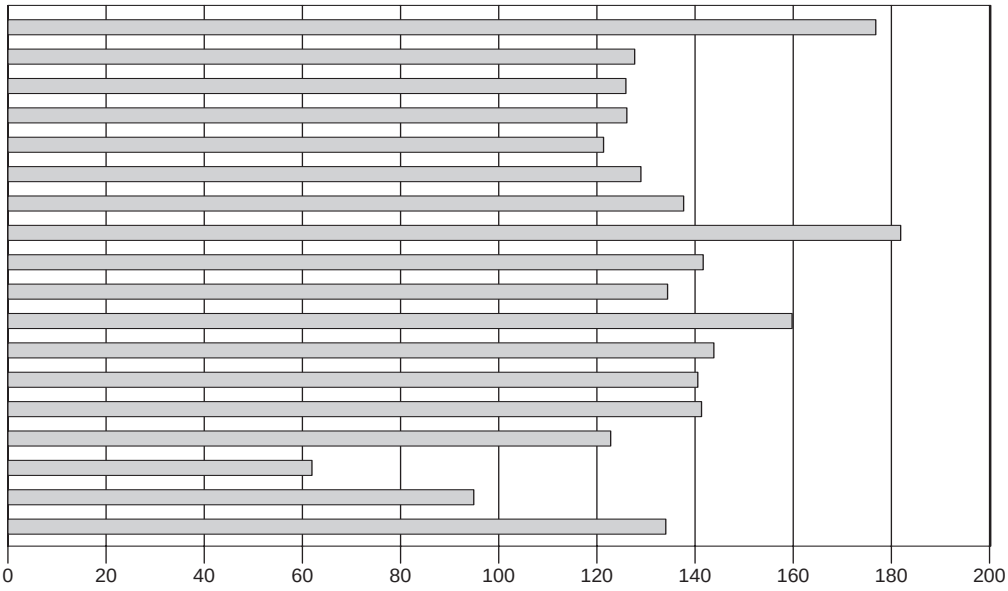
61.1 If yes, please give comments

- Clinical expert had personal problems. This delayed the compilation of response on clinical issues.

62. Date of restart of the clock (question 62 - length of the clock stop)

2 medicinal products < 120 days
119 days < 13 medicinal products < 150 days
3 medicinal products > 149 days
Not available 1
NA 1

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable



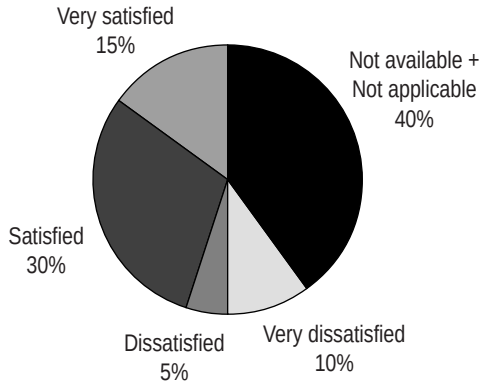
DAY 150

64. Date of receipt of the assessment report (question 64 - length of the clock stop)

0 medicinal product < 150 days
149 days < 8 medicinal products < 180 days
5 medicinal products > 299 days
Not available 6
NA 1

65. Clarity of the assessment report on the responses

1	2	3	4	NA	Not available
2	1	6	3	1	7



Comments :

- The assessment report was poorly written and did not help the process of resolving the key issues.
- The co-rapporteur circulated a dissenting opinion (part IV) with the joint assessment report.
- Additional late comments of poor quality received from one Member State.
- Unresolved differences between rappporteur and co-rapporteur.

DAY 170-180

73. Was an oral explanation requested ?

Yes 11 No 8 NA 1

If yes, when ? (question 73 - length of the clock stop)

169 days (3 medicinal products (200 days
3 medicinal products (199 days
Not available 5
NA 9

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

73.1 If yes, on request of :

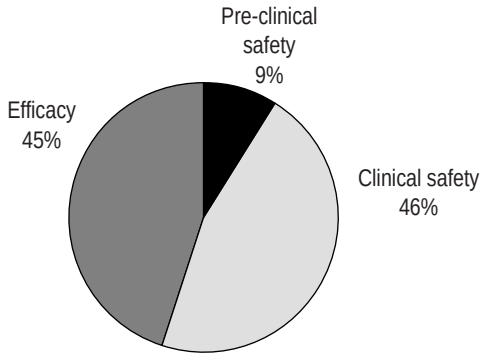
The applicant	The CPMP	Advice of the rapporteur
2	5	7

73.2 If yes, please specify the reasons

- A formal oral hearing was possible for a paediatric indication, but was decided without a formal oral hearing.
- Further explanation was requested regarding clinical safety.
- Responses to solve clinical questions still insufficient, as stated in the assessment report.
- To resolve the outstanding clinical issues.
- The possibility of an oral explanation was requested “just in case”, as the company was unsure about the overall acceptance of the responses by other CPMP members. However, the oral explanation never took place.
- Among CPMP members, dissenting opinions on clinical benefit. The CPMP requested an expert meeting. The opinion was given 3 months after the request for an oral explanation during CPMP meetings subsequent to an additional oral explanation.
- To discuss pending issues : risk/benefit ratio, efficacy and safety concerns.

73.3 On which part of the dossier ?

Quality	Pre-clinical safety	Clinical safety	Efficacy
0	1	5	5



74. Date of the clock stop, if requested

2 medicinal products < 200 days
5 medicinal products > 199 days
Not available 4
AN 9

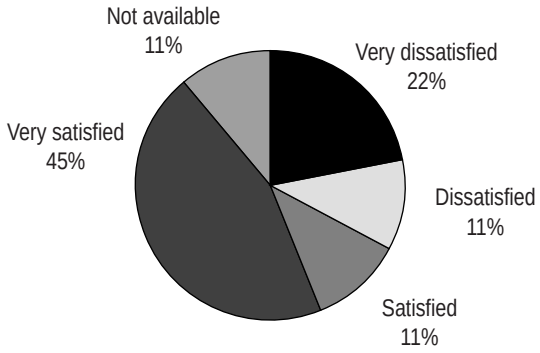
75. Was a preparatory meeting with rapporteur, co-rapporteur and project manager organised ?

Yes 8 (40%) No 3 (15%) NA 9 (45%)

75.1 If yes, how useful was the meeting ?

1	2	3	4	NA	Not available
2	1	1	4	9	3

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable



Comments :

- The clock stop was held over for an extra month at the request of the French CPMP member (not rapporteur or co-rapporteur). This was the cause of an extreme distress within the company, which was ready for the hearing.
- Very useful. The applicant met rapporteur and co-rapporteur only, but they provided good advice on how to approach the hearing and how to address some of the remaining issues.
- The meeting was held at the EMEA only a couple of hours before. The co-rapporteur neither discussed any of the issues nor disclosed the assessment he would give to the CPMP.
- Again the rapporteur was not the one familiar with the outstanding issues. A meeting with those members with objections would have been far more useful. This was proposed by the rapporteur, but was not possible due to clashes with other meetings.
- The meeting was organised not to prepare an oral explanation but to agree on the final SmPC changes prior to the final CPMP discussion. The meeting was not predictive of the real focus which would animate the final CPMP discussion on the following day, due to unexpected major objections by some CPMP members raised only on the final day.

DAY 181

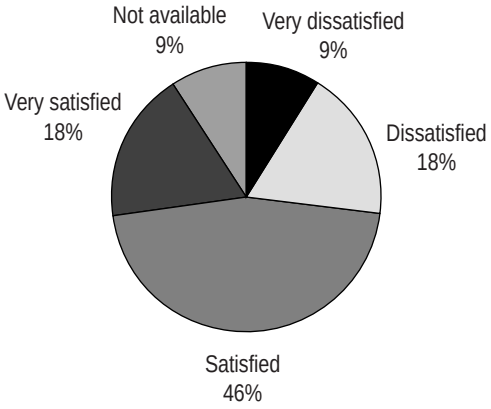
76. Date of restart of the clock/oral explanation (question 76 - length of the clock stop)

180 days < 6 medicinal products < 250 days
4 medicinal products > 249 days
Not available 1
NA 9

77. Quality of the oral explanation

77.1 with regard to the scientific discussion of outstanding major objections ?

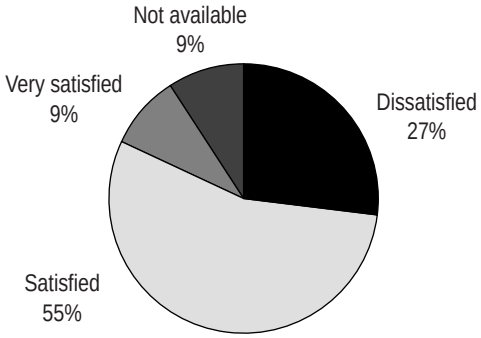
1	2	3	4	NA	Not available
1	2	5	2	9	1



77.2 with regard to organisation, facilities and timing ?

1	2	3	4	NA	Not available
0	3	6	1	9	1

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable



Comments :

- Objections raised extremely late, and were not in consolidated list. No privacy in the EMEA waiting area.
- Number of issues to be addressed : presentation, time too short, given only half a day before the hearing. Some questions from the CPMP members demonstrated that there was no common basis for a scientific discussion.
- The oral explanation was useful as it was the first occasion that the company had to discuss the issues face to face with those CPMP members who had raised the issues.
- Lobby at EMEA is not really an appropriate place to allow different groups to “prepare” for a meeting.
- No discussion but individual questions from CPMP members.

78. Were the issues resolved during the oral explanation ?

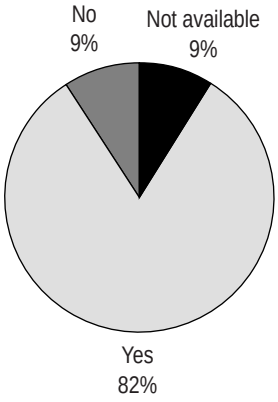
Yes 5 No 4 Not available 2 NA 9

78.1 If no, please give further comments

- Paediatric claim discussed with CPMP HIV working group.
- France, Germany, and Sweden had serious objections on indications which had to be removed.
- A second hearing was required after submission of further clarifying information.
- The CPMP seemed to have made up its mind prior to the oral explanation.

80. Do you think the oral explanation was useful ?

Yes 9 No 1 Not available 1 NA 9

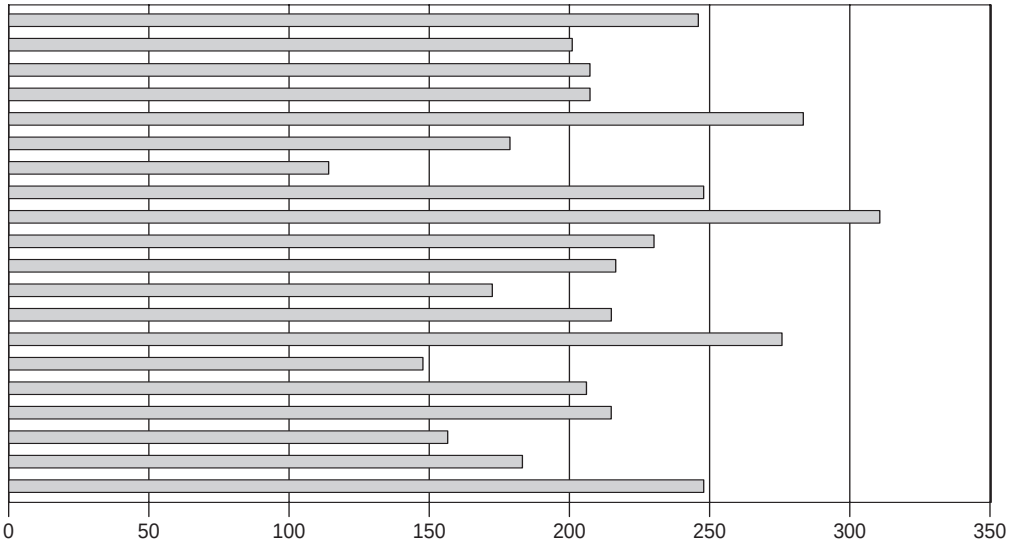


BEFORE DAY 210

81. Date of the CPMP opinion (question 81 - length of the clock stop)

10 medicinal products < 210 days
209 days < 7 medicinal products < 250 days
3 medicinal products > 249 days

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable



82. Please indicate any changes (and section concerned) between SmPC, Package Leaflet and Labelling applied for and approved

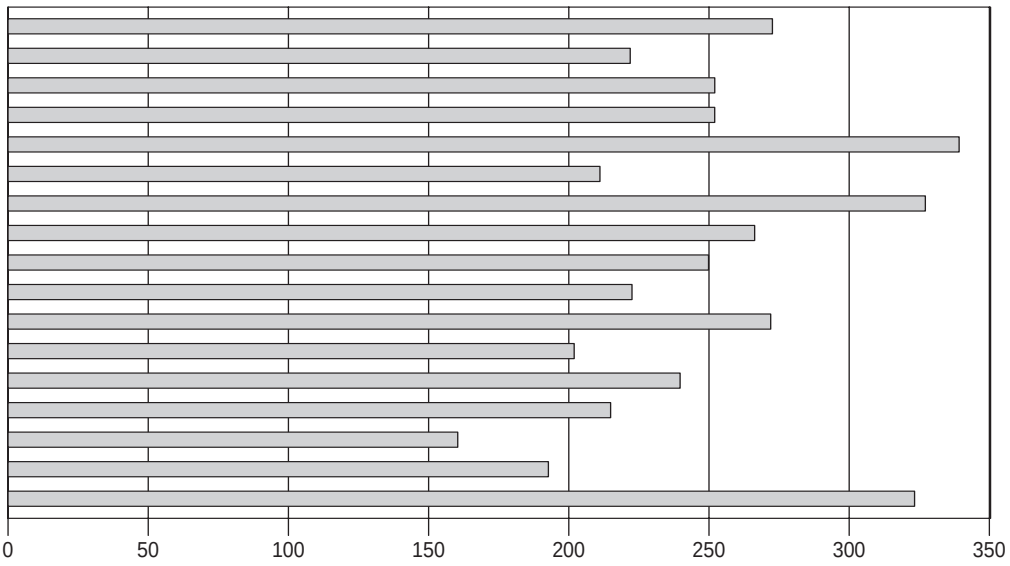
- Special warnings and special precautions for use.
- Several changes in SmPC and PIL.
- Therapeutic indications, posology, contra-indications, special warnings and precautions for use, overdose, and undesirable effects, in the SmPC, and related changes in the leaflet.
- Minor wording changes.
- A number of changes were made to the wording of the indications and the pharmacological properties.
- Drafting group of rapporteurs plus objecting Member States provided applicants with wording of SmPC, leaflet and labelling after the hearing. One of the two proposed indications was deleted. Several additional precautions and warning statements included.

- Indication claimed was granted only in part. Additional warnings. Omission of favorable pre-clinical fundings. Labelling of dose, strength (including layout) not accepted.
- There were a number of changes to virtually all sections of the SmPC. The PIL and labelling remained virtually unchanged.
- Deletion of a major efficacy claim (indications therapeutic and pharmacological properties). Deletion of one dosage from posology. Harmonisation of safety warnings with other products in the same class. Other minor changes throughout.
- Indication was restricted.
- Posology, contra-indications, special warnings and precautions for use, interactions, adverse reactions and overdose.
- Most sections changed during the review.
- All sections were subject to revision. Main changes : indication, contra-indication, precautions, and pharmacodynamic properties because of the implementation of new CPMP guideline.
- Simplification of indication wording, special warning and special precautions, pregnancy and lactation, and pre-clinical safety data.

BEFORE DAY 240

83. Date of receipt of final assessment report (question 83 - length of the clock stop)

8 medicinal products < 240 days
239 days < 6 medicinal product < 300 days
3 medicinal products > 299 days
Not available 3



Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

85. Receipt of last comments on translations from CPMP Members (question 85 - length of the clock stop)

6 medicinal products < 240 days
7 medicinal products > 239 days
Not available 7

85.1 In time

Yes 5 No 9 Not available 6

85.2 If a delay, how many maximum number of days ?

2 - 2 - 4 - 5 - 5 - 6 - 11 - 19 Not available 7 NA 5

85.3 Number of delegations having sent comments on translations to the applicant and the EMEA

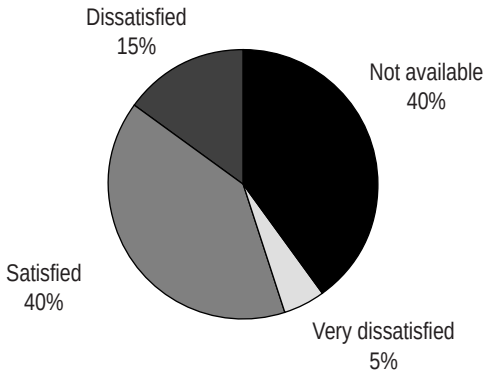
4 - 5 - 6 - 6 - 6 - 7 - 12 Not available 13

85.4 Comments

- Many minor comments. CPMP members in some countries responded slowly.
- Comments from France, Germany, Finland, Greece, Sweden, The Netherlands.
- Comments were made by all Member States with the exception of Italy.
- Minor linguistic comments.
- Several minor wording changes. Multiple consecutive unconsolidated comments.
- Comments were sometimes contradictory and sometimes irrelevant.
- Timetable too tight for a small company. No comments ever received from Greek CPMP members on Greek translations, despite frequent chasing.
- Some comments contradicted the EMEA translators. Some comments were sent to the EMEA only.
- The CPMP opinion was sent to all CPMP members. However, a number informed the company that they did not wish to see the translated opinion.
- As linguistic comments from Member States continued to be received after the deadline, the EMEA decided to work directly with the CPMP members to finalise the translations.
- Spain never replied.
- This process should be centralised by the EMEA.
- The company kept to each deadline concerning translations, but the CPMP members did not ! This, in spite of several reminders.
- A very bureaucratic process, where each additional step entailed making additional corrections.

86. Relevance of their comments

1	2	3	4	Not available
1	3	8	0	8



Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

BEFORE DAY 300

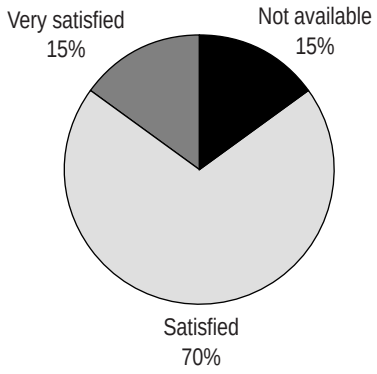
94.2 n the event of difficulties, please comment.

- The final assessment report was poorly written and contained a number of factual errors. This was not the fault of the project manager, as he clearly did not have sufficient time to do the job properly.

96. Final EPAR. Are you satisfied with :

96.1 Objectiveness

1	2	3	4	Not available
0	0	14	3	3

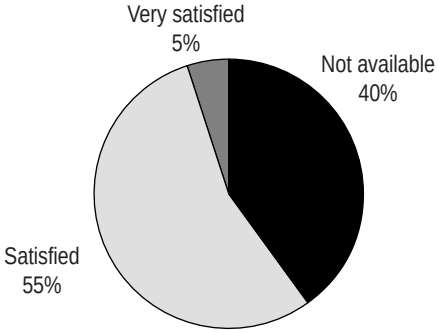


Comments :

- Bias toward minimising positive trends and unbalancing on statistically significant differences.
- The document was an objective summary of the data.

96.2 Clarity and legibility

1	2	3	4	Not available
0	0	11	1	8



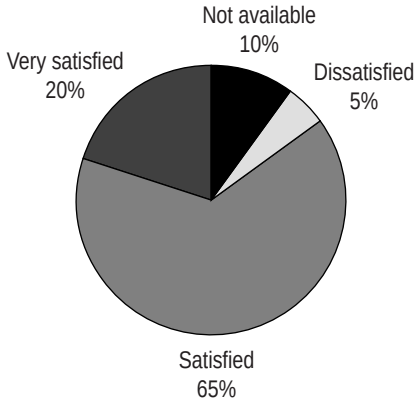
Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

Comments :

- The final document was clear and legible. This was only achieved after a great deal of discussion with the rapporteur.

96.3 Level of data protection

1	2	3	4	Not available
0	0	11	1	8

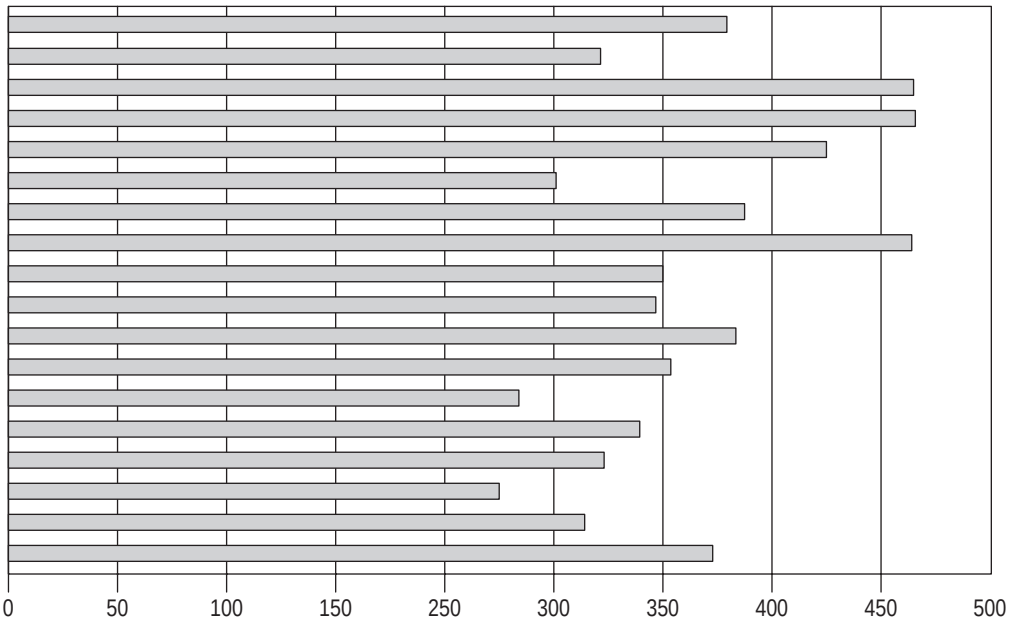


Comments :

- EPAR was prepared by the company.
- Comments from company were taken into account.
- Lack of clear policies for inclusion of data, e.g. comparative data. Several rounds of minor corrections made by the EMEA alone did not allow the applicant to keep an updated file of official texts.

97. Date of the Commission decision (question 97 - length of the clock stop)

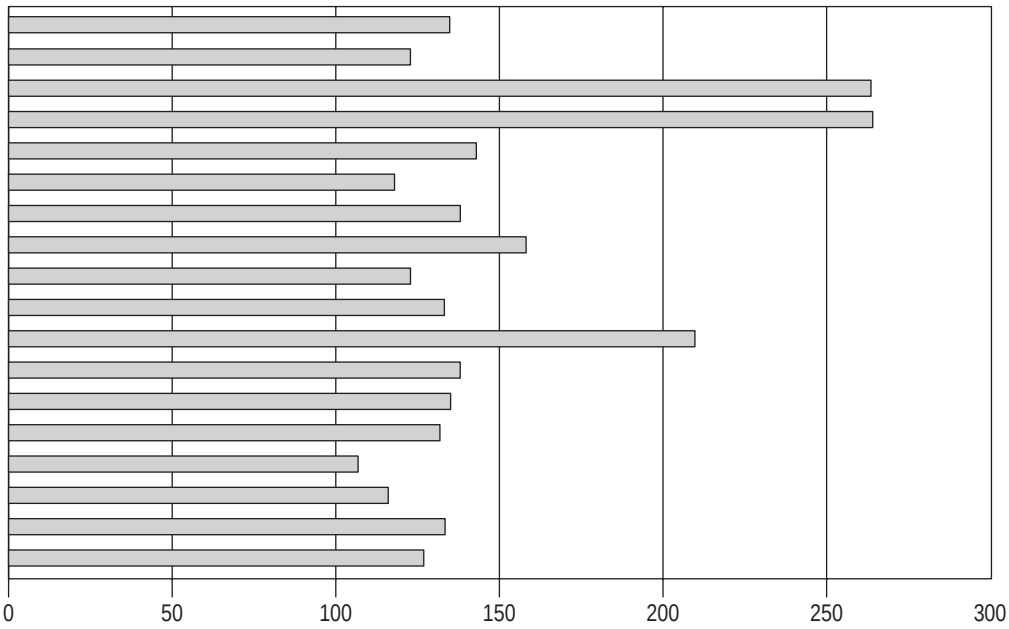
2 medicinal products < 300 days
299 days <(6 medicinal product < 350 days
10 medicinal products > 349 days
Not available 2



Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

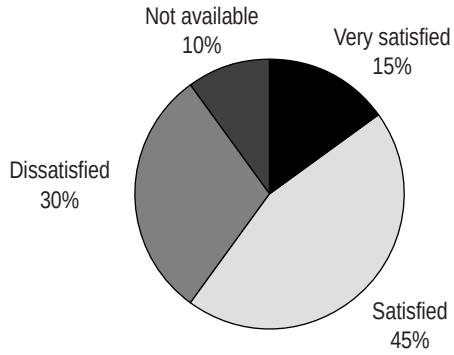
97.bis Time-periods from the CPMP opinions to the Commission decisions (question 97 - question 81)

2 medicinal products < 120 days
119 days < 12 medicinal product < 150 days
4 medicinal products > 149 days
Not available 2



101. Are you satisfied with the procedure as such ?

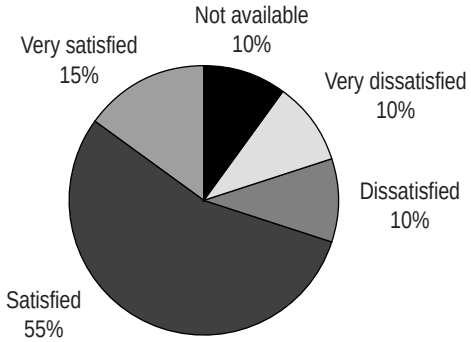
1	2	3	4	Not available
0	6	9	3	2



102. Are you satisfied with transparency, dialogue and advice from :

102.1 the EMEA ?

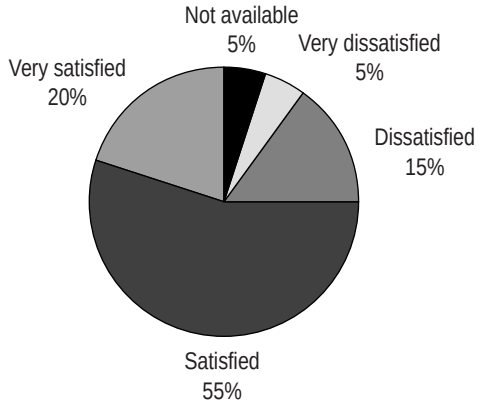
1	2	3	4	Not available
2	2	11	3	2



Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

102.2 the rapporteur/co-rapporteur ?

1	2	3	4	Not available
1	3	11	4	1



104. Other comments

- Requirements for blue boxes as outlined in the guideline on the “Packaging information of medicinal products for human use authorised by the Community” are not always in line with the exact national requirements. We had to finetune blue boxes with national authorities.

- The process of finalising SmPC, leaflet and packaging texts was very confusing with different versions going back and forth between the company, the EMEA and the Commission. This process should be better co-ordinated, maybe via a contact person at the EMEA or at the Commission itself.

- No major problem encountered. Good communication with rapporteur and EMEA. We appreciated transparency and effectiveness. Problems mainly related to mock-ups (why ask for them at time of submission ?), translations, and blue boxes.

- The co-rapporteur was largely unable to provide us with any help.

- There were a number of issues relating to product efficacy in one of the indications, which were raised extremely late in the procedure, in the consolidated list of questions. They might have been able to be resolved earlier. It was difficult for the applicant to talk directly to the Member States which raised these objections, which they found quite hard to deal with. However, contacts with the rapporteur, co-rapporteur and the EMEA project manager were excellent at all times.

- The amount of copying of volumes of data, and tight deadlines (especially for translations) placed a heavy burden on small companies with limited resources. The EMEA meetings did not start on time necessitating much waiting around, and wasting much time. Setting up meetings with the rapporteur proved to be an insurmountable problem. The EMEA process of reviewing the translations should start much sooner. After all, they are provided up-front at the time of submission of the dossier.

- The rapporteur was very sympathetic, whereas the co-rapporteur did not offer any help at all. Weak points of the procedure were : too-tight timelines for hearing, translations, and preparation. Finalisation of the SmPC was done under considerable time pressure in the EMEA lobby without giving a clear rationale for the requested change. Generally, following the advice of rapporteur did not provide definite solutions. Definite identification and decision on crucial issues only at the very end of the scientific evaluation.

Level of satisfaction score: 1= very dissatisfied, 2= dissatisfied, 3= satisfied, 4= very satisfied, N.A.= not applicable

- Even though we have stated that overall we were dissatisfied with the procedure, this was clearly very much due to the quality of the initial assessment report which very much set the scene for the whole procedure. The EMEA staff did an excellent job in very difficult circumstances. There is a definite need to ensure that the initial evaluation is undertaken by individuals who know the clinical area. In addition, the procedure for reviewing the translations needs to be simplified and purely semantic changes avoided.

- While the overall interaction with the EMEA and the rapporteur/co-rapporteur was transparent and constructive, the CPMP dynamics remained obscure to the company, limiting the possibility of an interactive dialogue with members raising objections. A major clinical claim had to be dropped from the SmPC on the last day of the CPMP opinion, although this had not been raised in the last CPMP list of questions. The company had no opportunity to debate this without jeopardising the timely issuing of the opinion.

- Delays in the decision-making process occurred due to some Member States' repeating objections that had been discussed by the CPMP.

- Steps between the joint assessment report on the response document and hearing/CPMP opinion to be clarified. The EMEA's advice improved after the procedure got under way. Disagreements between the rapporteur and the co-rapporteur raised problems for applicant. Submission of PSURs needs clarification: one single list of addressees for the centralised procedure. The questionnaire should contain questions on inspection and on follow-up measures.

- More scientific-level discussions also involving European clinical experts, should take place during the process. Discussion on labelling was not at all transparent. Absolutely too little time for those discussions. Obvious work overload of the CPMP members harms the quality of the process. The rapporteur vs co-rapporteur consistency not quite satisfactory. The co-rapporteur did not always stick to his assessment report at later phases of review. The impression was that the applicant often was not made aware of discussions and concerns of the CPMP. Some Member States' specific political issues often seemed to be hidden behind minor scientific arguments.

8. BLANK FORM OF THE QUESTIONNAIRE

JOINT EMEA/EFPIA QUESTIONNAIRE ON THE NEW EUROPEAN REGISTRATION SYSTEM - CENTRALISED PROCEDURE -

GENERAL INFORMATION (QUESTIONS 1 & 15 TO BE ANSWERED BY THE EMEA PROJECT MANAGER ONLY)

1. Name of the Applicant: _____
2. Country of the Applicant: _____
3. Person to be contacted for further information (optional): _____
4. Phone number: _____ Fax number: _____
5. Name of the Rapporteur: _____
6. Name of the Co-Rapporteur: _____
7. Name of the EMEA Project Manager: _____

PRODUCT INFORMATION

8. Name of the medicinal product: _____
9. Name of the active substance(s): _____
10. EMEA procedure no.: _____
11. Pharmacotherapeutic classification (ATC system): _____
12. Pharmaceutical form: _____ Strength: _____
13. Status of the product: ❑ Part A ❑ Part B

14. Basis for Part A status:

    ❑ recombinant DNA technology
    ❑ controlled expression of genes coding for biologically active proteins
    ❑ hybridoma and monoclonal antibody methods

15. Basis of Part B status:

    ❑ other innovative biotechnical processes
    ❑ innovative new delivery system
    ❑ novel indication
    ❑ based on radio-isotope which is of significant therapeutic interest
    ❑ derived from human blood/plasma
    ❑ manufacturing process which demonstrates a significant technical advance
    ❑ new active substance
    ❑ others

SCIENTIFIC ADVICE (QUESTIONS 16 & 18.2 TO BE ANSWERED BY THE APPLICANT ONLY)

16. During the development process before submission to the EMEA, was Scientific Advice sought from the CPMP?

    ❑ yes ❑ no

16.1 If yes, in which area was Scientific Advice sought?

Quality	❑
Biotechnology	❑
Safety	❑
Efficacy	❑

16.2. If yes, how useful was this Scientific Advice?*

❑ 1 ❑ 2 ❑ 3 ❑ 4

Comments: _____
_____

17. Did this advice influence the following steps?
1) Development of the product ❑ yes ❑ no

Comments: _____
_____

2) Subsequent assessment of the dossier ❑ yes ❑ no

Comments: _____
_____

18. Did you seek Scientific Advice from national authorities prior to this request?

❑ yes ❑ no

18.1 If yes, in which country(ies)? _____

18.2 If yes, was this advice of additional help?

❑ yes ❑ no

Comments: _____
_____
_____

DAY	STAGE OF PROCEDURE	See **	QUESTION	ANSWER
Not later than -120	EMEA/CPMP notified by letter of intended submission - foreseen date for submission - justification of part A or B status - proposals for 3-4 Rapporteurs	A	19. Proposed Rapporteurs (nationally)	19. _____
	- Identification of possible problems (Trade Mark, User Patient Leaflet, Legal Status, Inspection, Drug Master File, ...)	A	20. Identification of "possible problems" by the EMEA	20. _____
		A	20.1 If yes, date of notification to the company	20.1 ☐☐ ☐☐ ☐☐ Day Month Year
-90 appr.	After CPMP review, the EMEA notifies the Applicant of - confirmation of Part A or B status - choice of Rapporteur and Co-Rapporteur - name of Project Manager	A	21. Date of receipt of notification of the names of Rapporteur, Co-Rapporteur and Project Manager and identification of fee to be paid	21. ☐☐ ☐☐ ☐☐ Day Month Year
		A	22. Are you satisfied with the choice of the Rapporteur/Co-Rapporteur?	22. ❑ Yes ❑ No
		A	22.1 If no, please give comments	22.1 _____
Not later than -15	- Possible pre-submission meeting with the EMEA	A + B + C	23. Did a pre-submission meeting take place	23.
			1) with the EMEA only (administrative/ regulatory issues)?	1) ❑ Yes ❑ No
			If yes, when?	☐☐ ☐☐ ☐☐ Day Month Year
			2) with Rapporteur and Co-Rapporteur and the EMEA (scientific issues)?	2) ❑ Yes ❑ No
			If yes, when?	☐☐ ☐☐ ☐☐ Day Month Year

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

			3) with Rapporteur only at national level? If yes, when?	3) ❑ Yes ❑ No ☐☐ ☐☐ ☐☐ Day Month Year
			4) with Co-Rapporteur only at national level? If yes, when?	4) ❑ Yes ❑ No ☐☐ ☐☐ ☐☐ Day Month Year
			5) with Rapporteur and Co-Rapporteur jointly at national level? If yes, when?	5) ❑ Yes ❑ No ☐☐ ☐☐ ☐☐ Day Month Year
		A + C	24. Quality of the meeting with regard to organisation, facilities and timing* 1) with the EMEA 2) with Rapporteur and Co-Rapporteur and the EMEA 3) with Rapporteur only at national level 4) with Co-Rapporteur only at national level 5) with Rapporteur and Co-Rapporteur jointly at national level	24. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4 4) ❑ 1 ❑ 2 ❑ 3 ❑ 4 5) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____
		A + B + C	25. Please qualify the usefulness of the meeting(s)* 1) with the EMEA only 2) with Rapporteur and Co-Rapporteur and the EMEA 3) with Rapporteur only at national level 4) with Co-Rapporteur only at national level 5) with Rapporteur and Co-Rapporteur jointly at national level	25. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4 4) ❑ 1 ❑ 2 ❑ 3 ❑ 4 5) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

		A + C	26. Were any problems identified during the meeting which could have led to major objections during the assessment of the file?	26. ❑ Yes ❑ No
		A + C	26.1 If yes, please give comments	26.1 _____
		A + B	27. Have you been requested by the EMEA to provide further information?	27. ❑ Yes ❑ No
		A + B	28. If yes, in what category and give brief details	28. ❑ Administrative data: _____ ❑ Quality: _____ ❑ Non clinical Safety: _____ ❑ Clinical Safety: _____ ❑ Efficacy: _____
Not later than -15	- Submission of the application to the EMEA	A	29. Date of submission of the application	29. ☐☐ ☐☐ ☐☐ Day Month Year
		B	30. Date of receipt of the dossier	30. ☐☐ ☐☐ ☐☐ Day Month Year
	- Validation of the application	A + B	31. Were any problems identified during the validation phase?	31. ❑ Yes ❑ No
		A + B	31.1 If yes, please give comments	31.1 _____

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

1	Start of procedure	B	32. Date of start of the procedure	32. ☐☐ ☐☐ ☐☐ Day Month Year
70	Date of receipt of the Assessment Reports (AR) from Rapporteur/Co-Rapporteur by CPMP/ EMEA and Applicant	A + B	33. Date of receipt of the AR 1) from Rapporteur 2) from Co-Rapporteur	33. 1) ☐☐ ☐☐ ☐☐ Day Month Year 2) ☐☐ ☐☐ ☐☐ Day Month Year
		A + B	34. Quality of the Rapporteurís AR* 1) Quality part 2) Safety part 3) Efficacy part	34. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4
		A + B	35. Quality of the Co-Rapporteurís AR* 1) Quality part 2) Safety part 3) Efficacy part	35. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4
		A + B	36. Clarity of the issues raised in the AR*	36. ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____
		C	37. Quality of the dossier* 1) Quality 2) Safety 3) Efficacy	37. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____
		C	38. Quality of the expert reports provided by the Applicant* 1) Quality 2) Safety 3) Efficacy	38. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____
		A + C	39. In the case of Scientific Advice being given by the CPMP, to what extent was it followed in the development of the product and preparation of the file?*	39. ❑ 1 ❑ 2 ❑ 3 ❑ 4

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

		A + C	39.1 Please give comments	39.1 _____
		C	39.2 To what extent did the Scientific Advice facilitate the assessment of the dossier?*	39.2 ❑ 1 ❑ 2 ❑ 3 ❑ 4
		B + C	40. Quality of the SPC*	40.
			1) Quality of English version	1) ❑ 1 ❑ 2 ❑ 3 ❑ 4
			2) Consistency with expert reports	2) ❑ 1 ❑ 2 ❑ 3 ❑ 4
		B + C	41. Quality of the Package Leaflet*	41.
			1) Consistency with SPC	1) ❑ 1 ❑ 2 ❑ 3 ❑ 4
			2) Quality of English version	2) ❑ 1 ❑ 2 ❑ 3 ❑ 4
			3) Understandable wording for patients	3) ❑ 1 ❑ 2 ❑ 3 ❑ 4
		B + C	42. Quality of the Labelling*	42.
			1) Wording	1) ❑ 1 ❑ 2 ❑ 3 ❑ 4
			2) Consistency with legislation	2) ❑ 1 ❑ 2 ❑ 3 ❑ 4
		B	43. Quality of the translations of SPC, Package Leaflet and Labelling*	43. ❑ 1 ❑ 2 ❑ 3 ❑ 4
		B	44. In the case of major difficulties, please identify the issues and the language(s)	44. _____

100	Receipt of comments from CPMP Members	B	45. Comments by CPMP Members on AR due on	45. ☐☐ ☐☐ ☐☐ Day Month Year
		B	46. Number of CPMP Members who provided comments to Rapporteur and Co-Rapporteur	46. ☐☐
		C	47. Were any additional major objections identified?	47. ❑ Yes ❑ No

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

120	- CPMP validates and EMEA provides list of questions, overall conclusions and executive summary to Applicant - If needed, clock stop	B	48. Date of CPMP adoption of list of questions	48. ☐☐ ☐☐ ☐☐ Day Month Year
		A	49. Date of receipt of list of questions	49. ☐☐ ☐☐ ☐☐ Day Month Year
		A	50. Clarity of list of questions, overall conclusions and executive summary*	50. ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____
		A + B + C	51. Please specify if overall conclusions indicated whether the product was approvable or non approvable	51. ❑ No indication ❑ Approvable ❑ Non Approvable
		A + C	52. If the product was approvable, in which areas were there questions to be answered?	52. ❑ Quality ❑ Pre-clinical Safety ❑ Clinical Safety ❑ Efficacy
		A + C	53. If the product was not approvable, in which areas were there major objections to be addressed?	53. ❑ Quality ❑ Pre-clinical Safety ❑ Clinical Safety ❑ Efficacy
		A + C	53.1 Were any of these questions related to an issue for which Scientific Advice had been requested?	53.1 ❑ Yes ❑ No Comments: _____
		A + C	54. Did the CPMP reconsider their initial Scientific Advice?	54. ❑ Yes ❑ No
		C	54.1 If yes, please give details	54.1 _____
		A	55. If the CPMP reconsidered their Scientific Advice, do you think it was justified?	55. ❑ Yes ❑ No

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

		A	55.1 If no, please give comments	55.1 _____ _____ _____ _____
		A + B	56. Date of the clock stop (if applicable)	56. ☐☐ ☐☐ ☐☐ Day Month Year
		A + B + C	57. Was a meeting needed for preparing answers	57.
			1) with the EMEA only?	1) ❑ Yes ❑ No
			If yes, when did it take place?	☐☐ ☐☐ ☐☐ Day Month Year
			2) with Rapporteur and Co-Rapporteur and the EMEA?	2) ❑ Yes ❑ No
			If yes, when did it take place?	☐☐ ☐☐ ☐☐ Day Month Year
			3) with Rapporteur only at national level?	3) ❑ Yes ❑ No
			If yes, when did it take place?	☐☐ ☐☐ ☐☐ Day Month Year
			4) with Co-Rapporteur only at national level?	4) ❑ Yes ❑ No
			If yes, when did it take place?	☐☐ ☐☐ ☐☐ Day Month Year
			5) with Rapporteur and Co-Rapporteur jointly at national level	5) ❑ Yes ❑ No
			If yes, when did it take place?	☐☐ ☐☐ ☐☐ Day Month Year
		A	58. Quality of the meeting with regard to organisation, facilities and timing*	58.
			1) with the EMEA only	1) ❑ 1 ❑ 2 ❑ 3 ❑ 4
			2) with the EMEA, Rapporteur and Co-Rapporteur	2) ❑ 1 ❑ 2 ❑ 3 ❑ 4
			3) with Rapporteur only at national level	3) ❑ 1 ❑ 2 ❑ 3 ❑ 4
			4) with Co-Rapporteur only at national level	4) ❑ 1 ❑ 2 ❑ 3 ❑ 4
			5) with Rapporteur and Co-Rapporteur jointly at national level	5) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____ _____

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

		A + C A A + C A + C A + C A + C	59. Please qualify the usefulness of the meeting(s) with respect to scientific discussion and added value* 1) with the EMEA only 2) with Rapporteur and Co-Rapporteur and the EMEA 3) with Rapporteur only at national level 4) with Co-Rapporteur only at national level 5) with Rapporteur and Co-Rapporteur jointly at national level	59. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4 4) ❑ 1 ❑ 2 ❑ 3 ❑ 4 5) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____ _____ _____ _____
121 - Submission of written responses and new draft of English SPC, Package Leaflet and Labelling by the Applicant to Rapporteur, Co-Rapporteur, CPMP Members and the EMEA - Restart of the clock		A A + C A + C A + B C	60. Date of submission of the responses 61. Did the Applicant have any difficulties in providing responses within the time frame proposed by the CPMP? 61.1 If yes, please give comments 62. Date of restart of the clock 63. Quality of the responses* 1) Quality 2) Pre-clinical Safety 3) Clinical Safety 4) Efficacy	60. ☐☐ ☐☐ ☐☐ Day Month Year 61. ❑ Yes ❑ No 61.1 _____ _____ _____ _____ 62. ☐☐ ☐☐ ☐☐ Day Month Year 63. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4 4) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____ _____ _____ _____

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

150	Assessment Report on the responses to the list of questions	A + B	64. Date of receipt of the AR	64. ☐☐ ☐☐ ☐☐ Day Month Year
		A + B	65. Clarity of the AR on the responses*	65. ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____
	Checking of new draft of English SPC, Package Leaflet and Labelling	B + C	66. Quality* (according to format, allowed terms, consistency within documents...) of the 1) SPC 2) Package Leaflet 3) Labelling	66. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4
		B	67. Quality of the translations 1) SPC 2) Package Leaflet 3) Labelling	67. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 3) ❑ 1 ❑ 2 ❑ 3 ❑ 4
		B	68. If difficulties were encountered, in which language? Please comment.	68. _____

170	Deadline for comments from CPMP Members back to Rapporteur and Co-Rapporteur	B	69. Please specify the date	69. ☐☐ ☐☐ ☐☐ Day Month Year
		B	70. Was the deadline respected?	70. ❑ Yes ❑ No
		B	70.1 If no, please specify	70.1 _____
		B	71. Number of CPMP Members who provided comments to Rapporteur and Co-Rapporteur	71. ☐☐
		B+ C	72. Number of CPMP Members with new outstanding major objections	72. ☐☐

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

170 - 180	CPMP discussion and decision on the need for an oral explanation by the Applicant	A + B	73. Was an oral explanation requested? If yes, when?	73. ❑ Yes ❑ No ☐☐ ☐☐ ☐☐ Day Month Year
		A + B + C	73.1 If yes, 1) on request of the Applicant? 2) on request of the CPMP? 3) upon advice of the Rapporteur?	73.1 1) ❑ 2) ❑ 3) ❑
		A + B + C	73.2 If yes, please specify the reasons	73.2 _____ _____ _____ _____
		A	73.3 On which part of the dossier? 1) Quality 2) Preclinical Safety 3) Efficacy 4) Clinical Safety	73.3 1) ❑ 2) ❑ 3) ❑ 4) ❑
		A + B	74. Date of the clock stop, if requested	74. ☐☐ ☐☐ ☐☐ Day Month Year
		A + C	75. Was a preparatory meeting with Rapporteur, Co-Rapporteur and Project Manager organised?	75. ❑ Yes ❑ No
		A + C	75.1 If yes, how useful was the meeting?*	75.1 ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____ _____ _____ _____

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

181	Restart of the clock and oral explanation	A + B	76. Date of restart of the clock/oral explanation	76. ☐☐ ☐☐ ☐☐ Day Month Year
		A + C	77. Quality of the oral explanation* 1) with regard to the scientific discussion of outstanding major objections 2) with regard to organisation, facilities, timing	77. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____
		A	78. Were the issues resolved during the oral explanation?	78. ❑ Yes ❑ No
		A	78.1 If no, please give further comments	78.1 _____
		C	79. Quality of the presentation given by the Applicant during the oral explanation*	79. ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____
		A + C	80. Do you think the oral explanation was useful?	80. ❑ Yes ❑ No

BEF 210	CPMP Opinion + CPMP draft AR	B	81. Date of CPMP Opinion	81. ☐☐ ☐☐ ☐☐ Day Month Year
		A	82. Please indicate any changes (and section concerned) between SPC, Package Leaflet and Labelling applied for and approved	82. _____

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

BEF 240	Translations sent by the Applicant to CPMP Members and the EMEA. Finalisation of CPMP AR to be transmitted to the Applicant	A	83. Date of receipt of final AR	83. ☐☐ ☐☐ ☐☐ Day Month Year
		B	84. Date of receipt of final SPC, Package Leaflet and Labelling in all eleven languages	84. ☐☐ ☐☐ ☐☐ Day Month Year
		A+B	85. Receipt of last comments on translations from CPMP Members	85. ☐☐ ☐☐ ☐☐ Day Month Year
			1) In time	1). ❑ Yes ❑ No
			2) If a delay, how many maximum number of days?	2) ☐☐
			3) Number of delegations having sent comments on translations to the applicant and the EMEA.	3) ☐☐
			4) Comments	4) _____ _____
		A	86. Relevance of their comments*	86. ❑ 1 ❑ 2 ❑ 3 ❑ 4
		B	87. Deadline for the Applicant to provide final SPC, Package Leaflet and Labelling in all eleven languages	87. ☐☐ ☐☐ ☐☐ Day Month Year
		B	88. Date of receipt of finalised SPC, Package Leaflet and Labelling from the Applicant (receipt of all translations in all languages)	88. ☐☐ ☐☐ ☐☐ Day Month Year
BEF 240	Transmission of Opinion to Applicant, Commission and Member States in all languages	B	89. Date of transmission of Opinion in all languages to the	89.
			1) Applicant	1) ☐☐ ☐☐ ☐☐ Day Month Year
			2) Commission	2) ☐☐ ☐☐ ☐☐ Day Month Year
			3) Member States	3) ☐☐ ☐☐ ☐☐ Day Month Year
		B	90. Reason for delay, if applicable	90. _____ _____
		B	91. Date of receipt of Commissionís acknowledgement at the EMEA	91. ☐☐ ☐☐ ☐☐ Day Month Year

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

BEF 300	Finalisation of EPAR in consultation with CPMP, Rapporteur, Co-Rappor teur and Applicant	B	92. Date of receipt of proposal from the Applicant concerning the deletion of confidential data	92. ☐☐ ☐☐ ☐☐ Day Month Year
		B	93. Date of circulation of draft 1 of EPAR to the CPMP and the Applicant	93. ☐☐ ☐☐ ☐☐ Day Month Year
		B	94. Was the deadline for comments on draft 1 of the EPAR respected?	94. ❑ Yes ❑ No
		B	94.1 If no, who did not respect it?	94.1 ❑ Applicant ❑ CPMP
		A + B	94.2 In the event of difficulties, comment	94.2 _____ _____
		B	95. Date of CPMP adoption of draft 2 of EPAR	95. ☐☐ ☐☐ ☐☐ Day Month Year
		A + C	96. Final EPAR. Are you satisfied with* 1) Objectiveness	96. 1) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____ _____
		A + C	2) Clarity and legibility	2) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____ _____
		A	3) Level of data protection	3) ❑ 1 ❑ 2 ❑ 3 ❑ 4 Comments: _____ _____
		B	97. Date of Commission Decision	97. ☐☐ ☐☐ ☐☐ Day Month Year
		B	98. Date of notification of the Commission Decision to the Applicant	98. ☐☐ ☐☐ ☐☐ Day Month Year
		B	99. Date of transmission of the EPAR to the Applicant	99. ☐☐ ☐☐ ☐☐ Day Month Year
		B	100. Date of availability of the EPAR to the public	100. ☐☐ ☐☐ ☐☐ Day Month Year

**Please indicate level of satisfaction by scoring between 1 and 4. 1: very dissatisfied, 2 dissatisfied, 3: satisfied, 4: very satisfied*

*****Answer by: A=Applicant, B=EMEA, C=Rapporteur***

Please add supplementary sheets as necessary

OVERALL OVERVIEW:

101. Are you satisfied with the procedure as such?*

❑ 1 ❑ 2 ❑ 3 ❑ 4 (to be answered by the Applicant)

❑ 1 ❑ 2 ❑ 3 ❑ 4 (to be answered by the Rapporteur)

102. Are you satisfied with transparency, dialogue and advice* from

1) the EMEA

❑ 1 ❑ 2 ❑ 3 ❑ 4 (to be answered by the Applicant)

2) the Rapporteur/Co-Rapporteur

❑ 1 ❑ 2 ❑ 3 ❑ 4 (to be answered by the Applicant)

103. Are you satisfied with transparency, dialogue and assistance from the EMEA?*

❑ 1 ❑ 2 ❑ 3 ❑ 4 (to be answered by the Rapporteur)

104. Other Comments: _____
_____
_____
_____
_____
_____
_____
_____
_____

Filled in by..... Date.....

* Please indicate level of satisfaction by scoring between 1 and 4. 1 : very dissatisfied, 2 : dissatisfied, 3 : satisfied, 4 : very satisfied

**Answer by : A = Applicant, B = EMEA, C = Rapporteur

Please add supplementary sheets as necessary