Key Issues Regarding the EU-Review and Enlargement

Prof. Dr. rer. nat. habil. Harald G. Schweim
President of the Federal Institut for Drugs and Medical Devices (BfArM), Bonn
Agencies

- Are part of different social systems
- Are involved in the effective and secure use of drugs
- Are – besides industry and universities - the third independent column of drug-development

- Are in discussion and criticised:
  - Approval too slow
  - Approval too fast
  - Hurdles too high
  - Hurdles too low
Non German Examples:

- **1995**: The Republican speaker of the House of Representatives, Newt Gingrich referred to the FDA as "job killers: its excessive reviews, he claimed, delayed the launch of new drugs and thereby forestalled growth for the pharmaceutical industry.


Drugs in Europe (Selection)

DE
~ 82.4 million*

UK
~ 59 million*

SE
~ 8.9 million*

DK
~ 5.4 million*

~ 57 000**
marketable
drugs
within the competence of the BfArM 94%; PEI 6%
incl. Parallelimports
incl. registered homeopathic products

~ 26 000
marketable
drugs
incl. Parallelimports
incl. registered homeopathic products

~ 6400
marketable
drugs
without Parallelimports
without homeopathic/herbal products

~ 4650
marketable
drugs
incl. Parallelimports

*Inhabitants

** human AM
Drugs in Germany

- big (German-speaking) market (~ 100 Mio. people)
- 60,000 approved drugs with:
  - ~ 1000 usable approvals with standardised master texts ("Muster")
  - ~ 10,000 "freshly" appr. "old products" ("Nachzulassung")
  - ~ 20,000 MRP-ready approvals (Assessment Reports)
- big market for homeophtatics and herbals
- important medium-sized (and cooperative !) companies
- all global players in the market
- no pricing negotiations within approval procedure
Tasks of the BfArM

**Licensing and Registration of Medicinal Products**
- Marketing Authorization of finished medicinal products on the basis of the German Drug Law and 2001/38/EC
- Registration of homeopathic medicinal products acc. to Art. 14 of 2001/83/EC

**Monitoring of Risks from Medicinal Products**
- collects/evaluates reports on side effects of licensed products
- takes corresponding measures of risk prevention

**Narcotics and Precursors**
- Federal Opium Agency
- grants licences for participation in legal traffic
- controls manufacture, trade, import, export and cultivation

**Medical Devices**
- collects serious risks occurring during use
- recommends measures of risk prevention

**Research**
BfArM Staff

1046 employees (including part-time employees); thereof
684 females, 362 males
817 permanent positions;
342 thereof scientists

30.06.2003
### Staffing levels in BfArM divisions

<table>
<thead>
<tr>
<th>Division</th>
<th>P/VP</th>
<th>Z</th>
<th>E</th>
<th>IT</th>
<th>N</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>Total</td>
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<td>36</td>
<td>56</td>
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<td>96</td>
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<td>Scientists**</td>
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<td>15</td>
<td>18</td>
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<td>50</td>
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<td>23</td>
<td>10</td>
<td>24</td>
<td>152</td>
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<tr>
<td>Other***</td>
<td>13</td>
<td>210</td>
<td>18</td>
<td>40</td>
<td>57</td>
<td>66</td>
<td>34</td>
<td>44</td>
<td>15</td>
<td>17</td>
<td>10</td>
<td>42</td>
<td>48</td>
<td>19</td>
<td>233</td>
</tr>
</tbody>
</table>

* including part-time employees
** including Jurists etc.
*** including administrative/technical staff etc.

- **41.4 % of all positions for Tasks concerning Marketing Authorisation**
  - 152 Scientists
  - 233 Administrative staff members
- **27.6 % of all positions for Tasks concerning „Nachzulassung“**
  - 125 Scientists
  - 132 Administrative staff members
Staff development at BfArM from 1995 to 2003


Positions

- Time-limited
- Permanent
## Budget

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2002</th>
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<tbody>
<tr>
<td></td>
<td>Debits (T€)</td>
<td>Actual (T€)</td>
</tr>
<tr>
<td>Income</td>
<td>25,635 T€</td>
<td>27,093 T€</td>
</tr>
<tr>
<td>Expense</td>
<td>100,592 T€</td>
<td>86,435 T€</td>
</tr>
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</table>

Cost-recovery for Approval and „Nachzulassung“ in 2002: 83.5 %

Estimated Income in 2003: ~ 36,700 T€
Workload “Nachzulassung”

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original “old market”</td>
<td>140 000*</td>
<td>(notification 1978)</td>
</tr>
<tr>
<td>Applications for post-marketing approval</td>
<td>32 000*</td>
<td>(long application 1990)</td>
</tr>
<tr>
<td>Submitted by 02.02.2001</td>
<td>12 500*</td>
<td>(2001)</td>
</tr>
<tr>
<td>7300* Processing of content (EU verdict)</td>
<td>open 4080**</td>
<td>( - 3220)</td>
</tr>
<tr>
<td>3500* Homeopath. with indication;</td>
<td>open 2242**</td>
<td>( - 1258)</td>
</tr>
<tr>
<td>4700* Homeopath. without indication;</td>
<td>open 3159**</td>
<td>( - 1541)</td>
</tr>
<tr>
<td>5200* Withdrawals, formal processing;</td>
<td>open 0**, ***</td>
<td>( - 5200)</td>
</tr>
<tr>
<td>5300* Deletions, formal processing;</td>
<td>open 0**, ***</td>
<td>( - 5300)</td>
</tr>
<tr>
<td>26.000 Total load</td>
<td>open 9481</td>
<td></td>
</tr>
</tbody>
</table>

* rounded; **01.11.03, precise; ***apart from cost notices
Quality Management: Activities at BfArM

Current situation:
- Harmonisation of SOP format
- SOPs in all divisions
- Comprehensive collection of processes (flow charts) for medicinal product approval (supported by external experts)
- First steps to build-up QMS according to DIN EN ISO 9001 in several divisions

Future:
- Exchange of experience based on the ‘best practice’ examples in the BfArM
- To achieve broad acceptance of QM
- Implementation of QM system according to DIN EN ISO 9000 etc. seqq. in all divisions and units of the BfArM
Important Aspects of the Review

• Streamlining of EU-Committees (number of members; selection process; responsibility)

• Importance of clear definitions

• Scope for centralised / decentralised procedures

• Renewal versus pharmacovigilance
Need for Definition: "Serious Risk to Public Health"

- do national views / definitions differ from case to case and from country to country?
- are national views always objective?
- are national views potentially "historical"?
- are national views applicable to European harmonisation / single market?
- are national views "for home use" only
  - or a "mission" to other countries?
  - Conclusion: A European definition is highly necessary.
- Already on Commission agenda
Scope for Centralised / Decentralised Procedure

new drugs for: AIDS, oncology & neuro-
vegetative diseases (e.g. Alzheimer's),
diabetes: obligatorily CENTRALISED

.... and in the future more?

Generics
centralised and decentralised
line-extension

FOR ONE MEMBER STATE ONLY;
bibliographic approval;
Different Types of Marketing Authorization Procedures

Centralised Procedure
Regulation (EG) No. 2309/93

EMEA

Community authorization

Mutual Recognition Procedure
Directive 2001/83/EG
Art. 17, 18, 28

DE = CMS

National marketing authorization issued at the end of MRP

National Procedure including Registration Procedure

DE = RMS

BfArM

National marketing authorization

Assessment Report
Marketing Authorization Procedure

Phase 1
- Formal Pharmacy
- Pharmaceutical Quality
- Clinical Pharmacology
- Exp. Pharm. Toxicology

List of Objections/Withdrawals/Refusals

Clock Stop
2-6 months

pre-processing time

approval time for BfArM

Applicant
Application for marketing authorization
Filing Unit/Archive
Database
Clearing Unit/Validation
Project-assistant

~ 30%
List of Objections/Withdrawals/Refusals

BfArM
Marketing Authorization Procedure

BfArM

Applicant
- Applicant
- Response documents
- Project-assistant
- Formal Pharmacy
- Pharmaceutical Quality
- Clinical Pharmacology
- Exp. Pharm. Toxicology
- Decision

Phase 2

Project-assistant
- Formal Pharmacy
- Marketing Authorization
- Applicant

Commission acc. § 49

clock stop

approval time for BfArM
Deadlines are kept in European procedures.
Approval times have been improved in national procedures; e.g., in 2002 decisions were taken in approx. 72% of all applications (national* and European).

* 210 days
Organisation of Review Process – Centralised Procedures

EMEA

BfArM Project Management by European Division

Pharmaceutical Quality

Experimental Pharmacology and Toxicology

Clinical Pharmacology

Application Dossier

Assessment Report/ Objections/ LoQ

Dossier

Objections/LoQ/AR-Part II

Dossier

Objections/LoQ/AR-Part III

Dossier

Objections/LoQ/AR-Part IV
BfArM – Europ. Workload
Centralised Procedure 1995 bis 2003

<table>
<thead>
<tr>
<th>Centralised Procedure*</th>
<th>total number</th>
<th>BfArM as (Co)Rapp</th>
</tr>
</thead>
<tbody>
<tr>
<td>(without line extension)</td>
<td>394</td>
<td>52</td>
</tr>
<tr>
<td>(including line extension)</td>
<td>458</td>
<td>57</td>
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</table>

ca. 13 %
ca. 12 %

21 Applications from native German Companies:

<table>
<thead>
<tr>
<th>BfArM</th>
<th>Applications</th>
<th>Rapp</th>
<th>Co-Rapp</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>10</td>
<td>3</td>
<td>4</td>
<td>7</td>
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<tr>
<td>Bayer AG</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Merz</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Schwarz Pharma</td>
<td>2</td>
<td>-</td>
<td>2</td>
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<tr>
<td>Behringwerke</td>
<td>1</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Grünenthal</td>
<td>1</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medac</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

total number: 21

Conclusion: out of 21 applications within its legal responsibility the BfArM has acted in nearly 50 % as (Co)Rapporteur

*Date: 15. 11. 2003
For 2004*, 33 new substances are expected within the Centralised Procedure but 200 „orphans“ are „on the horizon“ in the next few years.

What is the future ??

How to get a rapporteurship from a smaler „cake“ ??

What’s about the new members and their „slice“ ??

(costs ? , fees ?, 240 EMEA - employees must be paid!)

* source: T. Lööngren, Rome 27.11.03
Mutual Recognition Procedure

- Applicant submits dossier
  - RMS submits Assessment Report
    - Validation CMS
      - Day 0 - 50
        - Evaluation of relevant parts by
          - Quality Division
          - Pharm.-Toxicol. Division
          - Clinical Division
          - Labelling and Licensing Unit
        - Comments/Objections to RMS and Applicant
      - Applicants Response Document
        - Evaluation of Response Document
          - Day 75
            - Breakout-Session /Discussion
          - Day 85
            - Final SPC
        - Day 90
          - Decision on the Application
          - Arbitration
      - Applicant submits national texts
        - Granting a marketing authorization/licensing
### Mutual Recognition*

<table>
<thead>
<tr>
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<th>EU</th>
<th>RMS</th>
<th>CMS</th>
<th>total</th>
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</thead>
<tbody>
<tr>
<td>Procedures:</td>
<td>2325</td>
<td>290</td>
<td>1334</td>
<td>1624</td>
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<tr>
<td>Applications:</td>
<td>4605</td>
<td>528</td>
<td>2721</td>
<td>3249</td>
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</tbody>
</table>

DE has taken 2002 the 4th position of all MSs acting as RMS.
DE - together with SE - took the leading position in the approval of new substances in the MRP.
DE has participated in more than 50% of all MRPs including 2/3 of all applications submitted in the EU.
DE has the biggest share of marketing authorisations through the MRP in Europe.

*Date: 15. 11. 2003*
Overview
Reference Member States in MRP
- Finished Procedures (Day 90)
01.01.2003 till 15.11.2003 -
Reference Member State

Timetable for the Mutual Recognition Procedure

- Nationale Authorisation with Assessment Report
- Start of Procedure in compliance with the Best Practice Guide (MRFG)
- Day 1 - 50 ➔ Receive comments (RMS/MAH) of CMS
- Day 51 - 60 ➔ Agreement on Response Document (MAH and RMS)
- Day 61 ➔ Distribution of Response Document by MAH to RMS/CMS
- Day 75 ➔ “Break-out Session" parallel to MRFG-Meeting
- Day 85-89 ➔ "final position" CMSs
- Day 90 ➔ End of Procedure
Overview
Concerned Member States in MRP
- Finished Procedures (Day 90)
01.01.2003 till 15.11.2003 -
Concerned Member State

REALIZATION OF THE REQUIREMENTS OF THE BEST PRACTICE GUIDE

- CHECK IN PROCEDURE
  - AUTOMATIC VALIDATION TIME
  → 10 WORKING DAYS

- POTENTIAL SERIOUS HEALTH ISSUE
  → NOT LATER THAN DAY 50
  ALWAYS BEFORE DAY 50

- OBJECTIONS AND ANY ISSUES OF CLARIFICATION
  SHOULD CAREFULLY SCREENED WITHIN THE NATIONAL AGENCIES

- AGREEMENT ON THE SPC BEFORE
  → DAY 90

- NATIONAL AUTHORISATIONS TO BE ISSUED WITHIN
  → 30 CALENDAR DAYS
EFPIA survey July 2001- Sep. 2002

30 - 60 Tage = 3 MS
60 - 90 Tage = 7 MS \(\leftarrow\) DE (BfArM)
90 - 120 Tage = 6 MS
> 200 Tage = 1 MS

Time within the responsibility of the BfArM:

2002 80 Days (mean value)

2003 60 Days (mean value)
New Active Substances by RMS
Mutual Recognition New Applications
finalised in 2002

- DE: 11
- DK: 4
- FR: 2
- NL: 6
- SE: 6
- UK: 10
# Variations

## Mutual Recognition Procedure

<table>
<thead>
<tr>
<th>Type IA</th>
<th>Type IB</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example: name/address of MAH or manufacturer, name of active substance,</td>
<td>Example: name of medicinal product, manufacturer of active substance, shelf life</td>
<td>Example: change of SPC (indications, Contraindications, Interaction or Side Effects, ...)</td>
</tr>
<tr>
<td>Notification Procedure</td>
<td>Notification Procedure</td>
<td>Approval Procedure</td>
</tr>
<tr>
<td>CMS: Validity</td>
<td>CMS: Validity</td>
<td>CMS: Quality and/or Clinical Assessment</td>
</tr>
<tr>
<td>RMS: Validity, Plausibility</td>
<td>RMS: Validity, Plausibility (Quality and/or Clinical Assessment)</td>
<td>RMS: Quality and/or Clinical Assessment + Assessment Report</td>
</tr>
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</table>
Variations
Receipt (E) + Completion (A)

2002 Number of completed procedures higher than number of receipts
<table>
<thead>
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<th>Variations 2002/ 1. Hj. 2003</th>
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<table>
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<th>nur B113</th>
<th>Qualität</th>
<th>Medizin</th>
<th>sonst.</th>
<th>gesamt</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Coordination of Assessment in Scientific Divisions
by the Variation Unit of the Regulatory Affairs Division

| dezentral, RMS, Type I | 304 | 268 | 2 | 2 | 575 |
| dezentral, RMS, Type II | 1 | 34 | 59 | 5 | 90 |
| dezentral, CMS, Type I | 3293 | 24 | 4 | 2 | 3323 |
| dezentral, CMS, Type II | 4 | 568 | 410 | 29 | 983 |
| zentral, RMS, Type I | 96 | 167 | 0 | 0 | 263 |

<table>
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<th>Qualität</th>
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<tr>
<td></td>
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</table>

national, zustimmungspflichtig

<table>
<thead>
<tr>
<th>national, zustimmungspflichtig</th>
<th>342</th>
<th>209</th>
<th>652</th>
<th>64</th>
<th>1134</th>
<th>374</th>
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<tr>
<td>national, nicht zustimmungspflichtig</td>
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<td>2124</td>
<td>750</td>
<td>472</td>
<td>7320</td>
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<td>380</td>
<td>1033</td>
<td>0</td>
<td>1406</td>
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Variations 2002

- Quality: 12564
- Information: 11351

- Zulassungsinhaber: 3996
- Hersteller: 4172
- Bezeichnung: 2729
- Packungsgrößen: 1850
- Mitvertreiber: 2472
- Darreichungsform: 123
- Parallelimporte (zugelassen): 1214
- Zusammensetzung: 1539
- Qualität ohne Darreichungsform und Zusammensetzung: 11351

Informationstexte
Possible Development I (Risks)

- Shift from national + decentralised procedures to centralised procedures
- Increase in monopolisation of licensing systems
- Decrease in competition
- Decrease in national identification with products
- Shifting of decisions from national to centralised anonymous EU authorities
Development II (Advantages)

- Common market
- Quality of supply with medicinal products of a consistently high European standard
- Uniform regulatory system
- Transparency
- Orientation for consumer and patient

But Pharmacovigilance always stays a national responsibility !!
Agencies Have to Define Their Position for the Future:

- Team leader and/or opinion leader?
- Centres of excellence for agencies or "full provider"?
  - according to approvals:
  - MRFG – RMS / Centralised - Rapporteur
  - according to projects / indications (e.g. antibiotics, HIV)
  - according to topics (Notes for Guidance, Points to Consider, Working Parties)
- Team player in all other cases! (The Network-System!)
Role and Tasks of the Agencies in the Future

to be clarified:

• How to survive?

• Centre of excellence or "full provider"?
My Proposed Solution

- Cooperation on a network-basis
- Promotion of research and development via scientific expertise
- Some agencies as "full providers"
- Other agencies as centers of excellence
- Cooperation within the procedures
BfArM's possible Contribution

- "Full-provider"
- Scientific expertise
- Effective and efficient licensing system
- Customer orientation
- Scientific co-operation with other regulatory authorities
- Fulfilment of European and international standards
- Development of a worldwide pharmacovigilance network
Aspects of the Enlargement
Where are the Problems to be found?

- Potentially everywhere:
  - Centralised Procedure
  - Article Procedures
  - Mutual Recognition (less for the „new“ Decentralised Procedure)
  - National Procedure
    - Full Applications, Generics, WEU, Herbal Pharmaceuticals
    - Any „Old“ and „New“ Member State

- Potentially at any time:
  - Before Accession (transitional observation)
  - During Transition (transitional behaviour)
  - After Accession (transitional arrangement?)
Contributions Provided by the BfArM

- Participation and Contribution to the EU-System (at the Eur. Commission and EMEA level)
- Participation and Contribution to the PHARE Programmes:
  - PERF I, II, and III
  - Twinning (ongoing with Poland [official start: 1-3.12.03])
    - scheduled with Latvia (start approx. 01.09.04))
- HoA-East Programme: platform for discussion among HoA-E, and also with HoA-W and with Industry Provision of relevant data bases
- Organisation of Participation in Training Programmes (example: BfArM: biostatistics for non-mathematics)
European Bodies Executing Medicines Regulation

- Eur. Commission: EMEA
- Pharmaceutical or CPMP Standing Committee: Working Parties, ad hoc Groups, TAG’s
  - Controlling approx. 10% of Pharmaceuticals via Centralised and Article Procedures
- Competent Authorities of the Member States
- Mutual Recognition: National Procedures
  - Controlling approx. 20%
  - approx. 70% of Pharmaceuticals on the EU-Member States Markets
European Bodies Executing Medicines Regulation: Responsibilities?

**Eur. Commission**
- Guardian acquis Communautaire
  - hard law / soft law
  - Transitional arrangements

**EMEA**
- simplification
- logistic support

**Member States**
- Facilitator to Accession
  - transparency
  - provision of experience

**New Member States**
- responsible for assessment
- competent for decisions (throughout the product lifetime)

**Pharmaceutical Industry** (trade associations, MAH's - „old“ / „new“ EU)
- „Old“ generics (without dossier?)
- Upgrading effort
- Use of simplified procedures
- Provision of dosisiers on time
<table>
<thead>
<tr>
<th>Current EU Member State</th>
<th>New EU Member State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally authorised product (CAP)</td>
<td>Simplified procedure available</td>
</tr>
<tr>
<td>Mutually recognised authorised Product (MAP)</td>
<td>Simplified procedure available</td>
</tr>
<tr>
<td>Referral/Arbitration harmonised product (RAP)</td>
<td>Early, on-time or no implementation?</td>
</tr>
<tr>
<td>Solely nationally authorised product (NAP)</td>
<td>Simplified procedure(s) available?</td>
</tr>
<tr>
<td>Originator authorised product</td>
<td>Current or Future EU-MS product?</td>
</tr>
<tr>
<td>Self-Standing Dossier (WEU)</td>
<td>Current or Future EU-MS dossier?</td>
</tr>
<tr>
<td>Essentially Similar Product (consented)</td>
<td>Consent to a Future EU-MS product</td>
</tr>
<tr>
<td>Essentially Similar Product (generic)</td>
<td>Claim to be based on MA of Originator</td>
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<tr>
<td>BE with local product?</td>
<td>BE with European product?</td>
</tr>
<tr>
<td>Module 3 (Part II) to be submitted</td>
<td>Module 3 (Part II) to be submitted</td>
</tr>
</tbody>
</table>
European Bodies Executing Medicines Regulation: Where are the Problems to be found?

Consequences?

- Cooperation
- Collaboration
- Networking

- Bilaterally (between Agencies, Twinning)
- Multilaterally (between Agencies, PERF)
- Specific Groups (CPMP, QRD, „HoA-East“)
**Timetable**

May is tomorrow!

- **January 2004**
  - DIA HoA Bonn
  - PERF III Producers Conference Ljubljana
  - PERF III Vets Conference Warsaw
  - MRP/CAP Industry Info Day

- **30 April 2004**
  - Ifis / DIA Paris

- **1st May 2004**
  - Commission Framework Act

- **March 2004**
  - Administrative Procedure (Early Process)

- **April 2004**
  - Variation Life - cycle
  - Administrative Procedure (clean-up)

- **May 2004**

- **January 2004**
  - QRD Meeting
  - Submission Linguistic elements

- **April 2004**
  - QRD Training
  - Checking Linguistic elements

- **January 2004**
  - QRD Meeting

- **30 April 2004**
  - MRP/CAP Industry Info Day

- **1st May 2004**
  - Ifis / DIA Paris

- **Commission Framework Act**

- **1st May 2004**
  - Administrative Procedure (clean-up)
As an example:
The great challenge
"Harmonisation of Summary of Product Characteristics"
E.G. : Article 11
75/319/EEC Procedure for originator

• When?
  Different national decisions on the drug

• Why?
  Harmonisation of national decisions

• Who starts?
  Member States, EU Commission, applicant/holder of author.

• Who is concerned?
  the drug
  applicant/holder of authorisation
  the reference drug
  Member States with existing authorisations
  Member States with withdrawn/suspended authorisations
Follow-up after Community Referral
Article 11

How? „

(If we even not agree on the spelling ?)

The procedure harmonises the "Summary of Product Characteristics" especially Parts III and IV of the Dossier (pharm-tox, clinical)

Not Part II, Quality. This part of the SPC can remain unharmonised

However, the authorisation holder is seriously advised to harmonise voluntarily or to file the Quality Dossier as a 'European Dossier'
CTS- Steps 2003 – 2004

10/04/03  Specialized Specification of the new Variations
10/04  Feature-definition completed by the CTS Usergroup
10/04  New Data-Model finished
12/05  CTS NextGen Server finished
30/06  CTS NextGen Client with new Variations finished
15/08  Interaction between 5.3.9 and NextGen-Client finished
30/08  Beta-Test with CTS Usergroup-Members
15/09  Testing Phase at all European Sites
01/10  Going Live with new Variations
May/2004  CTS NextGen completely replaces EMR 5.3.9
Enlargement Summit

This DIA conference is being organised in cooperation with the Federal Institute for Drugs and Medical Devices (BfArM), Germany

Programme Committee
Roel Bass, Federal Institute for Drugs and Medical Devices (BfArM), Germany
Roger Grase, Federal Institute for Drugs and Medical Devices (BfArM), Germany
Brenton James, ClaroSmithKline R&D, UK

Facility Members

Ingrid Klingmann, Pharmaplex, Belgium
Jacques Mascaro, Johnson & Johnson Pharmaceutical R&D, UK
Anu Tummauruori-Liemann, F. Hoffmann-La Roche Ltd, Switzerland

Programme Advisor
Harald Schweim, Federal Institute for Drugs and Medical Devices (BfArM), Germany

Cyprus
George Antoniou, Pharmaceutical Services, Ministry of Health

Czech Republic
Mirek Smid, State Institute for Drug Control

Estonia
Kristin Raudsepp, State Agency of Medicines

Hungary
Tamás L. Paul, National Institute of Pharmacy

Latvia
Jana Ozolina, State Agency of Medicines

Bulgaria
Borislav Borissow, Bulgarian Council of Medicines

Croatia
Sinisa Tomic, Croatian Agency

EMEA, UK
Anthony Humphreys
Hans-Georg Wagner

European Commission, Belgium
Irene Sacristán Sanchez

Lithuania
Vytautas Baty, State Medicines Control Agency

Malta
Maria Elia, Medicines Authority, Operations and Regulatory Affairs

Poland
Michal Pirozynski, Office for Registration of Medicinal Products, Medicinal Devices and Biocides

Slovak Republic
Ludovit Martinec, State Institute for Drug Control

Slovenia
Agency for Medicinal Products*

more meetings planned...... ?
my home – country: EUROPE*

Thank You for Your kind Attention!

*Intermediate stage 2004/7

and Turkey?
Procedure of the Ethics committee
Situation according to the current legislation

56 Ethics committees formed according to ´Länder-Law`: 
• 20 ECs of the Medical Practioner Association in the ´Bundesländer´
• 36 ECs of the Medical Faculties of Universities and Medical High Schools

Requirements according to GML
Favourable Opinion of EC competent for the coordinating investigator

Requirements according to professional law for MDs:
Each investigator should to be consulted by the concerned EC.

Sponsor

I₁ I₂ I₃ Iₓᵢ

EC₁ EC₂ EC₃ ECₓᵢ

Note
• no time limits for application and review procedure of EC
• risk of several discordant opinions in multi-centre trials
Application for an Ethics committee opinion

Procedure for single opinion in a multi-centre trial

§ 41 (2) 12. law amending GDL (draft), § 7 Ordinance on GCP (draft)

Sponsor provides a valid application to all Ethics Committees

EC1-x provide comments within 30 days to EC of coord. invest.

EC1
EC2
EC_C1
EC3
EC4

Single opinion provided by EC of coord. invest. within 60 days

Sponsor
Copy to competent authority
Application for an Ethics committee opinion

§ 41 (1) 12. law amending GDL (draft), § 7 (1) GCP-Ordinance (draft)

Application Receipt

Application not valid

Additional documentation or justification

10 days

14 days

Review on completeness
Application for an Ethics committee opinion

Procedure and time limits

§ 41 (2) 12. law amending GDL (draft), § 7 Ordinance on GCP (draft)

Receipt of Application (valide)

Reasons for non-acceptance

Receipt of additional documents

Acceptance or reasons for non-acceptance (final)

Clock stop

Multi-centre trials: 60 days
Single-centre trials (incl. 1. step phase I trials): 30 days
Phase I trials (Second + further steps): 14 days

Review

According to the prevailing standard of scientific knowledge:
• completeness of documents
• protocol, investigators brochure, modalities on the recruitment of trial subjects
• informed consent

Note
Time limit 90 days in clinical trials investigating Gentransfer, somatic cell therapy, genetically modified organisms
Extended to 180 days if external experts are consulted
Request for Authorisation to the competent authority
§ 41 (2) 12. Revision GDL (draft), § 8 GCP-Ordinance (draft)

- Covering letter (Eudract Nr.)
- Application form
- IMP Dossier
- Investigators brochure
- Protocol
- Certificates

Request Receipt

Request not valid

10 days

Additional documentation or justification

14 days

Review on completeness

"Bundesinstitut für Arzneimittel und Medizinprodukte"
**Request for Authorisation to the competent authority**

§ 41 (2) 12. Revision GML (draft), § 8 Ordinance on GCP (draft)

<table>
<thead>
<tr>
<th>Receipt of Request (valide)</th>
<th>Reasons for non-acceptance (30 days) otherwise accepted</th>
<th>Receipt of additional documents</th>
<th>Acceptance or reasons for non-acceptance (final)</th>
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<tbody>
<tr>
<td>30 days</td>
<td>90 days</td>
<td>15 days</td>
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<tr>
<td>14 days*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 days**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Review**
According to the prevailing standard of scientific knowledge:

- **Quality**
  - Drug substance
  - Drug product

- **pharm-tox. documentation**
- **clinical documentation**

**Note**

* 14d 2nd + further trials in phase I
* time limit 60d in clinical trials with IMPs according to Dir. 2001/20/EC Art. 9 (5) and (6)

Time period may be extended to max. 180d if BOB has to consult external expert groups