EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

How can non-contributing agencies be encouraged to participate

Kristin Raudsepp, MD
Director General,
Estonian State Agency of Medicines
HMA Management Group
HMA Resource Planning Working Group

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Population: 1,34 mill
(65% Estonians)

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

The presentation

- What do we mean with “contributing agency”
- What do we mean with “co-operative company”
- Why do they do it
- What can be done to encourage wider participation?
- Situation with different procedures
- Update of the medicinal products market in Estonia.

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Some useful links

- http://www.hma.eu

HMA
Heads of Medicines Agencies

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

What is new agency

- 1957: 6 countries in EU
- 1973: 3 new countries in EU
- 1981: 1 new country in EU
- 1986: 2 new countries in EU
- 1995: 3 new countries in EU
- 2004: 10 new countries in EU
- 2007: 2 new countries in EU
- 20.....

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

EU procedures needing resources from MS

- **(co)rapporteurs for concept papers/guidelines/documents for CHMP WP-s**
- **(co)rapporteurs for dossier evaluation referred to the WP**
- **(co) rapporteurs for scientific advice referred to the WP by the CHMP Scientific Advice WP**
- **CMDh - Mutual recognition new applications**
- **CMDh - Decentralised new applications**
- **CMDv - Mutual recognition new applications**
- **CMDv - Decentralised new applications**
- **(co)rapporteurs at the CHMP**
- **CHMP peer review appointments**
- **(co)rapporteurs (incl MRL) at the CVMP**
- **coordinators for PMF Certification**
- **monographs for HMPC**
- **COMP**
- **EC working groups**

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

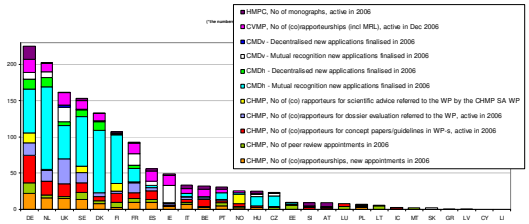
2007 EU new applications

- New applications MRP started - 396
- New applications DCP started - 1033
- The total number of new applications for initial evaluation in CHMP - 90

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

No of Selected Activities in the EU network in 2006

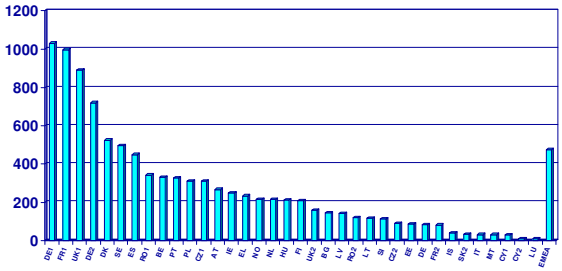


Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

No of employees in CA of EEA + EMEA

human+vet, and in some countries cosmetics, devices, reimb, pestic
HMA 2008



EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Contributing agencies

- Agencies with resources and motivation
- Agencies with no resources, but with motivation
- (Agencies with resources, but with no motivation)

- Estimated MRP/DCP procedures in MS range from 2 to 400 per year.

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Possible view of a MS about motivation

- Acting as a RMS or (co)rapporteur does not often mean the product will be put on the market of the MS after the granting of marketing authorisation.
- Being active and working diligently in the European market processes, does not help small countries to get products on their own.

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

State Agency of Medicines
ESTONIA;
e-mail: info@ravimiamet.ee;
homepage: www.ravimiamet.ee

Ravimiamet
State Agency of Medicines

What is our situation in Estonia

- The budget of SAM in 2008 is 2,5 million Euros which is 40 times less than budget of biggest CAs in EU
- We have 80 people (covering MA, drug information, adverse reactions, inspections, lab, clinical trials, veterinary medicines, medical devices, biological products)

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

What have we done to cope

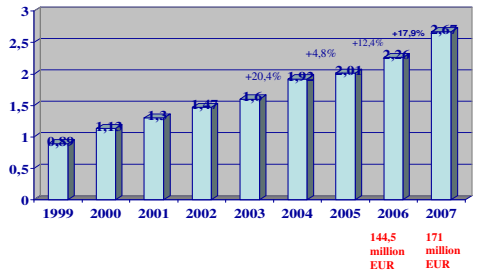
- Priority list of targets and actions
- Risk analyses
- Learning from the more experienced agencies
- Quality system
- Benchmarking
- Perfomance indicators
- Following the plan, but being flexible

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

The Estonian Medicinal Products Market

(billion EEK, wholesale data)



EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Patients' needs in small countries

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Patients' needs in small countries

- The same as in bigger and richer ones

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Patients' needs in small countries

- The same as in bigger and richer ones
  - i.e. Access to the medicines which efficacy, quality and safety has been proven and maintained through its cycle

Ravimiamet
State Agency of Medicines

The side effects of being small

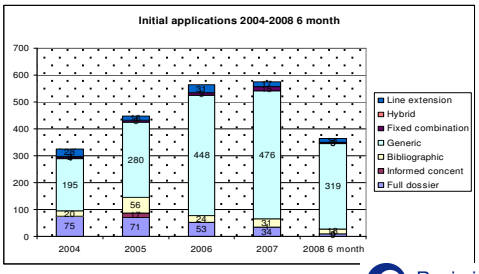
- Big opportunity to work as a fireman
- The risks are high, as one individual is responsible for too big part of your work
- The limited number of good people
- The same limited number of good people is attractive for the companies

Estonia as a RMS

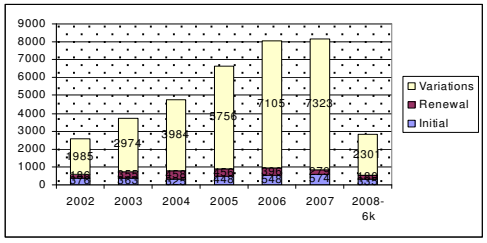
(applications received)

- 2005 – 3 MRP
- 2006 – 1 DCP
- 2007 – 11 DCP + 2 MRP + 1 RU MRP
- 2008 6k – 30 DCP
- First MRP ended 30.06.2005 ketoconazole

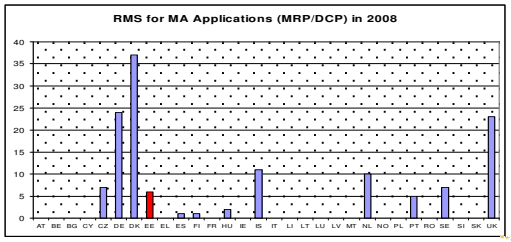
Initial applications per type in Estonia



MA applications in Estonia



Started procedures in EU



Source: Feb07 to Jan08 CMD(h) Press Releases

Dilemmas of the agency

- Do we trust each other enough to rely totally on mutual recognition
- How many centr assessments or RMS is enough
- Workload has increased considerably because of the broad range of topics (regulatory, procedural and scientific)
- Interest for fees
- The agency does not have legal way to refuse from EU work
- The agency does not have legal pressure about how much EU work should be done

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Concerns of industry

- Limited resources available in Member States to be Rapporteus, to be RMS, to run the process efficiently, to meet timelines
- Delay in some phase of the assessment
- Clock stop not very transparent- delays with restart
- Booking submission slots in advance
- Re-assessment of the Application in parallel by some CMS

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

The main criteria of the companies for selecting a RMS in MRP/DCP seem to be:

- Importance/size of the market within the (EU)
- Ability of the RMS to defend the product against other Concerned Member States (CMS)
- Long-term partnership
- Open to dialogue
- Respecting time lines
- Consideration of future variations
- Expertise in respective medical field
- Potential for specific up-front agreements
- In DCP the size of the market and respecting time lines criteria are not so important as the license will be granted at the same time for all the involved Member States.

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

MRP/DCP – is there any problem

- The latest trends show that Applicants aren't free to choose the RMS
- They have to take what is available
- Most of the agencies are willing to act as a RMS, but for several reasons the no of procedures per year is limited.

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

View of the Member State

- To take the RMS
  - feeling responsible for the EU market
  - the work is interesting
  - trusting expertise only from inside the country
  - motivation to be the part of the game
  - keeping continuous development of the personell
  - enough free resources
  - everyday practice and normal way of working
  - motivating fees
- Not to take the RMS
  - too new to understand the game
  - too old to fight for heavy workload
  - too small to attract the product to our market afterwards
  - too big to attract the product on our market anyway
  - not enough experts
  - too much other works to do
  - non-motivating fees

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

How do the agencies handle the requests for RMS-ship?

- Some: All requests are accepted
- Some: Depends on the type of the application
- Some: Procedure starts immediatedly after validation
- Booking system
  - Number of procedures in queue range from just one to 725. Totally (all agencies together) almost 1800 procedures are in queue. The booking time limits reported range from 6 months to no time limit, most agencies have a time limit of 18-24 months.
- Most of the agencies would like to participate as RMS in DCP to a larger extent
- Some agencies have differences in approach, but most agencies have described built in flexibility

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

CHMP – criteria for choosing the Rap/co-Rap

- *CHMP Rapporteur/Co-Rapporteur Appointment: Principles, Objective Criteria and Methodology. London 12 July 2006, EMEA/124066/2005*
- The procedure foresees, according to the new Pharmaceutical legislation, the criteria for Rapporteur appointment at the CHMP
- Different from the previous procedure:
  - the Applicant's proposals/preferences will not be considered for the appointment of Rapporteur/Co-Rapporteur
  - the workload statistics play a minor role
- The appointment of Rapporteur/Co- Rapporteur and their assessment teams shall be made on the basis of objective criteria, which will ensure the provision of objective scientific opinions and will allow the use of the best and available expertise in the EEA in the relevant scientific area.

Ravimiamet
State Agency of Medicines

The criteria for choosing Rap/Co-Rap

- **Ability of Rapporteur/Co- Rapporteur to fulfil their role,** which refers mainly to their ability to take responsibility for the scientific assessment /evaluation undertaken by the assessment team, coordination input etc
- **Assessment Team Objective Criteria** which refer to the scientific competence, regulatory experience, complementary cross-team scientific expertise and competence of the Assessment Team(s) as well as the availability of an adequate Quality Assurance System at the level of the EEA NCAs
- **Individual Objective Criteria** which refer to the academic expertise and the direct working experience and competence of the
  - Individual assessor/expert
  - Rapporteur/Co-Rapporteur (when acting as assessor/expert in the scientific assessment of the application)

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Thoughts about the Rules

- The timing to introduce this could not have been worse, as it came exactly at the time where new MS-s would have been introduced as Rapporteurs/Co-Rapporteurs
- Instead of trying to equalize the work-load, the rules favour the already hard-working NCA-s and leave little chance to new Rapporteur/Co-Rapporteur
- In reality, the new MS-s have been appointed Co-Rapporteurs. This has been possible either due to
  - lack of interest of the old MS-s
  - pragmatic breach of rules by the secretariat and CHMP chairman, as by definition the experience of new MS-s e.g. in EU regulatory affairs cannot compete with the old MS-s
  - lots of available work

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Thoughts about the Rules, II

- The appointment procedure seems to be less transparent than the old 'statistics' based system, as some of the the criteria, as listed above, are open to wide interpretation.
- This biases the system towards preference to bigger agencies, who can always list an A-team of highly experienced assessors, who will later have little to do with the actual assessment.
- Some agencies pick 'scientifically interesting' dossiers only, others take whatever is available and thirds hardly do anything.

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Historical reasons, fixed centres of expertise

- The system is pretty focused on the experience of the CHMP member/NCA behind her/him – this does not allow 'reformed agencies' or new MS-s to participate fully in the procedures.

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Centralised Procedure

- Are there applications for which rapporteurs are not found
  - The generic applications seem to draw little competition, as well as fixed combinations of old products and, possibly, OTC-s
  - Volunteers for SPC harmonisation referrals, re-examinations
- MSs interest for Fees
  - The rapp-ship bids are obviously dependent on fees. It is harder to find workforce for unpaid jobs like referrals or peer review.

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Proposals for better regulation of the situation in central procedures

- A system, more encouraging for new agencies, needs to be introduced in the interest of sustainability of the system.
- Incorporating these agencies into the CHMP work needs to be a formal goal. There is no excess of assessors at any of the agencies, not even the biggest. Any help needs to be used.
- The model for future needs to be that most of the agencies have regulatory competence and sustainable 'generalist' assessment teams, as well as a functioning quality system. The agencies need to work routinely in the CP, be it 1-2 new product dossiers per year for a small agency. If the need for a specific competence arises, the European expert network and co-operation with other agencies needs to be able to provide it.

Ravimiamet
State Agency of Medicines

What the agencies do to solve the availability problem of resources

- Serious effort to avoid public health problems
- HMA strategic discussions on resources
  - Ensuring that available resources are sufficient to support the work of the network.
  - Common ideas to strengthen the EU Regulatory System network
  - Creation of trust and mutual understanding in the network (Quality management systems, benchmarking)
  - Searching the ways to share resources between NCAs
- Competence development, top quality scientific expertise
- National initiatives

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Co-operative company

- To be good on agency side and perform excellent you must have good partners also - the good MA procedure starts with the receipt of high-quality application
- Constructive dialogue (pre-submission, during evaluation, post-authorisation)
- Keeping the deadlines and promises
- Declears very clearly the contact point for the agency (preferrably not the secretary)
- Is able to give quickly explanations during technical assessment
- Doesn't book parallel time slots.
- Puts enough energy into the quality of translations of product information

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

The dream

The reality

Ravimiamet
State Agency of Medicines

EU Regulatory Network
Challenges and Opportunities for Croatia
5th ALMP Anniversary
13-14 November 2008, Rijeka - Croatia

Conclusion

- Non-contribution has the reason and it is not associated only with size of the country or years in EU
- New agencies in EU procedures mean good opportunity (additional experts and knowledge, the number of possible RMS has more than doubled)

Ravimiamet
State Agency of Medicines