POST ACCESSION EXPERIENCE

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Content

1. Introduction
2. Pre-requisites for a smooth integration in the EU DRAs network
3. First post-Accession year: Challenges
4. Second post-Accession year – active involvement into EU DRAs network
5. Conclusions

1. Introduction

- The National Medicines Agency (NMA) was enthusiastic about starting and carrying on preparations for EU Accession, being very anxious to join the EU network of drug competent authorities as a well prepared member for this new role.
- To accomplish this goal, the NMA set up a detailed strategy for preparation for EU Accession as early as 2003, which it has updated and improved on an ongoing basis.
- In preparation for EU Accession, the NMA relied on its own efforts as well as on permanent collaboration with competent authorities in other candidate countries and EU Member States.
- In its endeavour, the NMA has had the benefit of stability and continuity with regard to both institution's staff and leadership.

2. Pre-requisites for a smooth integration in the EU DRAs network

2.1. National legislation transposition before Accession of entire drug Acquis communeautaire

- Transposition into national medicinal product legislation, even before Accession, of the entire ***Acquis communeautaire,*** is particularly important and a pre-requisite for developing specific activities as of the very first day after Accession.
- From the NMA viewpoint, 2006 was the peak year of pre-Accession in regard of transposition of the ***Acquis communeautaire*** into national legislation. This was the time for the transposition into Title XVII, The Medicinal product of Law 95/2006 on health care reform and orders of the minister of public health of all directives in force applicable and their implementation guidelines.

2. Pre-requisites for a smooth integration in the EU DRAs network

2.1. National legislation transposition before Accession of entire drug Acquis communeautaire (ctd.)

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use**,** as amended by Directives 2002/98/EC, 2003/63/EC, 2004/24/EC and 2004/27/EC
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

2. Pre-requisites for a smooth integration in the EU DRAs network

2.1. National legislation transposition before Accession of entire drug Acquis communeautaire (ctd.)

- Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

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2. Pre-requisites for a smooth integration in the EU DRAs network

2.2. Organisational structure to fit types of activities developed

- As a single institution, the NMA encompasses all important activities related to medicinal products for human use, thus ensuring consistent approach and facilitated communication:
  - Marketing authorisation
  - Clinical trial approval
  - Pharmacovigilance
  - GMP, GCP, GLP and Pharmacovigilance inspection
  - Laboratory control

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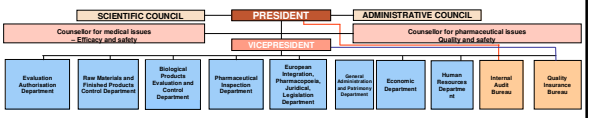
NMA ORGANISATIONAL CHART



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2. Pre-requisites for a smooth integration in the EU DRAs network

2.2. Organisational structure to fit types of activities developed (ctd.)

- A number of adjustments in the pre-existing structure were made during pre-Accession to become more suitable to activities to be carried out after Accession, and these mainly consisted of the following:
- Resizing of departments, along with increased weight allocated to the Evaluation-authorisation department
- Set up of a new operational subunit within the Evaluation-authorisation department for management of European procedures
- Reconsidering of laboratory testing activities as to better fit European legislation philosophy in matters of laboratory testing role and weight.

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2. Pre-requisites for a smooth integration in the EU DRAs network

2.3. Human and material resources insured as needed for work in the EU DRAs network

- Considered from this angle, NMA priorities during pre-Accession were as follows:
- **Provision of sufficient human resources** able to cope with new requirements after Accession (implementation into practice of European procedures: the centralised, the decentralised and the mutual recognition procedures, in parallel with the "pure" national procedure, participation as active members in EMEA, the Heads of Medicines Agencies and the European Commission committees and working groups, involvement in network joint activities)
- To this purpose, a motivating wages system has been set up in the NMA, allowing on one hand employment of new staff and, on the other hand, continuation of former staff in the context of a financially very attractive private pharmaceutical sector in Romania.

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2. Pre-requisites for a smooth integration in the EU DRAs network

2.3. Human and material resources insured as needed for work in the EU DRAs network (ctd.)

- **Provision of material resources** required to allow optimum development of all types of activities specific to the EU network of drug competent authorities, with particular emphasis on the following:
  - Development of an IT system suitable for connection to the European IT system of drug competent authorities and its continued operation at required standards;
  - Endowment of control laboratories in view of their integration in the Official Medicines Control Laboratories network.

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2. Pre-requisites for a smooth integration in the EU DRAs network

2.4. Staff training and introduction to EU bodies and procedures before Accession

The NMA has used all the opportunities at hand to train its staff in regard of European procedures and practices and better acquaint them with activities in the network of drug competent authorities:

- PERF activities
- CADREAC activities
- PHARE programme for Romania and Bulgaria
- Participation during pre-Accession as active observers in EMEA working groups.

2. Pre-requisites for a smooth integration in the EU DRAs network

2.5. Connection to EU DRAs IT network before Accession

- **Connection to the EudraNet in July 2006**
- **Connection to the CTS in December 2006**

2. Pre-requisites for a smooth integration in the EU DRAs network

2.5. Connection to EU DRAs IT network before Accession (ctd.)

- Implementation of these connections prior to Accession required adaptation of the NMA IT system and good cooperation with European bodies with specific tasks in the field, so as to be timely and operational at required standards.
- Lack of these connections before Accession would have made it impossible for the NMA to become involved in a number of activities, MRP and DCP included.

3. First post-Accession year: Challenges

3.1. Starting MRP and DCP as CMS as early as the first days after Accession

- NMA involvement in activities of the network of EU drug competent authorities had a dynamic start as of the very first days of January 2007, with MR and DC procedures having Romania as Concerned Member State.
- **17** applications were submitted in January 2007, and applications were submitted at a rapidly increasing rate: **57** in February, **32** in March, **58** in April a.s.o.
- Applications for DCP were predominant among applications.
- Only **88** MR/DC procedures were completed in 2007.

3. First post-Accession year: Challenges

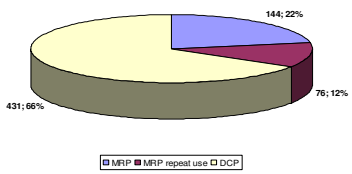
3.1. Starting MRP and DCP as CMS as early as the first days after Accession (ctd.)

To have more accurate image of the workload in marketing authorisation in 2007, one should also mention that, in parallel with MR and DC procedures having Romania as Concerned Member State (**651**), another **834** applications for marketing authorisation were also processed through "pure" national procedure.

3. First post-Accession year: Challenges

3.1. Starting MRP and DCP as CMS as early as the first days after Accession (ctd.)

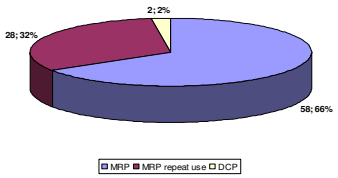
Number of applications with Romania as CMS received in 2007: 651



3. First post-Accession year: Challenges

3.1. Starting MRP and DCP as CMS as early as the first days after Accession (ctd.)

Number of MAs granted in 2007: 88



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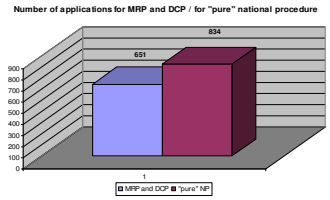

3. First post-Accession year: Challenges

3.2. Continued connection to EU DRAs IT network and starting reporting to EU databases

- Necessary proceedings were taken further in 2007 to start reporting of data into European databases (endowment with equipment and staff training).
- Reporting to the EudraGMP started in 2007.

3. First post-Accession year: Challenges

3.2. Continued connection to EU DRAs IT network and starting reporting to EU databases (ctd.)

- An additional number of preparations were made in 2007 and the NMA started reporting to the EudraVigilance and EudraCT at the beginning of 2008.
- The NMA has installed the software required for e-submission (EiY-eCTD) and is now performing additional training of assessors for use of the software.
- At the same time, an IT integrated system is now under implementation in the NMA, which will allow automated reporting the EudraPharm of information on medicinal products authorised for marketing in Romania.

3. First post-Accession year: Challenges

3.3. Organisational structure and infrastructure adjustment to new status requirements

- Mention should also be made of the fact that, in spite of NMA efforts to become better and in more detail informed on Accession realities, actual circumstances have in certain aspects exceeded its expectations, and a number of adjustments have been necessary in NMA organisational structure and institutional infrastructure.
- With the increasing number of applications submitted to the NMA for MRP and DCP with Romania as CMS, the structure of the European procedures service has been gradually altered and the number of staff involved in such procedures has been increased.

3. First post-Accession year: Challenges

3.3. Organisational structure and infrastructure adjustment to new status requirements (ctd.)

- The new NMA status has required employment of a significant number of staff specialised in various fields, with a good knowledge of English, to take part in the over 40 EMEA, Heads of Medicines Agencies, the European Commission, the European Council, EDQM scientific committees and working groups, which refers in fact to more than 40 people who, alongside with their daily professional activities, also provide an important amount of time to work in participation to such activities.
- Other particularly emergent activities involving great expenditures of time and resources are those related to transparency. The need has been identified to increase the number of staff involved in such an increasing area of work.
- The control departments have been relocated, work areas have been reorganized and new control equipment has been purchased as well.

3. First post-Accession year: Challenges

3.4. Rapid takeover and implementation of new EU drug legislation provisions in force after Accession

Following Romania's accession to the EU, provisions of Regulation 1901/2006 on medicinal products for paediatric use also had to be implemented, involving as follows:

- Appointment of representatives to the Paediatric Committee (PDCO) in June 2007
- Implementation of Article 49 provisions on introduction into national legislation of certain penalties for infringement of Regulation 1901/2006 provisions
- Communication to the EC by 26 January 2008 on any measures enacted in Romania to support research, development and availability of medicinal products for paediatric use, according to Article 39 provisions

3. First post-Accession year: Challenges

3.4. Rapid takeover and implementation of new EU drug legislation provisions in force after Accession (ctd.)

- Collection of available data on all existing uses of medicinal products in the paediatric population for further transmission to the EMEA in view of set up of an inventory of medicinal products for paediatric use according to Article 42 ; the NMA is now organising data gathered for further communication to the EMEA.
- As far as implementation of provisions is concerned of Regulation no. 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products, the NMA has already appointed its representatives in the Committee.

4. Second post-Accession year – active involvement into EU DRAs network

At the end of 2007, a year of better adjustment to the status as drug competent authority of an EU Member State, based on accurate assessment of resources and expertise available, the NMA decided to become gradually involved in network activities.

4. Second post-Accession year – active involvement into EU DRAs network

4.1. Paediatric Investigation Plans (PIPs) evaluation

So far, the NMA has become involved in evaluation of **24 PIPs** (15 as Rapporteur and 9 as Peer reviewer)

4. Second post-Accession year – active involvement into EU DRAs network

4.2. Evaluation for designation as orphan medicinal product

Up to date, the NMA has been involved in evaluation of **2** medicinal products in view of designation as orphan medicinal product.

4. Second post-Accession year – active involvement into EU DRAs network

4.3. GCP and GMP inspections participation for centrally authorised medicinal products

- Participation in GMP inspections = **2**
- Participation in GCP inspections = **4**

4. Second post-Accession year – active involvement into EU DRAs network

4.4. Sampling and testing participation for centrally authorised medicinal products

- Participation in sampling = **2** medicinal products
- Participation in sample testing = **1** medicinal product

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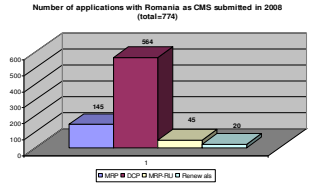
4. Second post-Accession year – active involvement into EU DRAs network

4.5. Status of MRP and DCP with Romania as CMS in 2008



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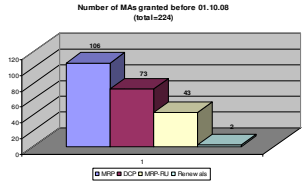

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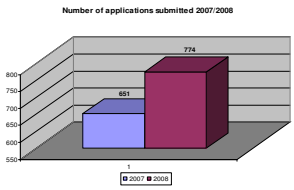

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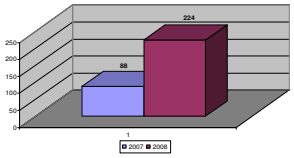

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4. Second post-Accession year – active involvement into EU DRAs network

4.6. RMS in MRP and DCP

-Reasons for NMA decision to act as RMS

- NMA understanding of the need to contribute to smooth progress of MRP/DCP given the very limited NCAs number willing to become involved as RMS
- There is a significant number of medicinal products for human use manufacturers in Romania (**45**), who have expressed their intention to require that Romania act as RMS for their products
- Romania is an interesting pharmaceutical market (**22** million inhabitants and the **7th** largest country in the EU): at present, almost every newly started procedure includes Romania as CMS

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4. Second post-Accession year – active involvement into EU DRAs network

4.6. RMS in MRP and DCP

-NMA preparations for acting as RMS

- Set of NMA strategy – the beginning of 2008
- Establishing of type of products to be accepted in the first instance taking into account NMA experience: 10.1 applications of RPs which have not been authorised through CP
- Posting of the notification on the NMA website, informing on NMA intention to act as RMS - 28.03.2008
- Establishing the target date for process start: October 2008, originally (and further postponement for November 2008)
- Intensive training of assessors to become involved in procedures having Romania as RMS
- NMA Team study visit to the Swedish Agency-April 2008

4. Second post-Accession year – active involvement into EU DRAs network

4.6. RMS in MRP and DCP

-Handling of requests submitted

- Monthly NMA top management meetings for acceptance/refusal of requests, followed by NMA response for each received request-usually in 30 days
- In case of a positive decision, pre-submission meeting with the Applicant
- 4 months in advance of Day -14, NMA request for electronic Marketing Authorisations Application: check of legal base, RP, comparative SPCs of RPs authorised in proposed CMSs, PhV System, RMP, BE studies

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4. Second post-Accession year – active involvement into EU DRAs network

4.6. RMS in MRP and DCP

-Current situation (before the 1st of October 2008)

- Applications accepted: **14** (MRP = 4; DCP = 10)
- Fully booked to January 2010
- **2 DCP pre-assessed**

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4. Second post-Accession year – active involvement into EU DRAs network

4.6. RMS in MRP and DCP

-NMA expectations

- Successful completion of procedures with Romania as RMS for 10.1 applications, without or a limited number of Referrals
- One procedure/month to be started
- Extension of NMA scope acting as RMS following the first 6 months of experience in acting as RMS

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5. Conclusions

- In many respects, pre-Accession was very demanding, and particularly the process involving transposition of European into national legislation in the medicinal product domain as well as updating of authorisation documentation.
- Moreover, the NMA has gone through an even more difficult period in the first year after Accession, given the multitude of new activities it had to adjust on the run.
- However, in spite of all such challenges, the Romanian competent authority in the field of medicinal products for human use appreciates it has all the resources available to continue improvement of its performance and become an even more active and useful member of the network of EU drug competent authorities.

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THANK YOU FOR YOUR ATTENTION!