

GETTING THE IMPLEMENTATION RIGHT!

The AESGP Conference near the EMEA in Canary Wharf on 18-19 October 2006 was the scene of lively discussions on whether the EU’s revised pharmaceutical legislation enacted about a year ago is having the right impact on non-prescription medicines in the European Union.

Getting the implementation right! 1
CHMP Chairman sets the scene 2
AESGP President: dialogue leads to better understanding 2
Lalis: Much progress has been made but fine-tuning is still ongoing..... 3
Lönngren: EMEA is prepared to do more for non-prescription medicines..... 6
Woods: How better regulation is becoming a reality 7
Roth-Behrendt: Why are non-prescription medicines not automatically recognised?..... 8
Le Courtois: How to file successfully in the centralised procedure..... 9
Wathion: A solution for the ‘invented name’ problems is in sight 10
Janse-de Hoog: Are the new procedures successful?..... 12
Backman provides background on CMD(h) referrals – The case of Glucosamine 14
CHM(h) members: How to improve the mutual recognition and decentralised procedures .. 15
Keller: New opportunities for herbal medicines 17
The EU’s pharmacovigilance system... 18
...and how to comply with it..... 18
AESGP keen to spread the ‘spirit of BROMI’ all over Europe 19



Daniel BRASSEUR, Chairman of the Committee for Medicinal Products for Human Use (CHMP), is flanked by AESGP President **Hans van ZOONEN** (r.) and AESGP Director General **Hubertus CRANZ**

CHMP CHAIRMAN SETS THE SCENE

The opening reception on 18 October was attended by many members of the EMEA's Committee for Medicinal Products for Human Use (CHMP) headed by Daniel Brasseur, the Committee for Herbal Medicinal Products (HMPC) headed by Konstantin Keller, the Co-ordination Group for the Mutual Recognition and Decentralised Procedures – Human (CMD(h)) headed by Truus Janse-de Hoog and a large EMEA delegation headed by Executive Director Thomas Lönngren.

Daniel BRASSEUR spoke about the new challenges for the EMEA in general and the CHMP in particular since the new EMEA Regulation came into force last November. This was reflected in more submissions under the centralised procedure and more requests for scientific advice. More scientific questions were also being addressed to the scientific advisory groups since last year, said Brasseur. This went hand in hand with a justified increase in EMEA staff.

Brasseur welcomed the new opportunities for non-prescription medicines created by the new legislation, including access to the centralised procedure and improved data protection. He mentioned that the possibility to discuss the implementation of certain new provisions with health professionals and patient groups had led to improved input and had therefore created a better legal framework. "This is important as it is the task of all partners to use the legal framework properly in the interest of all people in Europe," concluded Brasseur.

AESGP PRESIDENT: DIALOGUE LEADS TO BETTER UNDERSTANDING

AESGP President **Hans van ZONEN** pointed to AESGP's longstanding support for and commitment to the EMEA and its work for the past almost 12 years. "The reason is simple: for us, it was clear that the "atmosphere of Canary Wharf" would have an impact on the whole pharmaceutical climate. We see it as our role to be closely associated and we felt privileged to have had the occasion to host a long range of meetings in this area since January 1995. All of these meetings were successful in several aspects:

- They allowed us to give first-hand information to our wide-ranging membership;
- They hopefully also allowed us to give a coordinated industry feedback to policy makers and regulators;
- But above all, they provided the possibility for an informal exchange of views between those interested in pharmaceutical regulation... often the most important and fruitful outcome for building a common understanding."

Van Zoonen welcomed the participants at the conference on 19 October 2006 in the same spirit. "A legal framework is like a carefully designed garden which needs tender loving care after it is planted. As the garden is made up of living plants, these sometimes develop in unexpected ways and need several rounds of careful pruning to make the garden grow in the sense it was designed," said van Zoonen.

"As input to the first major round of pruning of the EU's pharmaceutical legislation developed in the first half of the 1990s, we therefore developed a comprehensive set of recommendations in 1999 called 'Deregulation 2001'. When the review was started in 2001, we followed every step of the legislative process with close attention. After its completion in 2004, it was widely felt

within AESGP that its overall outcome was positive, with many new opportunities for our industry such as access to the centralised procedure, one year of data exclusivity for innovative switches and new indications for well-known substances, an improved pharmacovigilance system, a new legal framework for traditional herbal medicinal products and a new scientific committee for all herbal medicinal products.”

“However, this does not mean that there are no clouds on the horizon,” said van Zoonen. “The European Self-Medication Industry still feels overregulated in a number of respects. Taking into account the safety profile of well-known substances, we believe we could do better with fewer burdens. Not only do we believe that these create unnecessary costs which have to be passed on to the citizens, but also that this worsens the competitiveness of our industry compared to other self-care product categories such as food supplements, cosmetics or medical devices. We still feel overregulated in quite a number of other areas as well, and this will be further discussed by a number of distinguished speakers today,” concluded van Zoonen.

LALIS: MUCH PROGRESS HAS BEEN MADE BUT FINE-TUNING IS STILL ONGOING

Georgette LALIS, the Director for Consumer Goods at the European Commission’s DG Enterprise, recalled the positive measures resulting from the pharmaceutical review for the non-prescription medicines industry and enumerated several of the implementing measures and follow-up guidelines clarifying the new provisions. “However,” said Lalis, “one year is too soon to draw final conclusions on the review’s impact.”

What has been achieved...

Lalis first highlighted several aspects of the guidance provided since October last year, and in particular:

- The EMEA fee regulation and the reductions it brought for certain types of applications compared with the previous regulation.
- The SMEs regulation establishing an SME Office within the EMEA and introducing the possibility for a 90% reduced fee for SMEs. “In only 8 months following its entry into force, more than 80 companies (10 per month!) have been assigned SME status by the Agency, and more than 25 have already benefited from the financial or administrative incentives,” said Lalis.
- The guideline on ‘serious potential risk for public health’ and the beneficial effect she expects it to have on the mutual recognition procedure.
- The guideline on the change of classification for the supply of a medicinal product which was updated in early 2006 and the corresponding changes in the *Notice to Applicants* (NTA) clarifying how the 12 months of data exclusivity can be obtained for a switch. “The contributions from AESGP were carefully considered for the update of the guideline,” said Lalis. The NTA now also provides guidance on the one-year data exclusivity period where an application is made for a new indication for a well-established substance “provided that significant pre-clinical or clinical studies were carried out in relation to the new indication”.

...and what remains to be done

Lalis announced that a guidance document is in preparation to clarify the notion of significant pre-clinical or clinical studies for the purposes of this data protection period. She also mentioned that a guideline on the optional scope of the centralised procedure is under discussion which will provide some practical guidance on notions such as ‘the interest of patients at Community level’.

“For example,” she said, “a non-innovative product can be in the interest of patients at Community level when it addresses a specific health issue within the Community, facilitates access to medicines, or provides another type of contribution to patient care in the Community. In any event, the eligibility of a medicinal product to the centralised procedure will be evaluated on a case-by-case basis and it will be for the applicant to demonstrate the existence of a patient interest at Community level.”

Naming policy in the centralised procedure...

Concerning the naming of a medicinal product in the centralised procedure, Lalis mentioned that much progress had been made over the past year to overcome the restrictions for the OTC industry imposed by the ‘one-name policy’ laid down in legislation and the current interpretation of this rule in version 4 of the EMEA guideline. “While having to insist on the need to respect the provisions of the legislation, we have had a fruitful discussion over the past months as regards the naming policy within the centralised procedure, which we hope will facilitate the choice of names in future,” said Lalis. “As a general rule we consider that any restrictions which are not justified on reasons of public health (in particular safety) should be avoided. This guiding principle should inform all our decisions on names of medicinal products, and will be reflected clearly in the revision of the guideline on invented names in preparation at the EMEA.”

...to be applied less restrictively in view of enlargement

“We understand that the derogation to the single name rule on trademark grounds has been applied in a restrictive manner in the past. In view of the enlargement, there is scope and reason for some flexibility to overcome the increasing difficulties to find names which are acceptable across the Community. We are reassessing the application of the derogation in a way that increases the options for invented names considerably,” concluded Lalis on this topic.

More details of the compromise currently being elaborated were provided by the EMEA’s Noël Wathion later at the conference.



Thomas LÖNNGREN, Executive Director of the European Medicines Agency; **Dagmar ROTH-BEHRENDT**, Vice president of the European Parliament; and **Georgette LALIS**, Director for Consumer Goods, Directorate-General Enterprise, European Commission (l. to r.)

Extension of ‘traditional-use registration’?

Concerning traditional herbal medicinal products, Lalis mentioned that the report to be submitted by the Commission to the European Parliament and the Council of Ministers in 2007 is to look at the possible extension of the ‘traditional-use registration’ to other categories of medicinal products. “We are starting our reflection in this regard, and look forward to a fruitful discussion with interested parties. I can already anticipate that a critical point will be the consideration given to Indian Ayurvedic and traditional Chinese medicine.”

Variations regime to be simplified

Simplification of the regime for variations of an existing marketing authorisation is in the interest of industry, national competent authorities and EMEA alike, said Lalis. Moreover, the regime should be adapted to ICH recommendations. This should be done in a two-tier exercise, first for centrally authorised products and later for nationally authorised products. “On the latter point, we may have to go back to the European Parliament and the Council for new legislation,” said Lalis. The consultations on the first point were expected to start before end 2006.

National implementation being closely scrutinised

Lalis called the implementation of Community directives “a crucial point in any discussion”. “It cannot be forgotten that an important part of the implementation of the new legislative package lies with the Member States responsible for transposing the new directives into their national legal orders and for giving effect to the new provisions. National transposition has unfortunately not been completed yet, although it is progressing, and the Commission is using the tools at its disposal to ensure a Community wide application of the new rules.”

Lalis recognised that an increasing number of the smaller national competent authorities had difficulties to cope with the multitude of applications in the mutual recognition procedure. Some of these used to rely on the decisions of larger Member States before joining the EU, said Lalis. “Therefore we need certain options for small authorities to cope with the complex system.” This was confirmed by a remark from an industry representative who remarked that “companies may seek to exclude small Member States voluntarily from the mutual recognition procedure because of the risk of triggering arbitration.”

SME definition can only be revised at EU level

Concerning the fee level for applications in the centralised procedure and the possibility for SMEs to obtain a fee reduction, Lalis said that “the SME definition is the same for all industrial policies at EU level, be it state aid, trade, or qualification for reduced EMEA fees. However, an adaptation of the definition is under consideration.”

Predictability for economic operators

Lalis concluded that there is a new European legislative framework that provides new incentives to reclassify medicines and to develop new indications for well-established products, and which improves the operation of the marketing authorisation procedures. Implementing provisions on fees and SMEs and on many other crucial elements of the ‘Review’ have been adopted which take into account many specific concerns of the self-medication industry. Pending issues will be clarified in guidelines in preparation, which will further complete the operation of the legal framework and the predictability for economic operators. These will include information to patients and a new regime for variations, and “in all cases we are looking forward to working with AESGP”.

LÖNNGREN: EMEA IS PREPARED TO DO MORE FOR NON-PRESCRIPTION MEDICINES

Changing environment

The EMEA's Executive Director **Thomas LÖNNGREN** highlighted the changed environment in which the Agency nowadays has to operate: as from next January, there will be two new Member States, 22 official Community languages and 48 regulatory agencies. The Agency's new challenges were already addressed in the EMEA's 'Road Map to 2010' but Lönngren wondered whether this should not be adapted in light of the latest changes.

Self-medication has a role in prevention

In light of the changing demographics, Lönngren looked in particular at what the self-medication industry could do to treat the ever more serious diseases in older patients, and indicated that much of this could be in the area of prevention. The new data transparency rules and the many new information sources could have dramatic consequences for future treatment options, predicted Lönngren. However, warned Lönngren, new transparency rules also meant an enormous additional workload, with the Agency currently debating which part of the scientific information, including that on approved and rejected applications and clinical trials, could or should be published on the EMEA website. "The FDA employs 100 persons to implement transparency rules alone!"

New opportunities for non-prescription medicines in the EMEA

Like Lalis, Lönngren enumerated the new possibilities for non-prescription medicines arising from the EU's new legislation. At the level of the Agency these consisted in the setting up of an SME Office, the installation of the new Scientific Committee for Herbal Medicinal Products (HMPC) and the establishment of Community monographs and lists by this committee, as well as in the possibility for non-prescription medicines to have access to the centralised procedure. He stressed however that the principles for access to this procedure had not dramatically changed. New elements were access for medicines that were in the "interest of patients at Community level" as well as access for generic and biosimilar products.

Are the fee levels right for well-established substances in the centralised procedure?

In light of the current fee level in the centralised procedure, Lönngren mentioned that an innovative non-prescription medicine applying for centralised approval could be as complex as a new chemical entity. He also said that not all products could qualify for the centralised procedure and that the EMEA should concentrate on the most difficult applications "to avoid the Agency being overloaded". However, should the workload involved in assessing a non-prescription medicine with a well-established substances allow a lower fee, the EMEA's Executive Director has the latitude to reduce the fee under the provisions of the Fee Regulation. "Let us now however first wait for an application, and then we can decide on this issue," said Lönngren.

In conclusion, Lönngren pointed to the constant change in the EMEA's environment as witnessed by the EMEA Road Map to 2010. "Access for non-prescription medicines at EU level is now a possibility, but will it become a reality?" asked Lönngren. "In the whole process, transparency will be a key issue, therefore we need to improve information and communication, and the learning process needs to be carried out together with stakeholders such as AESGP."

WOODS: HOW BETTER REGULATION IS BECOMING A REALITY

Better regulation is a priority for the UK Government

Kent WOODS, the Chief Executive Officer of the Medicines & Healthcare products Regulatory Agency (MHRA) in the UK, started his presentation with the following quote dating from 1867. The quote is from Walter Bagehot (1826-1877), Editor of 'The Economist' and Author of 'The English Constitution':

“A bureaucracy is sure to think that its duty is to augment official power, official business, or official members, rather than to leave free the energies of mankind; it overdoes the quantity of government, as well as impairs its quality.”



'Better regulation' to be extended to other sectors?

The UK Government has for the past 2-3 years been keen to 'cut red tape', said Woods. The current 'Better Regulation of Over the Counter Medicines Initiative' (BROMI) started from the key principle that it was important to make the most of the regulatory opportunities. In case BROMI was successful in the OTC sector, there would perhaps be scope to roll it out to other sectors of the innovative industry. Woods indicated that there were opportunities to put forward the BROMI principles during the Commission's review of the variation regulations, as explained earlier by Georgette Lalis.

Work accomplished...

After explaining BROMI's Terms of Reference and progress to date, Woods provided details of the work accomplished so far. This covers the patient information work stream. For the leaflet changes of this stream, a three-tier regulatory model has been approved:

- Self-certification with MHRA audit
- Third-party (PAGB) approval with rapid assessment by MHRA
- Formal assessment by MHRA.

According to Woods, this could affect over 40% of the current MHRA workload, with the MHRA in the role of enforcer rather than checker and only the change applied for to be checked.

This scheme, which has a number of built-in safeguards, was launched for OTC medicines in May 2006. It could according to Woods become applicable to prescription-only medicines in November 2006.

Another part of this work stream concerns pack design. Here a self-certification scheme of non-statutory information underpinned by an industry code of practice would start as a pilot in January 2007. As part of BROMI, the statutory warnings on the pack will also be reviewed as Woods mentioned that there is evidence that patients do not understand these.

...and in the pipeline

BROMI's second work stream concerns improving the MHRA work processes, with the following three work areas having been identified:

- Variations
- Abridged applications under Article 10c of Directive 2001/83/EC (as amended)

- Change of Ownership applications.

Example for the rest of Europe?

According to Woods, it is important to quantify the impact of the BROMI proposals on both industry and regulators so that they may be extended to other areas of healthcare. The opportunity to look at the rules for variations coincides nicely with the review of these rules at the EU level, said Woods. “Experience in the UK may eventually be shared with other national competent authorities as we go along”, concluded Woods.

ROTH-BEHRENDT: WHY ARE NON-PRESCRIPTION MEDICINES NOT AUTOMATICALLY RECOGNISED?

Legislation should be better from the start

In response to Woods’ plea for ‘better regulation’, **Dagmar ROTH-BEHRENDT**, Vice-President of the European Parliament said that the EU’s pharmaceutical legislation could have been less restrictive and better designed from the outset if the necessary support had been given by UK MEPs and Council representatives during the adoption process. Moreover, she said, the new provisions could have been better implemented “in the spirit of the legislator” in many Member States, including the United Kingdom.

“For this to happen on future occasions,” Roth-Behrendt maintained, “we need a clear political message for ‘better behaviour’ which should be shared with the EMEA, the European Commission and the national competent authorities.”

Why has there not yet been a central application for a non-prescription medicine?

As to why the non-prescription industry had so far not yet filed any centralised applications, Roth-Behrendt wondered whether the industry was “just shy”. However, she thought that there may have been other reasons, including:

- The fee problem – the same fee applies to a new chemical substances and a well-established use substance, but Roth-Behrendt thought there was less work with the latter.
- The interest of patients – there is no need to prove this in each Member State, said Roth-Behrendt.
- The SME definition – this is not perfect and some companies might fall outside the scope of the current definition.
- Invented names – “I have addressed this from the beginning. I know you are working on this but let’s do more”.
- Better regulation – this will be taken forward under the German Presidency. “We need better and leaner administrations and less bureaucracy.”
- Variations – “Please act quickly,” pleaded Roth-Behrendt.
- Mutual recognition procedure – “We need a ‘lite’ procedure. For non-prescription, herbal and well-established use medicines, the procedure should be automatic if the product is already approved in one Member State,” said Roth-Behrendt, “otherwise it would have been a prescription-only medicine.”

Information to patients

Concerning information to patients, Roth-Behrendt believed that this should not take the form of new legislation but that information to patients could be overseen by a body “perhaps including patient representatives” on a “post-event” basis.

Roth-Behrendt concluded by stating her aversion to price controls for manufacturers of non-reimbursed medicines. “As I recently said at the European Pharmaceutical Forum, it is bad enough that we have price controls on reimbursed prescription-only medicines, but where do the Member States think they get the right to control the prices of non-reimbursed medicines?”

LE COURTOIS: HOW TO FILE SUCCESSFULLY IN THE CENTRALISED PROCEDURE

Switch of already centrally authorised medicinal products

After explaining which products have access to the centralised procedure and mentioning that the CHMP has the final word on whether a product is eligible for the procedure, **Patrick LE COURTOIS**, who heads the Unit ‘Pre-Authorisation Evaluation of Medicines for Human Use’



at the EMEA, explained how centrally authorised products can obtain a switch of prescription status. These products, which have direct access to the switch procedure as they were already authorised through the centralised procedure, should of course match the criteria as defined in the ‘Guidelines on changing the classification for the supply of a medicinal product for Human Use’ which were revised in January 2006. These criteria, which are based on the legal provisions of Directive 2001/83/EC, as amended, impose some technical and scientific constraints. “When considering these criteria and the type of products authorised so far in the centralised procedure,” said Le Courtois, “very few products are likely to meet the criteria for switching.”

Options for a switch in the centralised procedure

When switching for an already centrally approved product is envisaged, said Le Courtois, several possibilities exist:

- File as a new dossier including new prescription status request (CTD format)
- File as an ‘informal consent’ followed by a variation or an Annex II for switching
- Switch within the existing marketing authorisation
- Data requirements are detailed in the European Commission guideline and are very much linked to the criterion
- Consider the one-year data exclusivity for significant pre-clinical tests or clinical trials where filing for a switch in accordance with article 74a of Directive 2001/83 and part 4 of the guidance.

New applications for self-medication

Switching through the optional scope, in particular for first launches as self-medication products, could also be considered. According to Le Courtois, these switches are “unlikely but not excluded”. Examples of a ‘significant innovation’ could for instance be a new delivery system, in the interest of patients, or products leading to improved patient care.

Advice for companies

Le Courtois drew the following conclusions from the experience gained so far:

- The scope of the centralised procedure has some technical and scientific constraints for self medication products.
- While limited, interest exists from industry since the Agency has been contacted by companies for ‘real products’ for all the situations described.

- Very early contact with the Agency for regulatory advice is essential and regular follow-ups are expected.
- Scientific advice is encouraged.
- Experience shows that within companies more communication between teams in charge of self-medication and teams having the experience of the centralised procedure would help.

WATHION: A SOLUTION FOR THE 'INVENTED NAME' PROBLEMS IS IN SIGHT

NRG expertise to be strengthened

Noël WATHION, the Head of the Unit 'Post-Authorisation Evaluation of Medicines for Human Use' at the EMEA, presented the 'state of the art' on the upcoming fifth revision of the [EMEA Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure](#), the fourth revision of which has been in force since May 2005.

Wathion started by explaining that the EMEA intended to increase transparency with regard to the Invented Names Review Group (NRG) and to strengthen its capacity by adding new members with linguistic, hospital, pharmacy and patient expertise. In his opinion, the issue of invented names merited the establishment of a more formal working group to allow sufficient discussion and to offer companies the possibility for oral clarification.

The information currently being published as part of the CHMP monthly report is mainly of a statistical nature as most of it is confidential until the central authorisation is granted.



Reasons for objections

Wathion presented some interesting statistics concerning the grounds for objections to proposed invented names in the centralised procedure.

Statistics on Grounds for Objections

[Corresponding to Revision of Guideline]	Until 31.01.02 [2]	01.02.02 to 30.04.05 [3]	01.05.05 to 31.07.06 [4]
Similarity with existing invented name	63.04%	45.35%	66.87% ¹
More than one word; use of letters/ numbers, abbr./suffix with no established meaning	23.55%	24.31%	23.50%
Similarity with INN / includes INN stems	8.70%	13.05%	2.31% ²
Conveys promotional / misleading message re. use of product	4.71%	17.29%	5.78%
Prodrug: IN should be different from IN of original AS	N/A	N/A	1.54%
Total objections	276	613	519

Wathion mentioned that several grounds for objections were possible for a single proposed invented name.

¹ Following enlargement with 10 new Member States.

² Big decrease following the introduction of a decision-tree process.

What will revision 5 mean for non-prescription medicines?

Wathion recalled the criteria currently applied by the NRG when reviewing the acceptability of invented names in the centralised procedure and added that from now on strength will also be considered (as is the case in the US). He then presented the key elements of current thinking on the proposed revision of the guideline based on the latest discussions between the EMEA and the European Commission following the hearing with interested parties on 11 September 2006.

Concerning the criterion that the invented name should preferably consist of only one word, Wathion said that further flexibility would be introduced for non-prescription medicines and that the use of short qualifications/abbreviations by letters and/or numbers (Arabic and Roman) should in principle be acceptable. Appropriate justification should be provided to the NRG, meaning that the qualifications/abbreviations should be useful for the person using the non-prescription medicine.

As to the criterion that the invented name should not convey any promotional message with respect to the therapeutic and/or pharmaceutical characteristics and/or the composition of the medicinal product, Wathion admitted that non-prescription medicines may anyway already have some promotional element as they can be advertised to the general public.

The invented names of fixed-combination medicinal products should, according to the current version of the guideline, be sufficiently different from the invented name borne by the individual active substances of the fixed combination to avoid medication errors. However, Wathion thought that more flexibility could be introduced on this point as well and that perhaps the complete name of the constituent parts might be acceptable for non-prescription medicines.

The rationale for this flexibility was that due account needed to be taken of the specific legal environment associated with this category of medicinal products, as they can normally be advertised to the general public, and are associated with differences in diagnosis, selection / identification of the medicinal product by the patient / pharmacist and the absence of a 'prescription-dispensing' phase. This meant that specific limitations valid for other categories of medicines "may not apply", said Wathion, but that on the other hand proper justification needed to be supplied to the NRG.

Outcome of hearing with interested parties

According to Wathion, the comments made by interested parties at the hearing on 11 September 2006 concerning the proposed modifications were overall positive. These modifications should lead to more flexibility and an increased acceptance rate for proposed invented names, bearing in mind that the general principle that due account should be taken of public health considerations, in particular safety concerns, had not been abandoned. All parties acknowledged the need for "special treatment" of non-prescription medicines due to their specificities, which should result in more flexibility.

There was however a need for further elaboration of outstanding issues in relation to the use of qualifiers as this was of particular concern for non-prescription medicines. Wathion saw the following solutions emerging:

- Short qualifiers such as XL, L, SR would be part of the invented name
- Qualifiers such as Depot, Retard, Forte, etc which are generally understood would also be part of the invented name

- Other qualifiers which he called ‘instructions for use’ such as Pain, Cold, etc. could be included as part of the labelling (and not part of the name) meaning that they could be translated in the language of the packaging.

Next steps

However, all the issues resulting from the interested parties hearing needed to be further discussed between the EMEA and the European Commission, said Wathion, and there would then be a new discussion of the revised Guideline with the NRG and the CHMP. Wathion expected a draft of Revision 5 of the guideline to be released for consultation to interested parties at the beginning of 2007.

JANSE-DE HOOG: ARE THE NEW PROCEDURES SUCCESSFUL?

Changes resulting from the new legislation

Truus JANSE-de HOOG, of the Medicines Evaluation Board in the Netherlands, who chairs the Co-ordination Group for Mutual Recognition and Decentralised Procedures (Human) – CMD(h), explained that the mutual recognition procedure is used for products with an existing marketing authorisation and for alterations (‘forced arbitration’). The decentralised procedure is only possible for new applications (i.e. for products which have not yet been authorised anywhere in the European Union). The following new features took effect with the coming into force of the EU’s revised pharmaceutical legislation on 30 October 2005:



- Start of the Coordination group - CMD(h)
- Decentralised procedure (new procedure)
- 60-day referral procedure

- Harmonisation of patient leaflet and labelling
- User consultation of patient leaflet: How? When?
- Public assessment reports
- European Reference medicinal product.

Harmonised view

According to Janse-de Hoog, it is important to develop a harmonised view between all Member States on the new requirements in these procedures. This is being done in the new Co-ordination Group CMD(h), which was specifically set up to examine any question relating to the marketing authorisation of a medicinal product in two or more Member States in accordance with the mutual recognition procedure (MRP) or the decentralised procedure (DCP). The group is composed of 1 representative per Member State appointed for a renewable period of three years. CMD(h) members may be accompanied by experts. Secretarial support is provided by the EMEA.

Tasks of the CMD(h)

The CMD(h) held its inaugural meeting on 14 November 2005, with [CMD\(h\) Rules of Procedure](#) being published on the CMD(h) section of the Heads of Agencies website shortly afterwards. It is the CMD(h)’s mission to:

- Aim for consensus and avoid referrals to the CHMP other than in exceptional cases
- Ensure consistency of standards and good-quality decision making across the EU
- Present a harmonised view on the interpretation of the legislation

- Promote harmonisation of SPCs of nationally authorised medicinal products.

The CMD(h) holds discussions on procedural / regulatory questions, develops Standard Operating Procedures (SOPs), holds scientific discussions on applications referred to it; and discusses with the EMEA to maintain a consistent approach in all the applications. It holds break-out sessions in parallel to the CMD(h) meetings as it is necessary to hold systematic discussions on ongoing MRP/DCP applications.

Statistics

Since the start of the CMD(h), nine new guidance papers have been published, with 12 existing guidelines being updated to take account of the new procedures. Moreover, new Q&As are published on a regular basis.

Statistics for January-September 2006		Type of procedures started in 2006		
Procedures (MRP) in process	167		MRP	DCP
Procedures (MRP) finalised	367	New active substance	12 (5 RU), 4 copies	2
Procedures (DCP) in process	273	Known active substance	70	17
Procedures (DCP) finalised	10	Abridged	311	240
Procedures referred to CMD(h)	57	Line extensions	37	11
Agreement reached in the CMD(h)	29	Prescription	418	266
Arbitrations referred to CHMP	17	Non-prescription	13	4

Potential serious risk to public health

On 8 June 2006, the European Commission published the long-awaited [Guideline on the definition of a potential serious risk to public health in the context of Article 29\(1\) and \(2\) of Directive 2001/83/EC](#) which provided examples of what is not considered to be a potential serious risk to public health. Before the guideline was published, the following potential serious health concerns were raised for discussion in the CMD(h): Bio-equivalence; Fixed combinations, Efficacy/safety balance; Major differences in SPC generic and innovator (*more or less indications*); Non-GCP compliance of the bio-equivalence study; SPC, different use in children; Patient leaflet (only one); Chemical-pharmaceutical data.

Timetables

The timetables for the two procedures are as follows:

MRP	Days	DCP	Days
National procedure	210		
Update assessment report	90	Procedure	210
Mutual recognition	90	National approval	30
National approval	30	Total	240³
Total	420		

³ The procedure can be finalised earlier when agreement is reached.

New opportunities

Several opportunities have arisen from the DCP, not least because of the consensus building potential during the procedure, continued Janse-de Hoog. Experience with non-prescription medicines has shown that most applications for non-prescription medicinal products are still national. She speculated that this probably was because of:

- The legal basis - bibliographic applications of products without harmonised SPCs are still being submitted through the national procedure.
- Different medical practices - different national legislation with regard to supply (pharmacies or drug stores) and reimbursement?
- Product information not harmonised?
- Fear of new procedures?

Results of discussions in the CMD(h) are that there is a harmonised interpretation of legislation (which help the European Commission) resulting in European guidelines. If the guidelines give room for different interpretations, the CHMP Working parties are asked to give additional advice. There is agreement on the same standards in assessment and, in future, identification of 'potential serious risks to public health'. Repetition of discussions on the same questions should be avoided. These are the conditions for success of the new procedures, concluded Janse-de Hoog.

BACKMAN PROVIDES BACKGROUND ON CMD(H) REFERRALS – THE CASE OF GLUCOSAMINE

Christer Backman of the Medical Products Agency in Sweden explained that the following applications for marketing authorisation normally go to the CMD(h): new applications; repeat-use procedures; and extensions. Variations go directly to the CHMP.

When can the referral procedure be used?

Directive 2001/83/EC, as amended, lists the situations in which the referral procedure should be used, i.e. if a Member State is unable to approve the assessment report (AR), the summary of product characteristics (SPC), the labelling or the package leaflet of a particular medicinal product. However, the Directive also states that a Member State can refuse to approve the assessment report only on grounds of a 'potential serious risk to public health'. As mentioned before by Truus Janse-de Hoog (see page 13), guidance on what constitutes a 'potential serious risk to public health' was clarified in a Guideline earlier in 2006.

What to do in case of disagreement?

The Directive also makes it clear what the disagreeing Member State should do, in particular that it should give a detailed explanation of the reasons for its position to the Reference Member State, the other Concerned Member States and the applicant. When this happens, the CMD(h) should "use their best endeavours to reach agreement on the action to be taken and allow the applicant to state his point of view orally or in writing" within 60 days. In case of disagreement, the CMD(h) Standard Operating Procedure (SOP) applies, the Annex of which contains the timing of the procedure. Withdrawal is possible at any time of the procedure, said Backman, but this may have certain consequences.

Backman confirmed that referral to the CMD(h) takes place on grounds of a potential serious risk to public health:

- In all cases involving the mutual recognition procedure

- After the draft assessment report is sent in the decentralised procedure but before day 120.

All members of the group take part in the CMD(h) discussions. Parties involved in reaching agreement are the Reference Member State and the Concerned Member States. However, the Concerned Member States do not take part where the application has been withdrawn before Day 120 in the decentralised procedure. In case the application goes for arbitration to the Committee for Medicinal Products for Human Use (CHMP), the applicant may request the Member States which were positive about the Assessment Report to authorise the product directly after the 60-day procedure.

Some figures

Backman mentioned that since the new legislation took effect a year ago, 50 CMD(h) referrals had been finalised, 31 of which resulted in agreement before day 60. 19 cases were referred for arbitration to the CHMP, 14 of which concerned three active substances (doxazosin, felodipine and ciprofloxacin).

What happened with Glucosamine?

Backman provided details on referral of the bibliographic application for Glucomed® (glucosamine hydrochloride tablets) for which Sweden was the RMS. He mentioned that the product was originally classified as a food supplement in his country but that it was later reclassified as a medicinal product following a Court decision.

Of the 24 Concerned Member States in the mutual recognition procedure, four had raised objections on grounds of potential serious risks to public health relating to the product's efficacy, dose and posology as well as its safety. The CMD referral, which also looked at quality issues, was started on 31 January and completed on 31 March 2006, with the CHMP arbitration referral starting on 27 April and ending in a positive opinion on 20 September 2006, meaning the whole procedure lasted around 7.5 months. At the same meeting, the CHMP also adopted a positive opinion on doxazosin.

Experience so far has taught us, concluded Backman, that questions are being raised on different levels and at different stages of the procedures. In his personal view, he questioned some of the grounds for raising a serious risk to public health, whether the Member States really had a good cost/benefit approach and whether they realised that any objection was very resource-intensive. He thought that arbitration to the CHMP should only be used for issues of major importance.

CHM(H) MEMBERS: HOW TO IMPROVE THE MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES

‘Centre of excellence’ for herbal medicines

In the panel discussion with members of the Co-ordination Group for the Mutual Recognition and Decentralised Procedures – Human (CMD(h)), **Christa WIRTHUMER-HOCHE** provided background on the new agency recently established in Austria called AGES PharmMed. This is responsible for human and veterinary medicines as well as medical devices. She mentioned that the agency also wants to establish itself as a ‘centre of excellence’ for herbal medicinal products in order to encourage companies to use Austria as a Reference Member State for these products.

Fewer withdrawals?

Wirthumer-Hoche said that experience with the use of Austria as a Reference Member State in both the mutual recognition and the decentralised procedures had shown the importance for companies of holding a pre-submission meeting with the agency to discuss points such as the legal basis. The validation period was often long, she said, because of disagreement on the classification or a poor dossier. If this is the case, the clock stop in which additional data are requested will be longer than three months. She hoped that there would be fewer withdrawals than up to now following publication of the guideline on potential serious risk to public health and that more agreement could be reached within the CMD(h) without the need for referral to the CHMP.



Pictured from l to r:
Katalin VARSANYI of the National Institute of Pharmacy, Hungary;
Christer BACKMANN of the Medical Products Agency, Sweden; and
Christa WIRTHUMER-HOCHE of AGES PharmMed, Austria

Fairly limited experience with decentralised procedure for non-prescription medicines

Shirley NORTON of the Medicines & Healthcare products Regulatory Agency (MHRA) said that the United Kingdom was keen to see the new procedures work well for non-prescription and prescription medicines according to the guidance published since last year. Although the UK has positive experience with the use of the decentralised procedure on which she provided some statistics, she encouraged manufacturers to use it for non-prescription medicines where use is still fairly limited. Norton praised the will of the CHD(h) to reach consensus in referral cases but said it was not always easy to work with the new guideline on potential serious risks to public health.

UK's efforts for improved patient information

Norton said that the UK is playing an active role in improving the quality of patient information leaflets (PILs) for a safe and effective use of the medicine, which is particularly important as patient choice expands with the move of products to OTC availability. Directive 2001/83/EC, as amended, gives the new order of information within the package leaflet in Article 59(1); provides for the package leaflet to reflect the results of consultation with target patient groups in Article 59(3); and requires the results of 'patient consultation' to be provided to the competent

authority in Article 61(1). The UK implemented some of these requirements early and will require full compliance with the ‘user consultation’ requirements by July 2008.

She advised manufacturers to plan early, to consider the patient information leaflet during product development and to involve users. It is also advisable to

- Address issues of ‘user consultation’ of the PIL with the application
- Provide justification for the absence of testing
- Liaise with the RMS and agree plans for achieving harmonisation of label and PIL and any necessary ‘user consultation’.

Norton also pointed to the EU guidance on patient information published in the past few months and mentioned that from 1 November 2006 it will no longer be possible to harmonise the label and leaflet in parallel to a repeat-use MRP.

From the UK perspective one year on, concluded Norton, the CMD(h) is fully functional and working well. Yet there are many opportunities for improvement including better regulation principles. Industry has a role to play in the whole system by encouraging patient choice and wider availability of medicines through non-prescription routes, and by improving of patient information.

The challenge for new Member States

Katalin VARSANYI of the National Institute of Pharmacy in Hungary said that the challenge for the national competent authority of any new Member States was to act right from the accession date as an ‘old’ Member State but that the (now defunct) Mutual Recognition Facilitation Group (MRFG) had been a good learning school. She said that the Hungarian agency was lucky to have a good pool of experts and that her country had been a Concerned Member State on 476 occasions and a Reference Member State on 75 occasions.

KELLER: NEW OPPORTUNITIES FOR HERBAL MEDICINES

Konstantin KELLER, who chairs the Committee on Herbal Medicinal Products (HMPC) at the EMEA, presented progress on the new opportunities for herbal medicines under the new pharmaceutical legislation. Most procedural guidance has now been established, while there is an ongoing discussion on the ‘Procedures related to different types of referrals to the HMPC’. Guidance is also available on ‘external preparations’, on quality and on quality control with the ‘Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products / Traditional Herbal Medicinal Products in the SPC’ and the ‘Concept Paper on Quality of Combination Herbal Medicinal Products / Traditional Herbal Medicinal Products’ still in the consultation phase.

Genotoxicity to be addressed in non-clinical documentation

Keller provided some background on the ‘Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration’, which was adopted in September 2006, and explained that the genotoxic potential of herbal preparations should be assessed. When an adequate assessment cannot be made, further genotoxicity testing is required, first by *in vitro* tests; in case the results are negative results *in vitro*, negative results *in vivo* may be

expected. However, in case there are positive results *in vitro*, these are to be clarified by appropriate (*in vivo*) investigations.

Keller also explained the best way to document the clinical safety and efficacy for the establishment of monographs and list entries for well-established herbal products and concluded by providing the latest work progress overview.

THE EU'S PHARMACOVIGILANCE SYSTEM...

Part III of Volume 9 to be published soon

Victoria NEWBOULD, Scientific Administrator at the EMEA spoke about the new requirements of the EU's pharmacovigilance system by explaining the legislation and guidance instruments and said that publication of Part III of the 'Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on the Electronic Exchange of Pharmacovigilance Information in the EU' was expected for November / December 2006. This new chapter of Volume 9A of the *Notice to Applicants* will set out how to prepare Individual Case Safety Reports (ICSRs); how to handle follow-up information; what need to be taken into account for the Data Privacy Laws; how to nullify reports; how to comply with expedited reporting requirements; and how to handle the EU's official languages. She also provided some advance indications about the retrospective population of the EudraVigilance database and about the EudraVigilance Medicinal Product Dictionary (EVMPD).

Two Committees established at the end of 2005, the EudraVigilance Steering Committee and the EudraVigilance Expert Working Group, oversee the practical implementation of a fully operational EudraVigilance system to support the EU's pharmacovigilance activities and the European Risk Management Strategy. As next steps, Newbould mentioned the establishment of a EudraVigilance Data Warehouse and Web-reporting tool; Quality checking; Notification of expedited reporting compliance; and a Risk management template (Annex I/C).

...AND HOW TO COMPLY WITH IT

Full pharmacovigilance service offered to subscribing companies

Elmar KROTH, the Head of Pharmacovigilance at the Bundesverband der Arzneimittel-Hersteller (BAH) in Germany, gave an update on the system established by BAH to make it easy for manufacturers to comply with the EU's pharmacovigilance system, the main challenges of which are:

- Efficient Literature screening
- Efficient reparation of periodic safety update reports (PSURs)
- Electronic submission of Individual Case Safety Reports (ICSRs) to the Regulatory Authorities.

Literature screening

He explained that the BAH/AESGP Joint Literature Screening service offers: Regular (weekly) screening of worldwide literature databases (Medline, ADIS, Embase); Assessment (seriousness, causality); Creation of CIOMS I forms for potential cases identified; and Automatic distribution of potential case reports to subscribers.

Moreover, AESGP is proposing a lower frequency of screening for well-established use substances (e.g. monthly) and limitation to one database (e.g. MEDLINE). This should be adequate for substances with known safety profile such as OTCs, herbals, or homeopathics and would not require any change in legislation under the current guidance in Volume 9a.

PSUR preparation and the harmonisation of ‘birth dates’

The main challenge in the preparation of periodic safety update reports (PSURs) are the PSUR cycles based on the date of the marketing authorisation’s initial submission (‘birth date’). The industry proposal to harmonise birth dates at the European level has already been partly met by the recent publication of the first list of harmonised birth dates (HBDs) covering 558 active ingredients with agreed EU HBDs and data lock points for the next PSURs notified by the originators. A second list with 90 active ingredients is in the clearing stage. Kroth explained that AESGP strongly appreciates the HBDs but that active ingredients authorised before December 1976 and all herbals, homeopathics, vaccines, blood products for the moment still fall outside of the scope of this harmonisation, meaning that no HBDs have been published yet. AESGP therefore proposes a second and third wave of HBDs with ingredients authorised before December 1976, herbals, etc.

E2B Database - electronic submission

Concerning the Electronic submission of Individual Case Safety Reports (ICSRs) to the Regulatory Authorities, Kroth mentioned that the services offered by BAH/AESGP are particularly interesting for SMEs as the vast majority of these companies deal with well-established use products, the rate of reporting is very low, their human resources are often limited and their existing pharmacovigilance system is often relatively simple. Through the Joint E2B database, BAH/AESGP offer the following services which guarantee fast and structured ICSR communication; improved reporting quality (MedDRA coding, ...); access to all national competent authorities; and the possibility of early detection of safety signals.

Useful for all companies

Kroth concluded that joint approaches are a reasonable strategy for both larger and smaller companies, not only to become compliant with EU pharmacovigilance requirements but also to get access to new technologies and save resources.

AESGP KEEN TO SPREAD THE ‘SPIRIT OF BROMI’ ALL OVER EUROPE

Positive climate for ‘better regulation’

AESGP Director General **Hubertus CRANZ** concluded the conference by pointing to the many positive statements heard at the conference. From the side of the European Commission, these referred in particular to improving the competitiveness of the European pharmaceutical industry in the framework of the Lisbon strategy and to better regulation, which is currently also high on the Commission’s agenda.

It was clear that ‘better regulation’ also has the support of the European Parliament and the governments of several Member States, including the United Kingdom - through BROMI, and Germany - which intends continuing the better regulation drive during its EU Presidency in the first half of next year.

The positive reference by Thomas Lönnngren to the prevention role of certain self-care medicines and their contribution to public health was also very encouraging, said Cranz.

Implementation of ‘new’ legislation...

AESGP has for the past year been following the implementation process of the ‘new’ pharmaceutical legislation into national law with a close eye, and comparisons on certain ‘hot topics’ such as Braille, renewals, user testing and the sunset clause were incorporated into the AESGP study Economic and Legal Framework for Non-Prescription Medicines. This has become a useful tool for exposing ‘best practices’ around Europe. AESGP is particularly keen to avoid unjustified new regulatory burdens being imposed on its members, possibly through an ‘inadequate’ interpretation of the new legislation. Cranz noted that the European Commission was also watching incorrect implementation and that it could take measures through infringement procedures.

...and new guidance

Concerning the new guidance measures, Cranz said that the updated switch guideline clearly describes the conditions for obtaining the 12 months of data exclusivity. Cranz only regretted that the period was shorter than in other countries such as the United States or Japan.

The guidance on consultation of patient groups (user testing) published last May was certainly very reasonable, said Cranz, whereas the guideline on potential serious risks to public health may help the mutual recognition procedure work better although expectations may have been higher and “one can wonder whether an ‘automatic’ recognition procedure should be put in place for well-established substances in the longer term.”

Concerning the guidance still in the pipeline, Cranz expressed the hope that reasonable solutions could be found for the conditions to obtain data exclusivity for a new indication of a well-established substance and for the somewhat overlooked problem of atypical substances.

As access for non-prescription medicines to the centralised procedure was now accepted by all parties, “it is up to companies to use this provision”. However, “money matters”, and the fee level may be an obstacle for small and even not so small companies. However, said Cranz, Lönngren has expressed understanding for the financial aspect and “now it is up to the companies to ask for his discretion on this”.

Cranz saw “very positive developments” in the invented names debate with the use of qualifiers becoming increasingly accepted but warned that the situation “has not yet been finally resolved” and that the legal provisions must be respected.

Developments in the herbal area

In the area of herbal medicinal products Cranz praised the solution chosen by the European legislator which “corresponded almost entirely to the AESGP proposals put forward in the second half of the 1990s”. The monographs system for plants, the establishment of which is making good progress as demonstrated by the Chair of the Committee for Herbal Medicinal Products (HMPC) Konstantin Keller, should allow companies to avoid resubmission of data. There are however some critical issues to watch. “To extend the requirements in relation to GMP seems somewhat exaggerated for plants;” said Cranz.

Cranz also recognised that pressure is mounting from the side of India and China to gain access to the European market for their traditional herbal products in case the traditional herbal medicinal products Directive is extended. However, in that case Ayurvedic and traditional

Chinese medicines will presumably be subject to the same requirements, e.g. those related to safety, as products with a European tradition, said Cranz.

AESGP offers companies assistance on pharmacovigilance requirements

The EU's improved pharmacovigilance system requires the submission of a large amount of data at regular intervals. In order to fulfil these requirements, companies may refer to the German AESGP member association BAH which offers assistance in the screening of literature, the preparation of update reports and the grouping of their submissions. This is being facilitated by the recent publication of the first batch of harmonised 'birth dates' for certain 'older' substances. As many substances are for the moment not yet on the list, Cranz asked for this work to continue and to expand it in particular to a whole range of herbal substances.

'Better regulation' to be continued in 'variations' revision

The revision of the EU's variations regulations offers a unique opportunity for 'better regulation' which "has now become a number one issue", concluded Cranz. AESGP will work for general EU acceptance of the 'do and tell' principle for all minor (1a and 1b) variations for both European and national procedures. This principle is already accepted for national procedures in Austria, Germany and now also soon in the UK (under BROMI). 'Do and tell' means that the change is notified to the authorities and carried through immediately. In case the authorities do not agree, they may still intervene afterwards.

"We hope the 'spirit of BROMI' can be expanded to other parts of Europe, and we will discuss this further at upcoming AESGP meetings, in particular at the spring conference in Dresden."

