



Aktuelle Informationen zu Anträgen von
Zulassungen und Registrierungen im
Arzneimittelwesen (LCM) und deren
Verlängerung

EU-Konformität der Zulassungs-Dossiers

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The AT-national legal situation



Austrian Medical Act came into force in **1983**

- Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz)

Before 1.1.1995: AT accession to the EU:

- The corresponding European pharmaceutical legislation was transposed into Austrian law (Federal Act BGBl. No 107/1994, 17 February 1994)
- including Art 10 of Directive 65/65/EEC („renewal“) = § 19a Austrian Medicinal Product Act
- No transitional provisions for „old products“ – why?

The AT-national legal situation



.... Because of the Austrian legal interpretation:

→ the **MAs granted prior to accession were in line with Community law** as regards demonstrating Q/S/E, **no additional requirements** for the adaptation of MAs granted prior to accession were incorporated into the Austrian Medical Act upon accession and no particular transitional provisions were stipulated

The AT-national legal situation



**Why were MAs granted prior to accession in AT
in line with Community law:**

The national application/dossier had to contain:

- Pharmaceutical data
- Non-clinical data, safety of ingredients
- Clinical data, usefulness of the combination

In addition a **scientific summary**



**82. Verordnung des Bundesministers für
Gesundheit und Umweltschutz vom 1. Februar
1985 über Zulassung und Änderung von Arzneispezialitäten
(Arzneispezialitätenverordnung – ASpV)**

**The MA-dossiers fulfil the requirements of
Directive 65/65/EEC**



AT - situation



..... the MA-dossiers fulfil the requirements of Directive 65/65/EEC?!?

- Reality?
- Before accession the dossiers were not re-evaluated according the provisions of the 65/65/EEC due to the
 - o AT interpretation of the legal situation
 - o Limited staff capacity
- No renewal of existing MAs
- No limitation of validity of MAs (5 years)

When were the national MAs renewed?



- All MP authorised after 17. Feb. 1994 – renewed according to § 19a AMG (=Art 10 of Dir 65/65)
 - REN-A
 - REN-B
- Few medicinal products concerned (MA after 17. Feb. 1994) are still not renewed:
 - partly not marketed
 - partly suspended
 - o The MAH of these products have already been requested by the Federal Office for Safety in Health Care to renew their dossiers.
 - o Has to be finalised end of 2009

When were the national MAs renewed?



- All MPs authorised before 17. Feb. 1994 – renewed only by order of the Ministry
 - Very rare cases!!!
 - Few Ph-Vig issues
 - In case AT-RMS

➔ It was clear that also these products have to be renewed, because ...
.... a MA dossier has to be EU-conform!

EU-conformity



A MA-dossier, which claims to be EU-conform
has to be:

 in line with Dir 2001/83 incl Dir 2003/63

COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

**amending Directive 2001/83/EC of the European Parliament and of the Council on the Community
code relating to medicinal products for human use**

EU-conformity



MA may be renewed on the basis of a **re-evaluation of the risk-benefit balance.**

➔ Consolidated version of quality, safety & efficacy

we have to define what does it mean:
„Consolidated version“???

Documents to submit



BPG on processing of renewals:

„A consolidated version of the file is requested consisting of the documents listed in Annex 2. Renewal applications should be submitted using the EU-CTD format. It is recommended that MAH take the opportunity to reformat the quality part of the dossier (Module 3) into CTD format and, although it will not be obligatory until 2009, provide this in electronic format.“

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Renewal/2008_11_BPG_Renewals_MRP-DCP_Rev5-Clean.pdf



ANNEX 2

DOCUMENTS TO SUBMIT

Renewal applications have to contain a consolidated version of the file, containing at least the documents listed below. They should be presented as follows, preferably in a tab-separated dossier and in accordance with the appropriate headings and numbering of the EU-CTD format:

- Module 1:**
- 1.0 Cover letter
 - 1.1 Comprehensive table of content
 - 1.2 Renewal Application form with the following annexes:
 - List of all authorised product presentations for which renewal is sought in tabular form
 - Details of contact persons:
 - Qualified person for pharmacovigilance
 - Contact person with the overall responsibility for product defects and recalls
 - Contact person for scientific service in charge of information about the medicinal product
 - List of EU Member states/Norway/Iceland where the product is on the market and indicating for each country which presentations are marketed and the launch date
 - Chronological list of all post-authorisation submissions since grant of the Marketing Authorisation or last renewal: a list of all approved or pending Type IA/IB and Type II variations, Extensions, Art 61(3) Notifications, USR, giving the procedure number (where applicable), date of submission,

EU-conformity



Actualisation of a dossier

- Update of the Quality dossier (Module 3)
- Update of the SPC, PL



Expert reports/Overviews

Clinical Expert Statement



„The applicant submits an **expert statement** to accompany the renewal application which addresses the **current risk/benefit** for the product on the basis of the consolidated version of safety/efficacy data accumulated since the granting of the initial MA or the last renewal, the PSUR data and makes reference to any relevant new information in the public domain e.g. literature references, clinical trials and clinical experience new treatments available, which may change the risk/benefit consideration made with the original authorisation or last renewal.“

Clinical Expert Statement



- A clear statement is required from the clinical expert that the product can be safely renewed at the end of the 5 year period for an unlimited period
- The expert should ensure that the updated risk/benefit evaluation has been addressed adequately, taking account of the consolidated version of the file and all relevant new information, either by endorsement of the statement within the PSUR or by appropriate supplementation within the expert statement.
- The clinical expert should also confirm that no new (pre-clinical or clinical) data are available which changes or results in a new benefit-risk evaluation.
- Where there are new pre-clinical data the MAH may submit a non-clinical expert report as appropriate.

Review discussion – renewal AMG-Novelle



Although the AT-MAs were not renewed by an official procedure
– there is always the obligation to update the dossier according to the state of the art!!!

Renewal of the old MAs:

Amendment to medicinal Products Act 153/2005 (1.1.2006)

- Provisions for all MPs which have not yet been renewed
 - No later than 1 Jan 2011, otherwise the MA would expire

Measures for updating existing MAs of old products



- MPs, which were granted a MA prior accession
 - whose MA, from our point of view, met the requirements at the time of accession according to Dir 65/65/EEC (as amended by Directive 75/318/EEC),
 - but have not yet been renewed in accordance with the requirements of §§ 19a or 20 of the Austrian Medicinal Product Act:
- § 94c (11) AMG : they must submit an application in this regard not later than 1 January 2011, otherwise the MA will expire



This activity is ongoing
Commission wanted to shorten the period

AT – MAs: really EU conform?



1999 – 2004 PERF platform

- Discussion with accession countries on how to update the dossiers
 - It was an obligation for all accession countries to update the MA-dossiers according to the EU-legislation
 - They were asking for dossiers assessed and accepted within the „old“ EU-MSs – and what happened
 - It was realised that some of them are not in line with the EU legislation
 - Accession countries complained, but the Commission said: „non compliance of the old MS is not an excuse for the new MSs.“

Discussion during the review



Renewal:

- To change from: a renewal every 5 years – to only one 5 year renewal
 - After implementation of the new pharm. legislation each MP should have one renewal – based on a consolidated dossier – afterwards MA for an unlimited period.
 - o It was up to the MS on how to implement this provision
- EU Reference Medicinal Product
-

Review discussion – renewal AMG-Novelle



- Implementation of Dir 2004/27 in respect
 - Validity of a MA and renewal (§ 20)
 - ... but §20 not mandatory for those which had a renewal acc. to §19a
 - o Although there was a discussion in the EU that one renewal on the basis of a consolidated dossier is still necessary
 - Provision concerning the EU-Reference Medicinal Product

EU Reference Product



Art. 10.1 (3rd para) Dir 2001/83:

The first subparagraph shall also apply if the reference MP **was not authorised** in the MS in which the application for the generic MP is submitted. In this case, the applicant shall indicate ... the name of the MS in which the reference MP **is or has been authorised**.

At the request of ... the MS in which the application is submitted, the ... MS shall transmit within a period of **one month**, a confirmation that the reference MP is or has been authorised together with the full composition of the reference product and if necessary **other relevant documentation**.

Concept of „Reference Medicinal Product“



Case C-527/07:

- Proceeding between Generics and the MHRA

Facts:

- Generics submitted via DCP a generic application to the MHRA
- EU Ref. Med. Product was Nivalin
 - This product has first been authorised in AT in 1963.
 - Change of indication in 1995
 - Despite the modification, the dossier had never been updated in accordance with the requirements of EU pharmaceutical directives
 - In 2001 the MAH withdrew Nivalin from the market.

Concept of „Reference Medicinal Product“



Questions:

- In Feb. 2007 the MHRA asked AGES PharmMed whether Nivalin is/was authorised according to the Aquis Communautaire?
 - o Answer: according to the provisions in the AT national law it was not necessary to renew products which were authorised prior to accession after accession, if they were considered as safe.
 - o Nivalin was not renewed
 - o ... but it was considered to be safe – therefore
 - o ... it can be considered to be a safe Reference Medicinal Product
- ... BUT

ECJ - decision



The ECJ clearly pointed out that

- only those MPs may be considered as „Reference Medicinal Products“ in the sense of Art 10(2)a of Dir 2001/83
- And consequently be the basis of a generic application which have been authorised in accordance with Community law.

Consequences for AT because of this Court Case



- It became obvious that
 - There were products on the market in AT after accession which were not renewed.
- Commission has to take actions
 - Units involved:
 - Legal service
 - DG Competition
 - DG Enterprise & Industry

Activities/decisions



2 April 2009: letter from the Commission:

- „Apparent infringement by Austria of Community pharmaceutical legislation“:

4 May 2009: answer from the Ministry to the Commission

- Explanation of the legal situation in AT, focussing on the renewal situation

23 July 2009: meeting with the Commission (unit F2)

- Discussion of possible update procedures

No answer or further action until now.

Our proposals



- Continue with the provisions in §94c for old products
- Implement a further provision in the Austrian Medicinal Product Act for those products which have not had a renewal according to the provisions of the new pharmaceutical legislation (after the review)
 - The dossiers have to be submitted not later than **June 30th 2012**
 - It will take us at least five years for the processing of the applications

Available guidelines



The guidelines available for renewals cannot really be used, because of

- Pure national simple §24 variations (meldepflichtige Änderungen)

The MAH is responsible for ensuring that the dossier is kept up to date throughout the life of the product by way of the variation process.

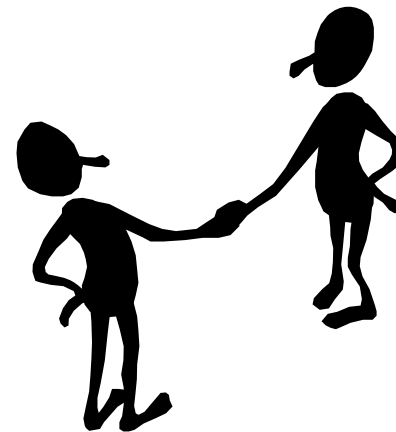
We will work on and publish national guidelines in order to facilitate the procedures.

Still for discussion



- How to deal with those products which are already withdrawn – and therefore won't be updated?
 - Nivalin was such a case
- And a lot of other questions

Danke für Ihre
Aufmerksamkeit!



Meine Bemerkungen sind nicht zwangsläufig
die offizielle Meinung der AGES