BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

Innovations in the Decentralised Procedure and in Mutual Recognition

6th DGRA Annual Conference

16. - 17. 06. 2004

Bonn

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Review 2001 - (1)
= Review of the EU-Legislation for Medicinal Products

Consists of three parts:

- Directive 2001/82/EC
  Community code relating to veterinary medicinal products
- Directive 2001/83/EC
  Community code relating to medicinal products for human use
- Council Regulation (EEC) No 2309/93
  Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of medicinal products

Review 2001 - (2)

Implementation

- published in the Official Journal: **30. 04. 2004**
- Regulation (EC) No 726/2004 of 31 March 2004
  - Title IV: in force 20th May 2004
  - other parts are in force after 18 months (20th November 2005)
- transposition of the Directives into national law: max 18 months (30th October 2005)

Review 2001 - (3)

Directive 2001/83/EC

of 6 November 2001

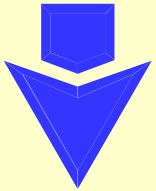
as amended by

- Directive 2003/63/EC of 25 June 2003 (= Annex I)
- Directive 2004/24/EC of 31 March 2004 (= ‚Herbal Directive')
- Directive 2004/27/EC of 31 March 2004 (= „Review 2001")

How to apply for a MA?

central

national



„Council Regulation (EEC) No 2309/93 Annex Part A Part B“

National Marketing Authorisation: Scope

- new active substances (if not mandatory for the centralised procedure)
- line extensions to national authorisations
- abridged applications to national authorisations
  - informed consent
  - generic products to national (**and centralised**) authorised originators/innovators (if not a biotechnological medicinal product)
  - bibliographic applications (well established use (WEU))
- known substances in new combination
- Homeopathics
- Herbal medicinal products

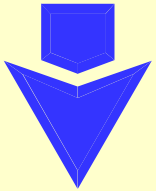
Authorisation of Medicinal Products

Article 126 a

„1. In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.“

How to apply for a MA?

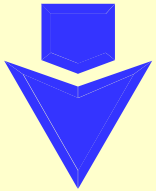
central



Council Regulation (EEC) No 2309/93
Annex Part A
Part B

MRP

national



national MA for MRP

MA for only one EEA-MS

bibliographic application Article 10 (2)

What is the Mutual Recognition Procedure (MRP)?

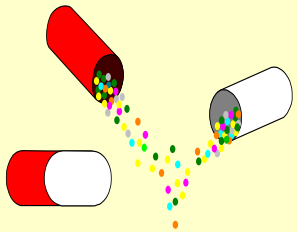
- describes the procedure to get national MAs in MSs if the same medicinal product is already approved in one MS (= RMS)

  → mandatory procedure

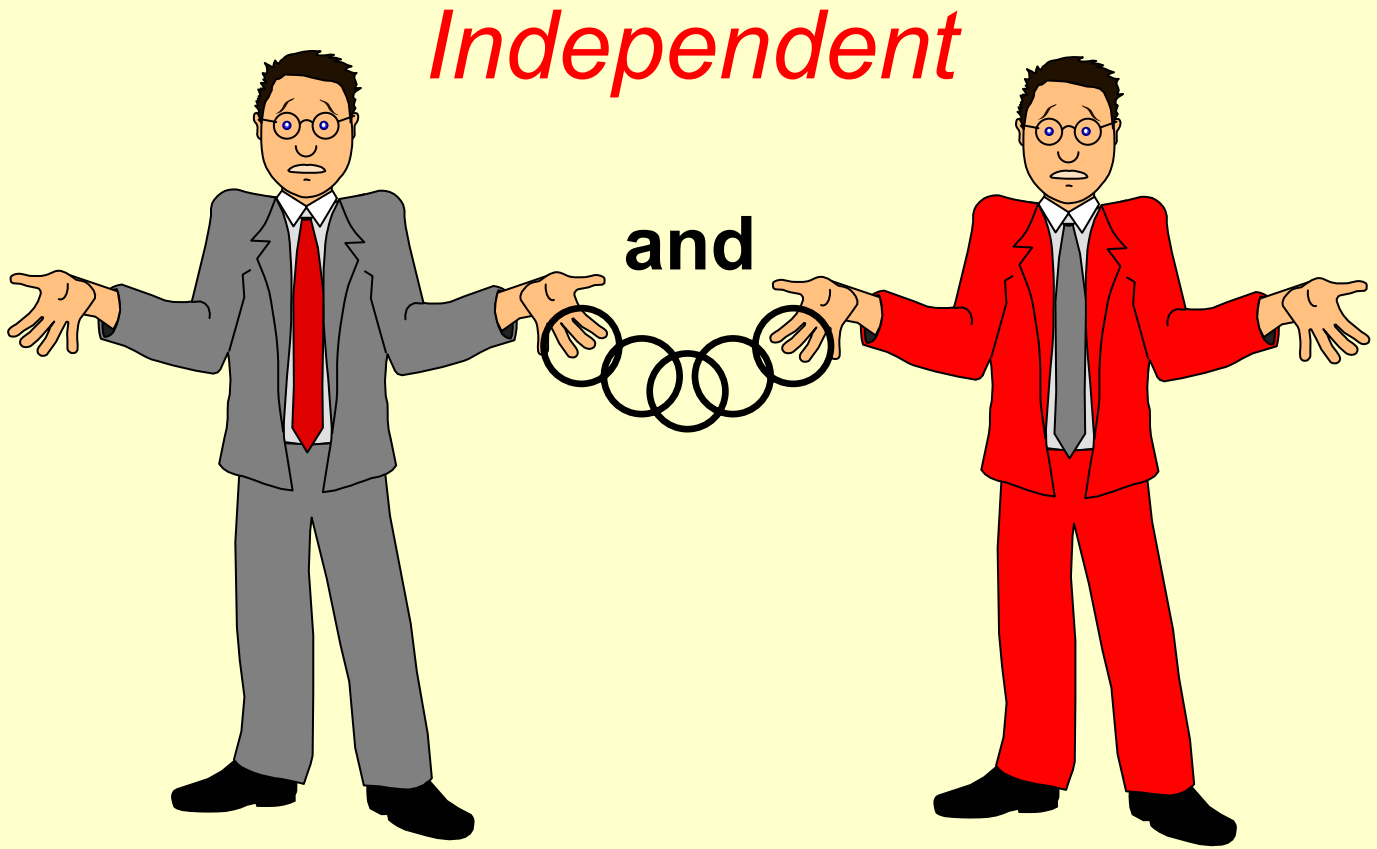
- method of work sharing between MS

Same medicinal product ?

- **Same qualitative and quantitative active ingredient**
  - There may be the differences in excipients provided that there is no impact on safety and efficacy
- **Same pharmaceutical form**
- **Link between companies**
  - all license holders
  - all legal entities
    - Commission Communication July 1998

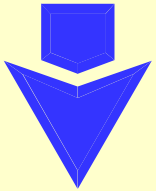


~~Same~~ medicinal product



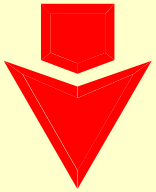
How to apply for a MA?

central



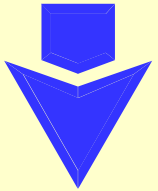
Council Regulation (EEC) No 2309/93
Annex Part A
Part B

MRP



More than one EU-MS

national



national MA for MRP

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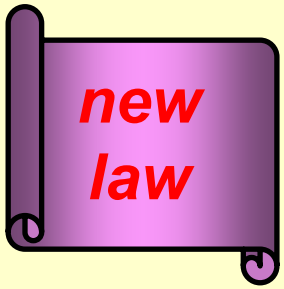
bibliographic application Article 10 (2)



Review 2001
or
Future Medicine Legislation (FML)

Definition: Marketing Authorisation

Article 6 (a)

*"When a medicinal product has been granted an **initial marketing authorisation** … any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation … or be included in the initial MA. All these MA shall be considered as belonging to the **same global marketing authorisation** , in particular for the purpose of the application of Article 10(1)."*

Marketing Authorisation

Article 21

The competent authority shall make public without delay

- the Marketing Authorisation and SPC
- the Assessment Report (without commercially confidential informations), to be updated if necessary
- has to give a justification for each indication applied for

Name of medicinal product

- … the name of the medicinal product followed by its strength and pharmaceutical form
- "…must also be in Braille format on the packaging."
- PL: a list of names authorised in each Member State (MRP/DCP)

Reference Product - (1)

Article 10 (1): Reference Product

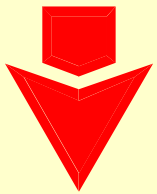
- *"… is a generic of a reference medicinal product which is or has been authorised … for not less than eight years in a Member State or in the Community."*
- *"A generic … cannot be placed on the market until ten years have been elapsed from the initial authorisation of the reference product."*
- … but this periods of protection should not apply to reference medicinal products for which an application for authorisation has been submitted before october 30th, 2005.

Reference Product - (2)

Reference product cont.

- *"… shall also apply, if the reference medicinal product was not authorised in the Member State in which the application for the generic … is submitted"*

→ Will this solve the problem of withdrawals based on national substitution/reimbursement policy?

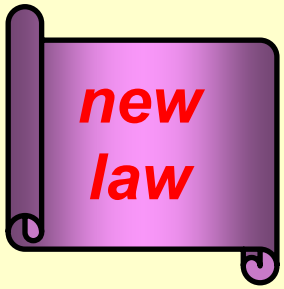


Present

Originator	MA RMS	CMS 1	CMS 2	CMS 3
	=	X	X	ok
Generic	MA RMS	CMS 1	CMS 2	CMS 3

Future

Originator	MA RMS	CMS 1		CMS 3
	=	X		ok
Reference	MA RMS	! Substitution/Reimbursement !		
	=	X		ok
Generic	MA RMS	CMS 1	CMS 2	CMS 3



Review 2001
or
Future Medicine Legislation (FML)

Mutual Recognition Procedure (MRP) and the new Decentralised Procedure (DCP)

Procedures

Decentralised Procedure - (1)

Two routes for receiving a MA

1. Mutual recognition procedure

   where the medicinal product has already received a MA at the time of application or

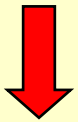
2. Decentralised procedure

   where the medicinal product has not received a MA at the time of application

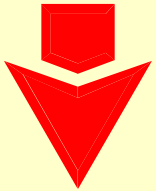
Decentralised Procedure - (2)

What's new for both procedures?

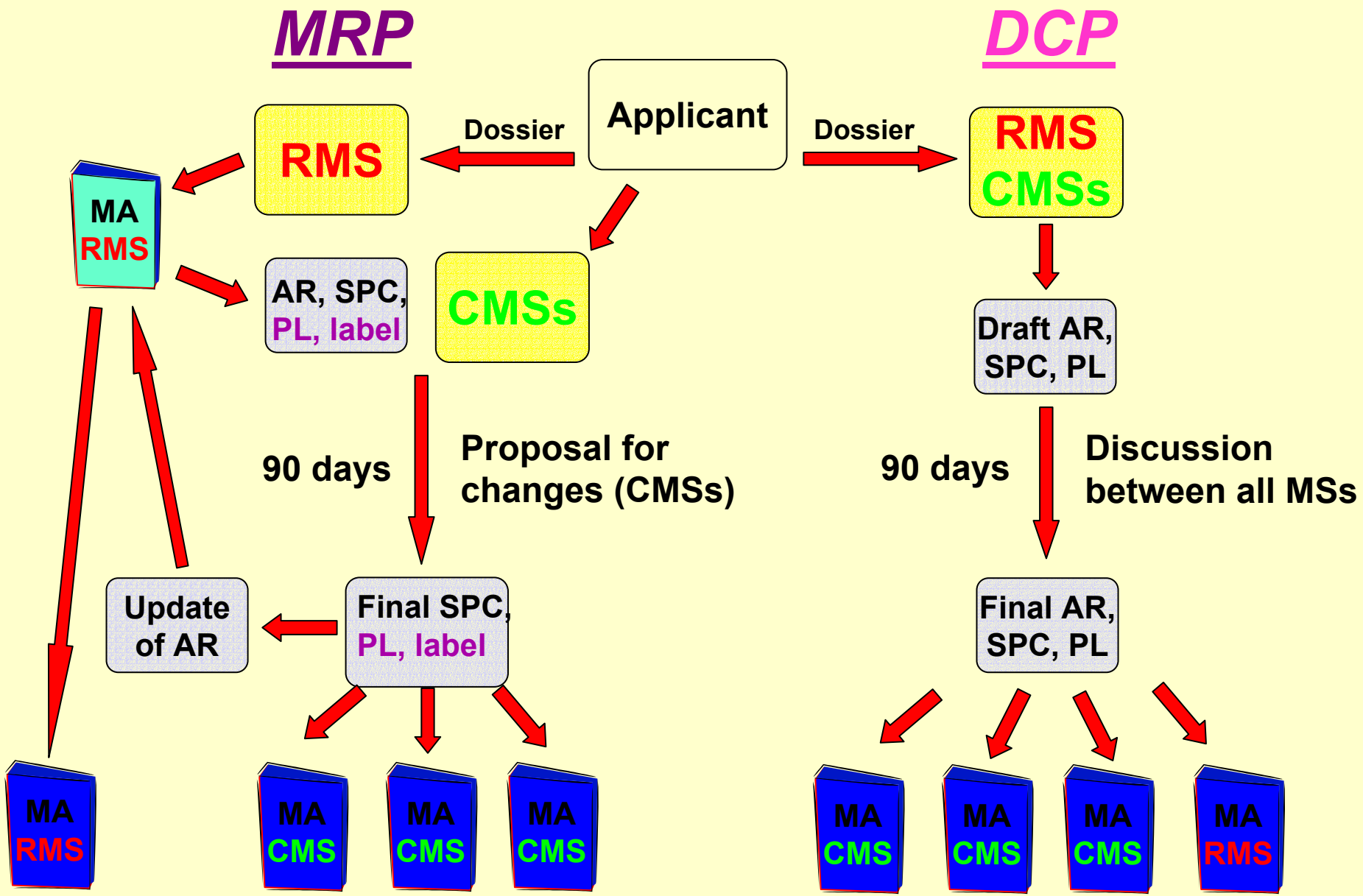
PL and labelling is part of the approval



harmonisation between MSs



'Blue Box' necessary !!!!


MRP
DCP
Applicant
Dossier
Dossier
RMS
RMS
CMSs
MA
RMS
AR, SPC,
PL, label
CMSs
Draft AR,
SPC, PL
90 days
Proposal for
changes (CMSs)
90 days
Discussion
between all MSs
Update
of AR
Final SPC,
PL, label
Final AR,
SPC, PL
MA
RMS
MA
CMS
MA
CMS
MA
CMS
MA
CMS
MA
CMS
MA
CMS
MA
RMS

Decentralised Procedure - (3)

What is new ?

- Applicant can choose procedure (and RMS)
- consultation between MS´s **before** the first MA is issued
- introducing a ‘clock-off’ period
- final AR, SPC, PL and labelling
- granting a MA at the ‘same time’ in MS´s of the EEA

Decentralised Procedure - (4)

Implications for competent authorities

- early involvement as CMS
- working together
- tighter time-limits, but also ´clock stop´
- discussion between MS will be positive for public health (if new active substance)

Decentralised Procedure - (5)

Possible procedure

Day - 30	*pre-procedural step - submission of dossier, validation*
Day 0-120	*National step - RMS assessment, PAR, comments from CMS, consolidated LoQ to applicant*
CLOCK STOP	*Applicants response document*
Day 120-210	European step - *draft AR/SPC/PL, CMS comments, break out, FAR, approval and closure (or referral)*
Day 210-240	National step - *granting of MA*

DCP - proposed flow chart - (1)

!!!!!!! First ideas !!!!!!!

1. Pre-procedural Step

Day - 30 *Submission of the dossier to RMS and CMSs*

Validation of the application

Communication with the MS of the Reference Product (?)

DCP - proposed flow chart - (2)

2. National step – 120 days

Day 0 *RMS starts the procedure and the assessment of the dossier*

Day 85 *RMS forwards PAR to CMSs and Applicant*

Day 110 *CMSs send comments to RMS*

Day 120 *RMS sends consolidated LoQ to Applicant*

→ **Clock-off period**

DCP - proposed flow chart - (3)

Clock-off period

- *recommended period of 6 months, which could be extended if justified*
- *Applicant sends the response document*
- *RMS validates the response document*
- *RMS prepares the draft AR, SPC, PL and labelling*

→ **European step**

DCP - proposed flow chart - (4)

3. European step – 90 days

Day 121 *RMS sends draft AR, SPC, PL and labelling to CMSs and Applicant*

Restart of the procedure

Day 150 *CMSs send comments on draft AR, SPC, PL and labelling to RMS*

Day 155 *RMS sends the consolidated LoQ to the Applicant*

Day 165 *Applicant sends the response document to RMS and CMSs*

DCP - proposed flow chart - (5)

Day 170	*Possibility of a Break-out Session*
Day 175	*CMSs send final comments*
Day 180	*RMS circulates the final AR*
	Final discussion of AR, SPC, PL and labelling
	Withdrawal from CMSs
Day 210	*Mutual approval of final AR, SPC, PL and labelling - closure of the procedure*
	or disagreement and referral to the Coordination Group

DCP - proposed flow chart - (6)

4. National step – 30 days

Day 210-240 *granting of MA*

MRP/DCP
Proposed changes to procedures - (1)

If no agreement between RMS/CMS can be reached at end of procedure

- Referred to Coordination Group (CG)
  - 60 days for negotiation between the MS concerned (RMS and CMSs)
  - consultation of the applicant in written or oral form

MRP/DCP
Proposed changes to procedures - (2)

- Still disagreement after this consultation – the elements of disagreement are forwarded to the Agency

  → „forced“ arbitration (?)

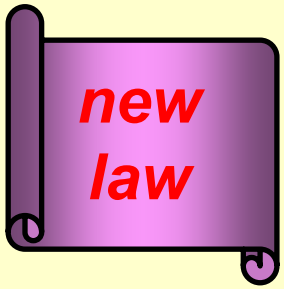
→ MS´s that are in agreement with the AR and SPC may authorise the medicinal product, without waiting for the outcome of the procedure

MRP/DCP
Proposed changes to procedures - (3)

necessary prerequisite:

Definition of 'Serious Risk to Public Health'

EU-Commission together with MRFG / VMFRG



Review 2001
or
Future Medicine Legislation (FML)

The Coordination Group (CG)

MRFG versus Coordination Group - (1)

- legal basis for operation
- wide scope - to examine any question related to authorisations of medicinal products in more than one MS
- to assist procedures for authorisation of MPs in more than one MS
- new responsibilities – mix of procedural, regulatory and scientific work

MRFG versus Coordination Group - (2)

- one representative from each MS, appointed for 3 years (renewable)
- members could be accompanied by experts
- rules of procedure for the CG – to be approved by the EC-Commission

Coordination Group - (1)

- Dialogue between MS´s
  - Procedural / Regulatory
    - ✓Regulatory SOP´s, guidelines and recommendations
    - ✓Harmonised view on the interpretation of Directive and Regulation

Coordination Group - (2)

- Scientific
  - ✓Scientific discussion to resolve scientific problems, arbitration only in exceptional cases
  - ✓Identification of the need to modify or develop new guidelines (establishment of ad-hoc groups)

Coordination Group - (3)

- Harmonisation of SPC´s

  ✓once a year the CG will elaborate a list of products where the SPC need to be harmonised

  - proposal of candidates by the MS to CG
  - CG will discuss and compile a list to be send to the EU-Commission
  - EU-Commission (?) will start Article 30 procedures

Coordination Group - (4)

- Risk management
  - ✓close liaison with the Pharmacovigilance Working Party (PhVWP)
  - ✓arrangements for work sharing of PSUR´s

Coordination Group - (5)

- Organisational aspects
  - Elected chairperson and a vice-chair
  - Rules of procedures
  - Meetings
    - ✓ monthly at the EMEA – plenary meeting
    - ✓ Break-out sessions – will be reported to the plenary meeting
  - Secretariat
    - ✓ provided by the EMEA

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Federal Institute for Drugs and Medical Devices (BfArM)

... thank you

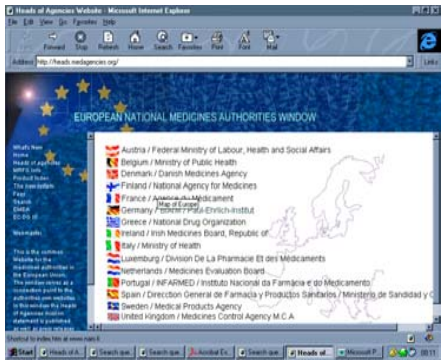
Information on Drug Regulatory Affairs

European Institutions

http://pharmacos.eudra.org
= European Commission, DG Enterprise

http://www.emea.eu.int
= European Medicines Evaluation Agency

http://heads.medagencies.org
= (National) Medicines Authorities in the European Union



Zulassungen international/International Registration Procedures/Dr. B.Lehmann - BfArM 18

List of Abbreviations - (1)

(F)AR	(Final) Assessment Report
CA	Competent Authority
CTD	Common Technical Document
CG	Coordination Group
CHMP	Committee for Herbal Medicinal Plants
CMPH(V)	Committee of Medicinal Products for Human (Veterinary) Use
(D)CP	(De) Centralised Procedure
EEA	European Economic Area
EM(E)A	European Medicine (Evaluation) Agency

List of Abbreviations - (2)

ICH	International Conference on Harmonisation of…
LoQ	List of Questions
MA(H)	Marketing Authorisation (Holder)
MRP	Mutual Recognition Procedure
NtA	Notice to Applicants
(R,C)MS	(Reference, Concerned) Member State
PL	Package Leaflet
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate