6th DGRA Annual Conference:

Implementation of the review 2004 in the enlarged European Union

16th and 17th June 2004

Bonn/Germany

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Regulatory Challenges from EU-Commission view point

Major changes to the existing system

Status of Legislation

- http://europa.eu.int/eur-lex/en/archive/2004/l_13620040430en.html

OJ L 136
Volume 47
30 April 2004

- http://pharmacos.eudra.org/F2/pharmacos/new.htm

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

- Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

- Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products

- Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

Objectives

- To improve the high level of public health protection
- To contribute to the completion of the single market
- To adapt the system to the forthcoming enlargement
- To strengthen the competitiveness of pharmaceutical industry

- Directive 2004/27/EC
- Regulation (EC) No 726/2004

Directive 2004/27/EC

Definition of medicinal product

Articles 1 & 2

- Article 1(2)(b) – Possible types of physiological action to take account of new therapies: “by exerting a pharmacological, immunological or metabolic action”

- Article 2(2) – Application of the pharmaceutical *acquis* “in cases of doubt”

Directive 2004/27/EC

Data protection rules

Article 10

- Article10(1) Harmonised 10-year data protection period
- Article10(1) Extension to 11 years if, during the first 8, the MAH obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to authorisation, are held to bring a significant clinical benefit in comparison with existing therapies -
- Article 10(5) Additional 1 year where an application is made for a new indication for a well-established substance, provided that significant pre-clinical or clinical studies are performed in relation to the new indication

Directive 2004/27/EC

Reference Medicinal Product

Article 10

- Article 10(1) No need for the reference medicinal product to be authorised in the MS where the generic application is made
- Article 10(1) No longer necessary for the reference medicinal product to be authorised at the time of application
- Article 10(1) Possibility of filing an application after 8 years of authorisation of the reference product
- Article 10(2) Definitions of reference medicinal product and generic medicinal product
- Article 10(5) Studies and trials during patent or SPC protection period

Directive 2004/27/EC

Specific provisions applicable to homeopathic medicinal products

Articles 13 – 16

- Article 14 simplified registration
- Article 16 other than those referred to in Article 14(1) shall be authorized and labelled in accordance with Articles 8, 10, 10a, 10b, 10c and 11.

Directive 2004/27/EC

Mutual recognition procedure and Decentralised procedure

Article 21

- Article 21(3) Publication of Marketing Authorisation and Summary of Product Characteristics

- Article 21(4) Publication of Assessment Report

Directive 2004/27/EC

Renewal and sunset close

Article 24

- Article 24(1), (2) & (3) Validity of national MAS: one 5-year renewal, followed by an unlimited period of validity

- Article 24(4), (5) & (6) MAs will cease to be valid if not placed on the market after 3 years of authorisation, or where a medicinal product previously placed on the market is no longer present on the market for 3 consecutive years. Exceptional exemptions on public health grounds

Directive 2004/27/EC

Mutual recognition procedure and Decentralised procedure

Article 29

- Article 29(1) and (2) mutual recognition procedure: medicinal products with a Marketing Authorisation

- Article 29(1) and (3) decentralised procedure: medicinal products with no Marketing Authorisation

Directive 2004/27/EC

Co-ordination Group

Articles 27-32

- Responsible for the examination of any question relating to the marketing authorisation of a MP in two or more Member States
- The Agency shall provide the secretariat for the group
- One representative per Member State (possibility to be accompanied by experts)
- Renewable period of three years
- Own rules of procedure

Directive 2004/27/EC

Mutual Recognition Procedure

Article 28 (2)

- Existing Marketing Authorisation by the time of application
- Member State(s) concerned shall recognise the MA granted by the Reference Member State
- MAH shall request the RMS to prepare an assessment report or to update any existing assessment report
- Report within **90 days** (note: amended by Council instead of 60 days) of receipt of a valid application
- Report, approved SPC, labelling and package leaflet shall be forwarded to CMS(s) and the applicant

Directive 2004/27/EC

Decentralised Procedure

Article 28 (3)

- No Marketing Authorisation by the time of application
- The applicant shall request the RMS to prepare a draft assessment report and drafts of the SPC, labelling and package leaflet
- Preparation of drafts within 120 days of the receipt of a valid application
- Drafts to be sent to CMS(s) and to the applicant

Directive 2004/27/EC

Mutual recognition procedure and Decentralised procedure

Article 29 (1)

- MS cannot agree on grounds of a potential serious risk to human health
- Detailed statement of the reasons shall be provided to RMS, other CMS(s) and the applicant

- Points of disagreement shall be referred without delay to the co-ordination group

Directive 2004/27/EC

Mutual recognition procedure and Decentralised procedure

Article 29 (3)

Co-ordination Group (Procedure)

- MS shall use their best endeavours to reach agreement
- Opportunity for the applicant to comment orally or in writing
- Procedure finished within 60 days
- If agreement: RMS shall record the agreement, close the procedure and inform the applicant accordingly
- Adoption of decision in each MS where an application has been submitted within 30 days of the acknowledgement of the agreement

Directive 2004/27/EC

Mutual recognition procedure and Decentralised procedure

Article 29 (4)

- If no agreement within 60 days: immediately information of the Agency
- Start of procedure as laid down in Articles 32, 33 and 34
- Detailed description of the matters on which agreement could not be reached and the reasons of disagreement
- Applicant has to provide all information to Agency

Directive 2004/27/EC

Mutual recognition procedure and Decentralised procedure

Article 29 (6)

- MS that has approved the assessment report, SPC, labelling and package leaflet of the RMS may, on request by the applicant, grant a MA for the MP without waiting for the outcome of procedure laid down in Article 32. In that case, the authorisation granted shall be without prejudice to the outcome of that procedure.

Directive 2004/27/EC

Referral procedures

Articles 29 -31

- Article 29 Mutual recognition referral-Automatic referral in case of disagreement ("potential serious risk to public health"

  → Possibility for MS to grant MA without waiting for the outcome of the referral

- Article 30 Divergent decision referral

  → Yearly list of products for which harmonisation necessary drawn up by Co-ordination Group

- Article 31 Community interest referral
  Specific provisions for class referrals

Directive 2004/27/EC

‘Switch’

Article 74

Article 74a

- Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised.

Directive 2004/27/EC

Inspections and controls

Articles111 & 122

Article 111

- Quality control extended to raw materials
- General reinforcement of inspections
- Increased coordination via a Community database

Article 122

- System for the recognition of inspections

Directive 2004/27/EC

Pharmacovigilance

Articles104, 106-107

Article 104

- More frequent safety reports
- Increased coordination between MS

Article 106

- Use of international terminology in the reporting of adverse reactions

Article 107

- Commission to ask MS to take temporary measures with immediate effect in case of urgency
- Reinforced inspections linked to MAH's obligations - reference to Article 111

Directive 2004/27/EC

Further Provisions

Article 81

- The obligation of continuous supply

Article 126a

- Medicinal Product placing on the market in the absence of a marketing authorisation or of a pending application for justified public health reasons

Regulation (EC) No 726/2004

Scope

Article 3

- Article 3(1)
  CP <u>obligatory</u> for
  - MP listed in the annex (Biotech products)
  - including new active substances

- Article 3(2)
  CP optional

Regulation (EC) No 726/2004

Scope

Article 3

- Article 3(1)
  CP <u>obligatory</u> for
  - MP listed in the annex (Biotech products)
  - including new active substances
- acquired immune deficiency syndrome
- cancer
- neurodegenerative disorders
- diabetes

  - and with effect from 20 May 2008
    Auto-immune diseases and other immune dysfunctions
    Viral diseases

- Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000

Scope

Article 3

- **Article 3(2)**
  CP <u>optional</u> for
  - if MP is a significant therapeutic, scientific or technical innovation
  - or the granting of a centralised MA is of interest at Community level to patients health

- **Article 3(3)**
  - generic of a centrally authorised MP in MRP

Procedures

Article 10

Article 10(2)

- Decision Making Process by Commission:
  - in general, only 15 days
  - in cases of urgency even shorter deadlines

Article 10(3) Standing Committee

- - in general, only 22 days not shorter than 5 days

Regulation (EC) No 726/2004

Transparency

Articles 11 -13

Article 11

- Publication of withdrawal

Article 12

- Publication of refusal

Article 13

- Publication of:
  Assessment Report, reasons for its opinion in favour of granting authorisation

Regulation (EC) No 726/2004

Renewal and Sunset Close; Procedures

Articles 14

- Article 14(3) ..once renewed, the marketing authorisation shall be valid for unlimited period… on justified grounds…additional five-year renewal
- Article 14(4)&(5) three years not present on the market …authorisation shall cease to be valid
- Article 14(7) …an authorisation my be granted subject to certain specific obligation…such authorisation shall be valid for one year, on renewable basis
- Article 14(9) … where MP of major interest from point of view of public health and in particular from point of view of therapeutic innovation
  - time limits reduced from 210 to 150 days (exemption from Article 6(3))

Regulation (EC) No 726/2004

Good Manufacturing Practice

Articles 19 & 20

Article 19

- Inspection

Article 20

- If obligations not fulfilled
  - Commission, following an opinion by the EMEA, shall adopted the necessary provisional measures, to be applied immediately
  - final decision to be adopted within 6 months by normal procedure

Article 20 (4)

- Where urgent action necessary, a MS may, on its own initiative or at the Commission's request, suspend the use of a MP

Regulation (EC) No 726/2004

Pharmacovigilance

Articles 23 – 24 & 26

Article 23

- Qualified person responsible for pharmacovigilance

Article 24(2)

- generally, to be communicated electronically in the form of a report and according to the guide – PSUR

Article 24 (3)

- either immediately on request or at least every 6 months (2 years) once a year (2 years), thereafter, at 3-years intervals

Article 26

- availability of pharmacovigilance data
  - data base (EMEA) permanently accessible for MS
  - EMEA shall make available appropriate pharmacovigilance information to the public

Regulation (EC) No 726/2004

European Medicines Agency (EMEA)

Articles 56 & 61

Article 56 **Scientific committees**

- Committee for Medicinal Products for Human Use*
- Committee for Medicinal Products for Veterinary Use*
- Committee on Orphan Medicinal Products (Regulation (EC) No 141/2000 Article 4(3))
- Committee on Herbal Medicinal Products (Directive 2004/24/EC Article 16h (2))

- **Establish standing and temporary working parties and scientific advisory groups**

*Article 61

(1) One member and one alternate per Member State per Committee

(2) The committees may co-opt a maximum of five additional members chosen on the basis of their specific competence

Regulation (EC) No 726/2004

EMEA

Article 65 **Management Board**

- One representative of each Member State
- Two representative of the Commission
- Two representative of the European Parliament
- Two representatives of patients organization
- One representative of doctors' organization
- One representative of veterinarians' organization

Further Regulations/Direcitves/Guidelines/Guidance requested by

- Regulation (EC) No 726/2004
- Directive 2004/27/EC

Regulation (EC) No 726/2004

→ Article 3(1)	Scope
→ Article 14(7)	Conditional marketing authorisation
→ Article 24(2)	Reporting of suspected unexpected adverse reactions
→ Article 26	Draw up a guide on the collection, verification and presentation of adverse-reaction reports…communication of information on adverse reactions
→ Article 57(2)	EudraPharm database and clinical trials information
→ Article 70	Fee regulation (SME – reduced fee)

Directive 2004/27/EC

→ Articles 1& 2	Borderline – products
→ Article 10	Reference Medicinal Product
→ Article 28	Time-lines decentralised Procedure
→ Article 29	'Serious risk to public health'
→ Articles 46 & 47	GMP starting material and excipients
→ Article 65	Guidance for information to patients
→ Article 74a	update of SWITCH guideline

EU Pharma legislation

Other starting materials

Blood / Blood comp.
2002/98/EC, 2004/33/EC

Tissues / Cells
2004/23/EC

Clinical Trials
2001/20/EC

Pharma Review

Medicinal Products
Community Code
Dir. 2004/27 & 28/EC

Medicinal Products
Centralised procedure
Reg. 726/2004

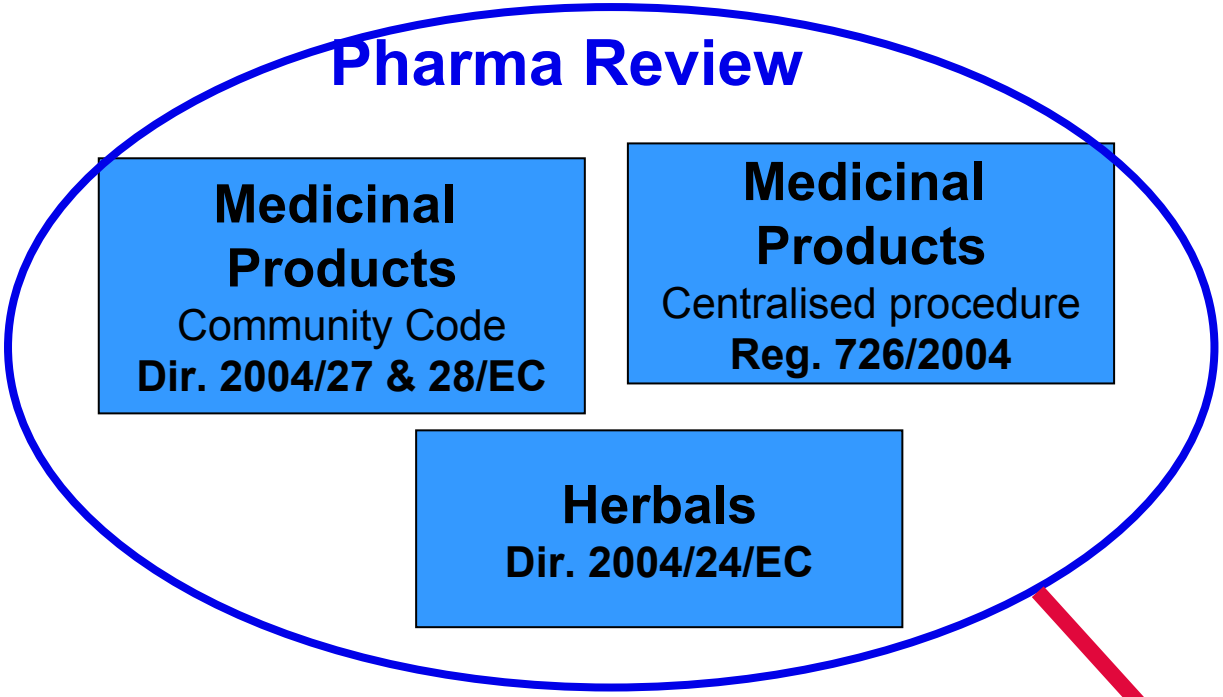
GMP
2003/94/EC

Herbals
Dir. 2004/24/EC

Annex I
2003/63/EC

Variations
1084/2003/EC
1085/2003/EC

Other initiatives:
Paediatrics;
Tissue-Engineering



Notice to Applicants

Transition Rules for the new Member States

The Treaty of Accession 2003

ACT
CONCERNING THE CONDITIONS OF ACCESSION
OF THE CZECH REPUBLIC, THE REPUBLIC OF ESTONIA, THE REPUBLIC OF CYPRUS, THE REPUBLIC OF LATVIA,THE REPUBLIC OF LITHUANIA, THE REPUBLIC OF HUNGARY, THE REPUBLIC OF MALTA, THE REPUBLIC OF POLAND, THE REPUBLIC OF SLOVENIA AND THE SLOVAK REPUBLIC
AND THE ADJUSTMENTS TO THE TREATIES
ON WHICH THE EUROPEAN UNION IS FOUNDED

Article 24 reference to the Annexes V – XIV containing transitional measures for each of the new Member States

http://europa.eu.int/comm/enlargement/negotiations/treaty_of_accession_2003/treaty_accession_28.htm

Austria

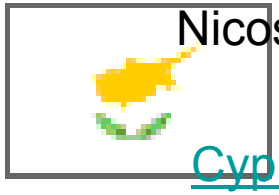
Vienna

Brussels

Belgium

Estonia

Tallinn



Nicosia

Cyprus

Luxembourg

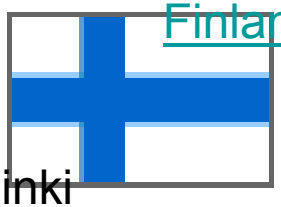
Luxembourg

Czech Republic

Prague

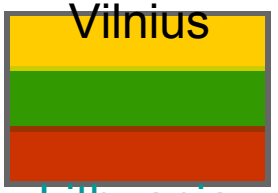
Germany

Berlin



Finland

Helsinki



Vilnius

Lithuania

Copenhagen

Denmark

Athens

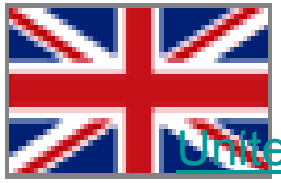
Greece

Rome

Italy

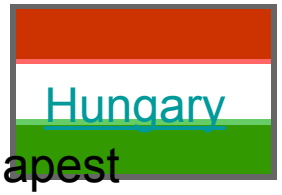
Riga

Latvia



London

United Kingdom

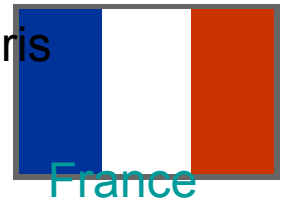


Hungary

Budapest

Valetta

Malta



Paris

France

Lisbon

Portugal

Slovakia

Bratislava

Poland

Warsaw

Madrid

Spain

Slovenia

Ljubljana

Ireland

Dublin

Sweden

Stockholm

Amsterdam

The Netherlands

Objectives

- To improve the high level of public health protection?
- To contribute to the completion of the single market?
- To adapt the system to the forthcoming enlargement?
- To strengthen the competitiveness of pharmaceutical industry?

Objectives

- To improve the high level of public health protection

- Strengthening the pharmacovigilance system, including database
- Better information to patients (Braille)
- Harmonised information to patients

Objectives

- To contribute to the completion of the single market

- New (decentralised) procedure
- Harmonisation of information to public (Summary of Product Characteristics, Patient Information Leaflet ,Labelling)
- Data-base (EuroPharm)

Objectives

- To adapt the system to the forthcoming enlargement

- Strengthening of the Procedures
- Members in Committees

Objectives

- To strengthen the competitiveness of pharmaceutical industry

- Harmonised ‘data protection times’
- New procedures (fast track)

Objectives

To improve the high level of public health protection ✓

To contribute to the completion of the single market ✓

To adapt the system to the forthcoming enlargement ✓

To strengthen the competitiveness of pharmaceutical industry ✓

Next Review

Recital (30)

of Regulation (EC) /2309 amended

It is necessary to provide for the coordinated implementation of Community procedures for the authorisation of medicinal products, and of the national procedures of Member States
which have already been harmonised to a considerable degree by Directives 2001/83/EC and 2001/82/EC. It is appropriate that the operation of the procedures laid down by this Regulation be re-examined by the Commission every ten years on the basis of Experience gained.

Willkommen (DE)

Welcome (UK)

Bienvenue (FR)

Welkommen (DK)

Benvenuti (IT)

Üdvõzõljük (HU)

Välkommen (SE)

Bienvenido (ES)

Tere tulemast (EE)

Vitejte (CS)

Welkom (NL)

Labdien (LV)

Sveiki atvykę (LT)

Bem-venido (PT)

Tervetuloa (FI)

Vitame Vás (SK)

Merhba (MT)

Dobrodošli (SL)

Serdecznie Witamy (PL)

Καλώς ορίατε (EL)


Thank you
for your attention