AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Organizzazione di AIFA*

Procedure per l'autorizzazione all'immissione in commercio: Mutuo Riconoscimento, Decentrata, Centralizzata e Nazionale*

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15/03/2019

*slides gentilmente trasmesse Dott.sse Dell'Utri e Cogliandro

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

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N.B. I am not receiving any compensation

AGENZIA ITALIANA DEL FARMACO
Art. 48 Legge 326/2003

Regolamento di organizzazione, funzionamento e ordinamento del personale di AIFA
G.U. n. 140 del 17.06.2016

Piano di attività AIFA per l'anno 2019 (Delibera CDA n. 6 del 27/02/2019)

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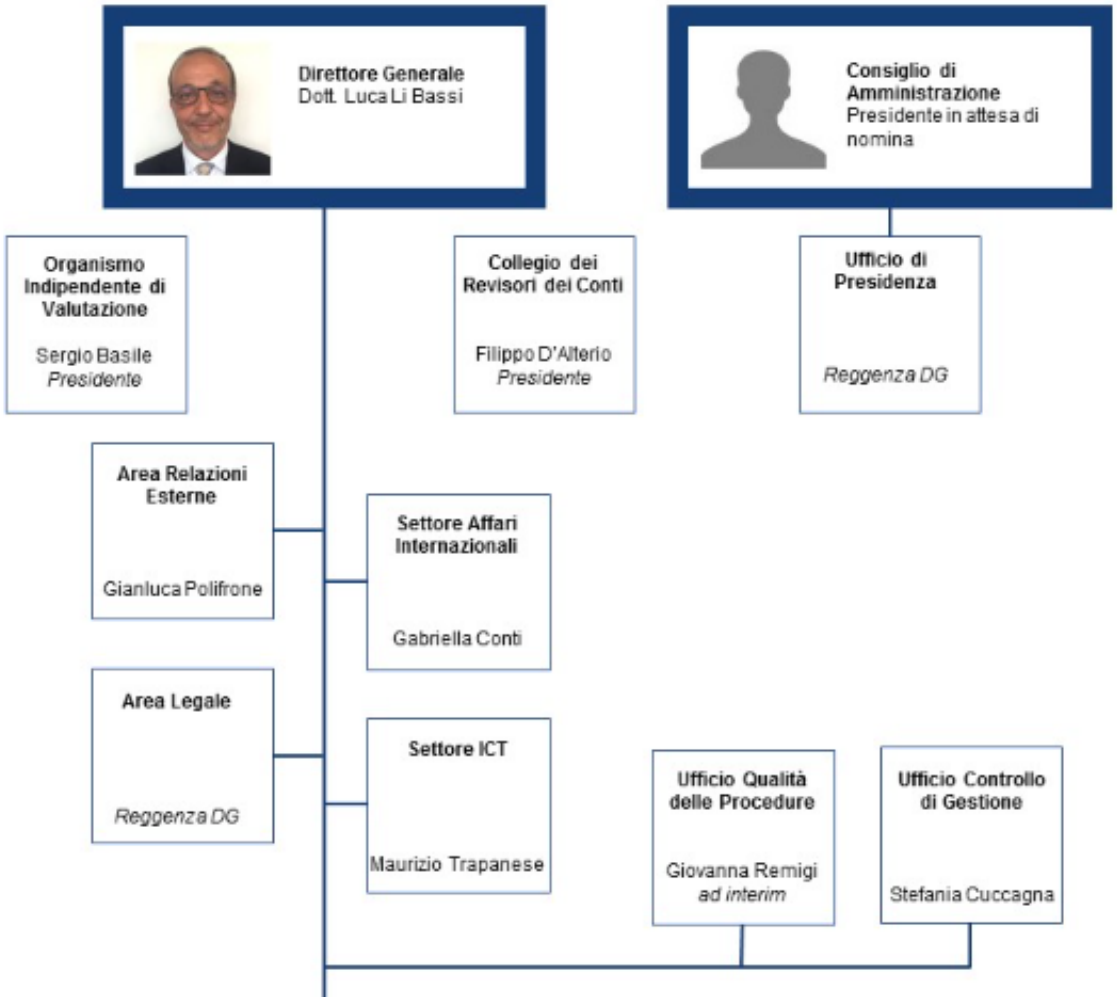
- L'Agenzia Italiana del Farmaco (AIFA) è l'autorità nazionale competente per l'attività regolatoria dei farmaci in Italia

- E' un Ente pubblico che opera in autonomia, trasparenza ed economicità, sotto la direzione del Ministero della Salute e la vigilanza del Ministero della Salute e del Ministero dell'Economia e Finanze

- Collabora con le Regioni, l'Istituto Superiore di Sanità, gli Istituti di Ricovero e Cura a Carattere Scientifico, le Associazioni dei pazienti, i Medici e le Società Scientifiche, il mondo produttivo e distributivo

PRIORITÀ STRATEGICHE DI AIFA

L'ORGANIZZAZIONE DI AIFA



.... segue


Area Amministrativa
Reggenza DG
Area Pre-Autorizzazione
Sandra Petraglia
Area Autorizzazioni medicinali
Isabella Marta
Area Vigilanza Post-Marketing
Anna Rosa Marra
Area Strategia ed Economia del Farmaco
Reggenza DG
Area Ispezioni e Certificazioni
Domenico Di Giorgio

LE AREE OPERATIVE DI AIFA

Area Amministrativa

Area Pre-Autorizzazione:

- Ufficio Sperimentazione Clinica
- Ufficio Ricerca Indipendente

Area Autorizzazione Medicinali:

- Ufficio Autorizzazione all'immissione in commercio
- Ufficio Procedure post autorizzative
- Ufficio Valutazioni medicinali biologici
- Ufficio Certificazioni e Importazioni Parallele

Area Vigilanza Post-Marketing	➢ Ufficio Farmacovigilanza ➢ Ufficio Gestione dei Segnali ➢ Ufficio Misure di Gestione del Rischio ➢ Ufficio Informazione scientifica
Area Strategia ed Economia del Farmaco	➢ Settore HTA ed economia del farmaco ➢ Settore Innovazione e Strategia del farmaco
Area Ispezioni e Certificazioni	➢ Ufficio Ispezioni e autorizzazioni GMP medicinali ➢ Ufficio Ispezioni e autorizzazioni GMP materie prime ➢ Ufficio Qualità dei prodotti e Contrasto al Crimine Farmaceutico ➢ Ufficio Ispezioni GCP ➢ Ufficio Ispezioni GVP

Medicines approval system within the EU

- Whether for human or veterinary use a medicinal product must be the subject of a valid Marketing Authorisation (MA) before it can be placed on the market for sale and supply. The Marketing Authorisation Holder (MAH) has to market the product in compliance with the terms of the authorisation.

- All applications for a MA are assessed based on supporting data provided for safety, quality and efficacy. A product only receives a MA if its benefits outweigh any risks.

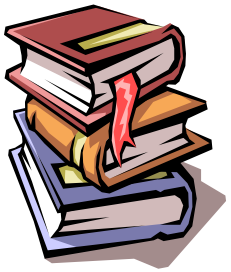
- Not all products for which MA applications are submitted are subsequently granted a Marketing Authorisation. Some applications are refused due to insufficient and/or inadequate data.

Italian Medicines Agency (AIFA)

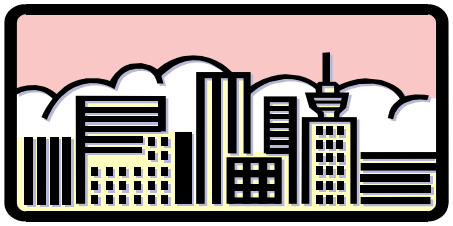
- The Italian Medicines Agency (AIFA) is the only national authority responsible for drugs (human) regulation in Italy
- AIFA is a public body operating autonomously, transparently and according to cost-effectiveness criteria, under the direction of the Ministry of Health and under the vigilance of the Ministry of Health and the Ministry of Economy
- AIFA cooperates with the Regional Authorities, the National Institute of Health (ISS), Research Institutes, Patients' Associations, Health Professionals, Scientific Associations the Pharmaceutical Industry, Drug Distributors and with all Regulatory Authorities Worldwide

The Assessment Process

Company dossier



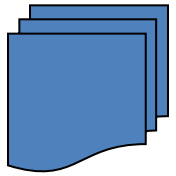
Competent authorities



Product

Output

Assessment Report



Resources

Assessors (Experts) – Internal / External

Legislation and Guidelines – Harmonised interpretation

Product information

S P C

P L

. . . .

CTD (Common Technical Document)

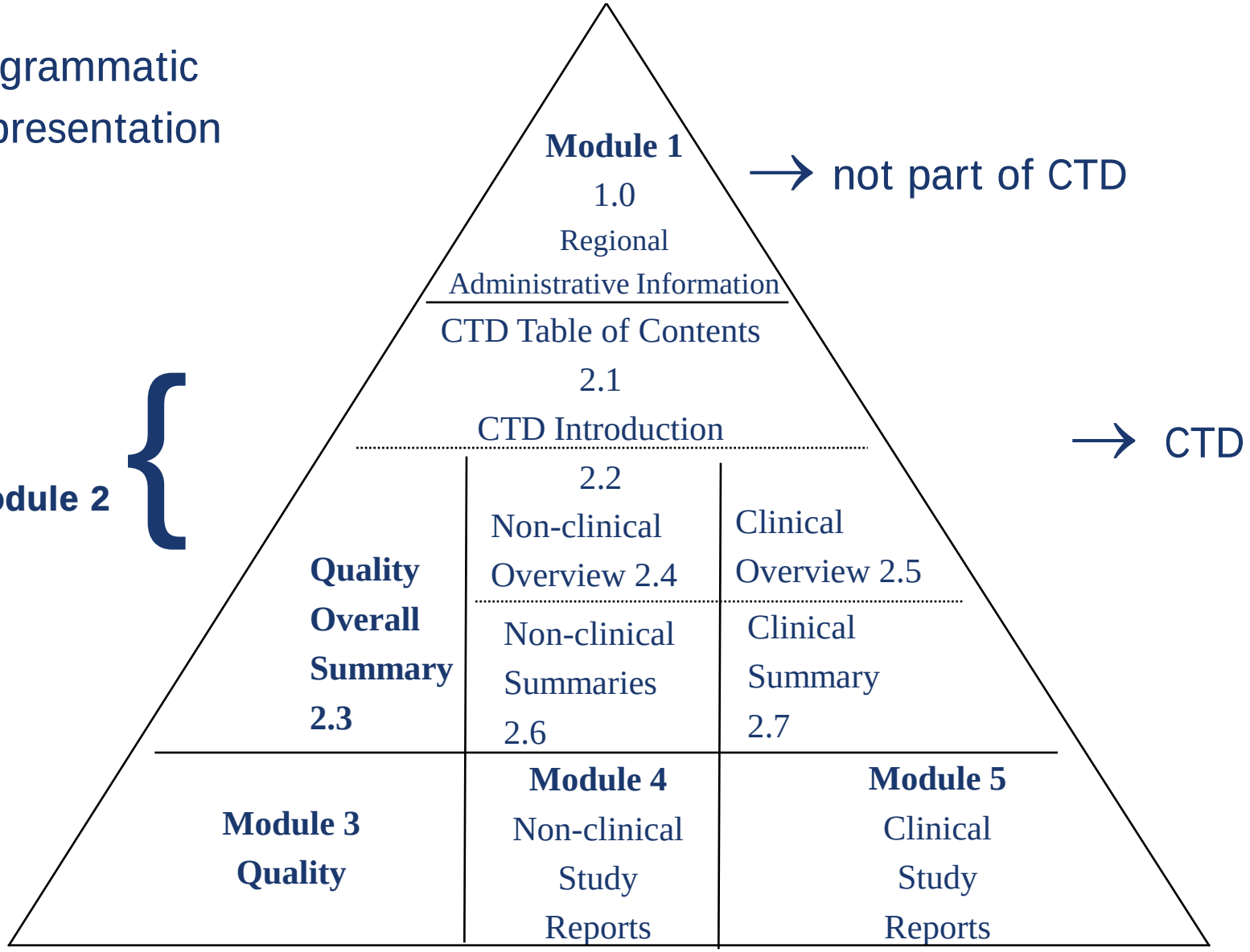
Format approvato a livello internazionale utilizzato:

- per la presentazione di domande di registrazione dei prodotti medicinali in Europa, USA e Giappone (regioni ICH)
- per tutte le tipologie di domande di registrazione (sia “full” che “abridged”)
- per tutte le categorie di prodotti medicinali (inclusi radiofarmaci, vaccini, herbals etc...)

Scopo del suo utilizzo è armonizzare le differenti filosofie regolatorie e i diversi approcci alla revisione dei dati salvaguardando tempo e risorse e facilitando la revisione da parte delle agenzie regolatorie migliorandone la comunicazione

  - Rif. Notice to Applicants vol. 2B - Presentation and content of the dossier

Diagrammatic Representation



What legislation controls medicines?

- EU Legislation - The body of EU legislation in the pharmaceutical sector is compiled in Volume 1 and 5 of the publication "Rules governing medicinal products in the EU http://ec.europa.eu/health/documents/eudralex/index_en.htm

- EU Directives are implemented through national legislation.

Normativa per l'autorizzazione all'immissione in commercio

Nel 2001 è stata emanata la Direttiva 2001/83/CE (successivamente modificata dalla Direttiva 2004/27/CE e dalla Direttiva 2010/84/UE e Regolamenti 1235/2010 e 520/2012 che modificano il Titolo IX – Farmacovigilanza) definita "*Codice comunitario*" in quanto raccoglie in un unico testo gran parte della normativa relativa ai medicinali per uso umano

La Direttiva 2001/83/CE, con le sue successive modifiche ed integrazioni, è stata recepita in Italia con il Decreto Legislativo 219/2006 e successivi emendamenti: L. 248/2006, D.P.R. n. 86/2007, D.L.vo 274/2007 e relativo errata corrige (G.U. 9/4/2008 n. 84), Legge n. 189 del 8 novembre 2012 (conversione D.L. Balduzzi)

Regolamento CE 726/2004 relativo alla *Procedura centralizzata*

Regolamento 1234/2008 relativo alle *Variazioni all'AIC* (in vigore dal 1/01/2010)

Rules governing Medicinal Products in the European Union

The '*Introduction and general principles*' of Annex I of Directive 2001/83/EC, as amended, defines the principles governing the assurance of quality of medicinal products:

(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.

(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

European Pharmacopoeia

- The texts of the European Pharmacopoeia (Ph. Eur.) concern the tests to be carried out on medicines, on the raw materials used in the production of medicines and on the intermediates of synthesis

- It contains texts covering substances, excipients as well as dosage forms and containers

Requirement for a substance consists of:

Specific monograph + relevant general monograph(s)

- Whole set of requirements define quality

Scientific guidelines

- Aim: guidance to industry and regulators providing a basis for practical harmonisation of assessment of scientific data in the dossier and facilitate the preparation of dossiers for MA by the Pharmaceutical industry
- Guidelines referred to in the legislation are applicable throughout the EU, irrespective of the procedure used (national, mutual recognition, decentralised, centralised)
- Guidelines are not legally binding as Ph. Eur (they are not legislation). Their purpose is to set out principles and general requirements that should be followed
- Important is the spirit of a Guideline: derogations can be acceptable provided that they are adequately justified
- Main tool used by regulators for assessment of applications
- Quality GLs are complementary to chapters and monographs of the Ph. Eur.

Assessment Report

- The template allows for a lot of cutting and pasting directly from the dossier, thus, there is a temptation to say simply ‘acceptable’ or ‘not acceptable’ resulting in a long, rather sterile document
- Remember to give a critical reasoned argument to say why it is not acceptable, in particular for major issue

AR should:

- ➢ Focus on value judgements rather than copy a simple summary of the dossier
- ➢ Highlight critical points, departures from guidelines etc. and adequately discuss them
- ➢ Give a clear overall conclusion
- ➢ Pose questions in a clear way

Relevance of questions is important

We should always:

- question whether the additional info requested will be of value to make an informed decision or is only confirmatory Example: requests for Certificates of Analysis for excipients, reagents, solvents, intermediates is considered to be of limited value since they only provide confirmatory info, important is the specifications of these materials, we should focus on them

- keep in mind the significance of each question. Ask yourself – what is the risk for the patient?

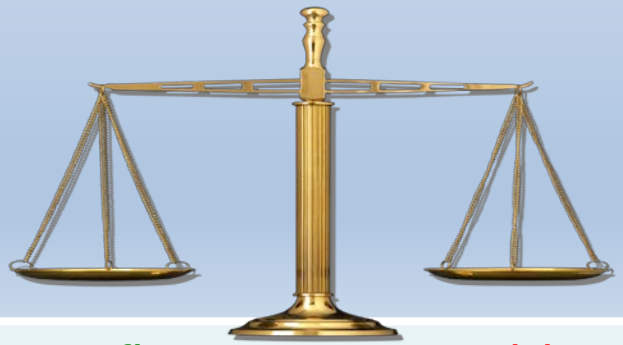
- look at other parts of the dossier . For example quality assessor consult with nonclinical & clinical colleagues in order to refine the judgment of the risk

- consider dropping issues that are clearly risk-free

Risk-Based Pharmaceutical Assessment in relation to Efficacy and Safety: examples

Active ingredient	**Main Reason for concern (i.e. Q in relation to..**	**Links to other parts of dossier to be consulted to determine a valid 'weighting factor' for the concern**
Particle size	Bioavailability - Efficacy	Link size distribution to that of material used in bioavailability studies/clinical trials M5
Polymorphism	Bioavailability - Efficacy	Link polymorph data to that of material used in bioavailability studies/clinical trials M4, M5
Impurities	Safety	Link to toxicology studies M4 Check all impurities are qualified.

Criteria for Authorising Medicines



Benefits Risks

The evaluation of Benefit-Risk balance of a product is based on the assessment of the registration dossier

MA is granted when the Benefit-Risk balance of a product is positive, meaning that benefits from use of this product outweigh risks associated with its use

How long is a Marketing Authorisation valid for?

A national Marketing Authorisation (MA) is initially valid for five years from the date of first authorisation.

At the end of the five year period it will be subject to renewal, which is a mechanism for reviewing the product to ensure the benefit/risk balance remains favourable. This review takes into consideration any further information obtained about the product from the experience gained of its use since it was first authorised, e.g. pharmacovigilance data. This is to ensure that the product's MA is still appropriate.

Following this review the MA will be valid indefinately, or the MAH will be asked to submit another renewal in a further five year's time.

How can a product be authorised?

There are four different routes to obtaining a Marketing Authorisation

- National
- Mutual Recognition (MRP)
- Decentralised (DCP)
- Centralised (CP)

These routes determine the procedures, processes and timelines used in progressing an application for a new MA in accordance with EU legislation.

Once granted, the authorisation will be classified as

- nationally authorised, assessed and approved on a national basis only
- mutually recognised (MRP and DCP) assessed and approved at a European level involving at least two Member States
- centrally authorised assessed and approved on a community level involving all EU Member States

Legal basis (e.g. generic application): determines the documentation to be submitted

What is the centralised procedure?

- The centralised procedure is a European authorisation route resulting in a centrally authorised product with a single Marketing Authorisation.
- If a product has been authorised using the centralised procedure it has been assessed on an EU wide basis and approved by the European Commission. The European Medicines Agency (EMA) organises the process of evaluation using scientific expertise from the Member States.
- The centralised procedure is mandatory for some products and optional for others.

What is the Mutual Recognition procedure?

- The mutual recognition procedure (MRP) is a European authorisation route resulting in a mutually recognised product.
- Mutual recognition must be used when a product is already authorised in at least one Member State on a national basis and the Marketing Authorisation Holder wishes to obtain a Marketing Authorisation (MA) for the same product in at least one other Member State.
- The Member State that has already authorised the product is known as the Reference Member State (RMS). The RMS submits their evaluation of the product to other Member State/s, these are known as Concerned Member States (CMS). The CMS is asked to mutually recognise the MA of the RMS.
- If the applicant is successful, the CMS will then issue a MA for that product permitting the marketing of that product in their country.

What is the Decentralised procedure?

- The decentralised procedure (DCP) is a European authorisation route resulting in a mutually recognised product (MRP).
- The difference between MRP and DCP is that a product must already be authorised in at least one Member State on a national basis in order for MRP to be used. DCP may be used if the product is not already authorised in any Member State (MS), but does not want to use the centralised procedure, or the product is not eligible for the centralised procedure.
- One of the proposed MSs will be asked by the applicant company to act as Reference Member State (RMS). The RMS does the initial evaluation of the product and issues a draft assessment report. The other MSs, known as the Concerned Member States (CMS), either agree with the RMS's evaluation or they ask further questions/raise objections.
- If all the issues are resolved and the application is successful, each MS will then issue a MA for that product permitting it to be marketed in their country.

Co-ordination group for mutual recognition and decentralised procedure – human (CMDh)

- Article 27 of Directive 2001/83/EC of the European Parliament and of the Council on the Union code relating to medicinal products for human use as amended, establishes the coordination group for examination of any question relating to a marketing authorisation of a medicinal product in two or more Member States.

- 1 member + 1 alternate (recommended) nominated by each of 28 MSs

- Main task: the coordination group shall consider points of disagreement raised by Member States during mutual recognition or decentralised procedures, in relation to the assessment report, Summary of Product Characteristics, Labelling and Package Leaflet of a medicinal product on the grounds of potential serious risk to public health and make every effort to resolve issues to avoid referrals to the Committee for Medicinal Products for Human Use (CHMP) or the Committee on Herbal Medicinal Products (HMPC) for arbitration.

Flow Chart for MRP

Approx 90 days before submission to CMS	Applicant requests RMS to update Assessment Report (AR) and allocate procedure number
Day -14	Applicant submits the dossier to CMS. RMS circulates the AR including SmPC, PL and labelling to CMSs. Validation of the application by CMSs
Day 0	RMS starts the procedure
Day 30	CMSs send their comments to the RMS, CMSs and applicant
Day 40	Applicant sends the response document to CMSs and RMS
Until Day 48	RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 55	CMSs send their remaining comments to RMS, CMS and applicant
Day 55-59	The applicant and RMS are in close contact to clarify if the procedure can be closed at day 60 or if the applicant should submit a further response at day 60.
Day 60	If CMS have no remaining comments at Day 55, the RMS closes the procedure. In case a CMS has remaining comments (MRP) or PSRPH (RUP) at Day 55, the applicant sends the response document to CMSs and RMS.

... (2) Flow Chart for MRP

Day 60-90	The period 60-90 will only be used if a CMS has remaining comments (MRP) at Day 55.
Until day 68	RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 75	CMSs send their remaining comments to RMS, CMSs and applicant.
Until Day 80	A break-out session (BOS) can be organised around Day 75 (but may take place between days 73-80)
Day 85	CMSs send any remaining comments to RMS, CMS and applicant.
Day 90	CMS notify RMS and applicant of final position (and in case of negative position also the CMDh secretariat of the EMA) If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMSs are referred to CMDh by the RMS within 7 days after day 90
Day 150	Final position adopted by the CMDh: If consensus is reached at the level of CMDh, the RMS closes the procedure. If consensus is not reached at the level of CMDh, the RMS refers immediately the matter to EMA for CHMP arbitration
5 days after close procedure	Applicant sends high quality national translations of SmPC, PL and labelling to CMSs
30 days after close procedure	Granting of national marketing authorisations in the CMSs subject to submission of acceptable translations.

Flow Chart for DCP - step I

Before Day -14	Applicant discussions with RMS RMS allocates procedure number. Creation in CTS.
Day –14	Submission of the dossier to the RMS and CMSs Validation of the application. Positive validation should only be indicated in CTS, not via e-mail.
Assessment step I	
Day 0	RMS starts the procedure. The CMS are informed via CTS
Day 70	RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SmPC, PL and labelling) on the dossier to the CMSs and the applicant
Until Day 100	CMSs send their comments to the RMS, CMSs and applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments
Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.
Clock-off period	Applicant may send draft responses to the RMS and agrees the date with the RMS for submission of the final response. Applicant sends the final response document to the RMS and CMSs within a period of 3 months, which can be extended by a further 3 months.
Day 106	RMS restarts the procedure following the receipt of a valid response or expiry of the agreed clock-stop period if a response has not been received. The CMS are informed via e-mail and CTS will be updated accordingly.

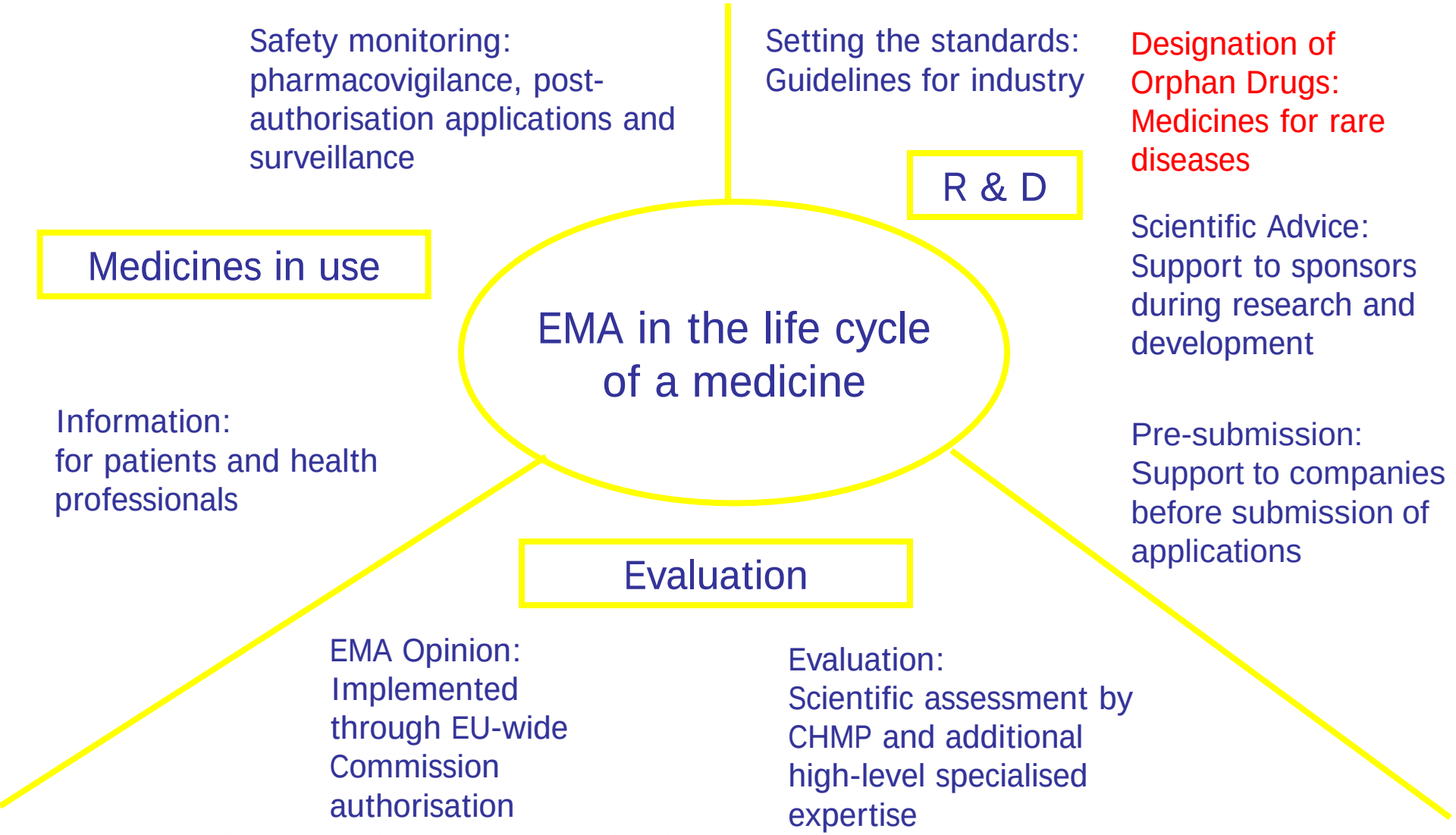
Flow Chart for DCP – step II

Assessment step II	
Day 120 (Day 0)	RMS sends the DAR, draft SmPC, draft labelling and draft PL to CMSs and the applicant
Day 145 (Day 25)	CMSs send comments to RMS, CMSs and the applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments.
Day 150 (Day 30)	RMS may close procedure if consensus reached Proceed to national 30 days step for granting MA
Day 160	Applicant sends the response document to CMSs and RMS
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification, prepare a short report and forward it to the CMSs and the applicant
Day 195 (at the latest)	A Break-Out Session (BOS) may be held at the European Medicines Agency with the involved MSs to reach consensus on the major outstanding issues
Between Day 195 and Day 210	RMS consults with the CMSs and the applicant to discuss the remaining comments raised.

Flow Chart for DCP – final steps

Day 210 (Day 90)	-If consensus is reached: - In case of positive position from RMS, Closure of the procedure including CMSs approval of assessment report, SmPC, labelling and PL, and proceed to national 30 days step for granting the MA. -In case of negative position from the RMS, Closure of the procedure negatively. The End of Procedure letter plus final Day 210 overview AR is circulated. - If consensus is not reached: In case of negative position from CMS, CMS notify the RMS, the other CMSs, applicant and the secretariat of the Co-ordination group (CMDh). Referral to the CMDh.
At the latest, within 7 days after Day 210	If consensus on a positive RMS AR was not reached at day 210, the points of disagreement submitted by CMS will be referred by the RMS to the CMDh for resolution
Day 270 (at the latest)	Final position adopted by CMDh with referral to CHMP/CVMP for arbitration in case of unsolved disagreement
National step	
7 days after close of procedure	Applicant sends high quality national translations of SmPC, labelling and PL to CMSs and RMS
30 days after close of the procedure	Granting of national marketing authorisation (MA) in RMS and CMSs if outcome is positive and there is no referral to the CMDh. (National Agencies will adopt the decision and will issue the MAs subject to submission of acceptable translations).
30 days after close of CMD referral procedure	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the CMDh and no referral to the CHMP/CVMP. (National Agencies will adopt the decision and will issue the MAs subject to submission of acceptable translations).

EMA ROLE IN HUMAN MEDICINES FIELD



Centralised procedure

Review process for approval of a medicinal product in EU:

- 1 marketing authorisation valid in EU (1 fee to EMA)
- 1 invented name
- 1 common labelling: all EU languages
- Max. time limit: 210 calendar days
- Peer reviewed
- Transparent system (e.g. European Public Assessment Reports)

Better utilisation of resources (EU network of experts)
- Shared scientific opinions
- Harmonised information to Physicians/Patients
- Access at the same time to potentially nearly half a billion users

Regulation EC No 726/2004

REGULATION (EC) N. 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down Community procedures for the authorisation and supervision (and pharmacovigilance) of medicinal products for human and veterinary use and establishing a European Medicines Agency (EMEA – now EMA)

- Establishment of a Committee for Medicinal Products for Human Use (CHMP)
- Definition of mandatory scope/optional procedure

Mandatory scope

- Biotech products
- Advanced therapy medicinal products as defined in Art. 2 of Reg.(EC) No 1394/2007 (Gene therapy, Somatic cell therapy medicinal products, Tissue engineered products)
- Orphan designated products (Reg. (EC) No 141/2000)
- New active substance (NAS) for:
  - Acquired immune deficiency syndrome (AIDS)
  - Cancer
  - Neurodegenerative disorders (e.g. multiple sclerosis)
  - Diabetes

  Since 2008 also for:
  - Autoimmune diseases (Chron's disease)
  - Viral diseases (e.g. anti hepatis C)

Optional scope

- A medicinal product containing a new active substance which, on the day of entry into force of the Regulation (20 November 2005) was not authorised in the Community (Article 3(2)a)

  i.e. new active substance in a non-mandatory therapeutic area, *e.g. Rasilez (aliskiren) in treatment of hypertension*

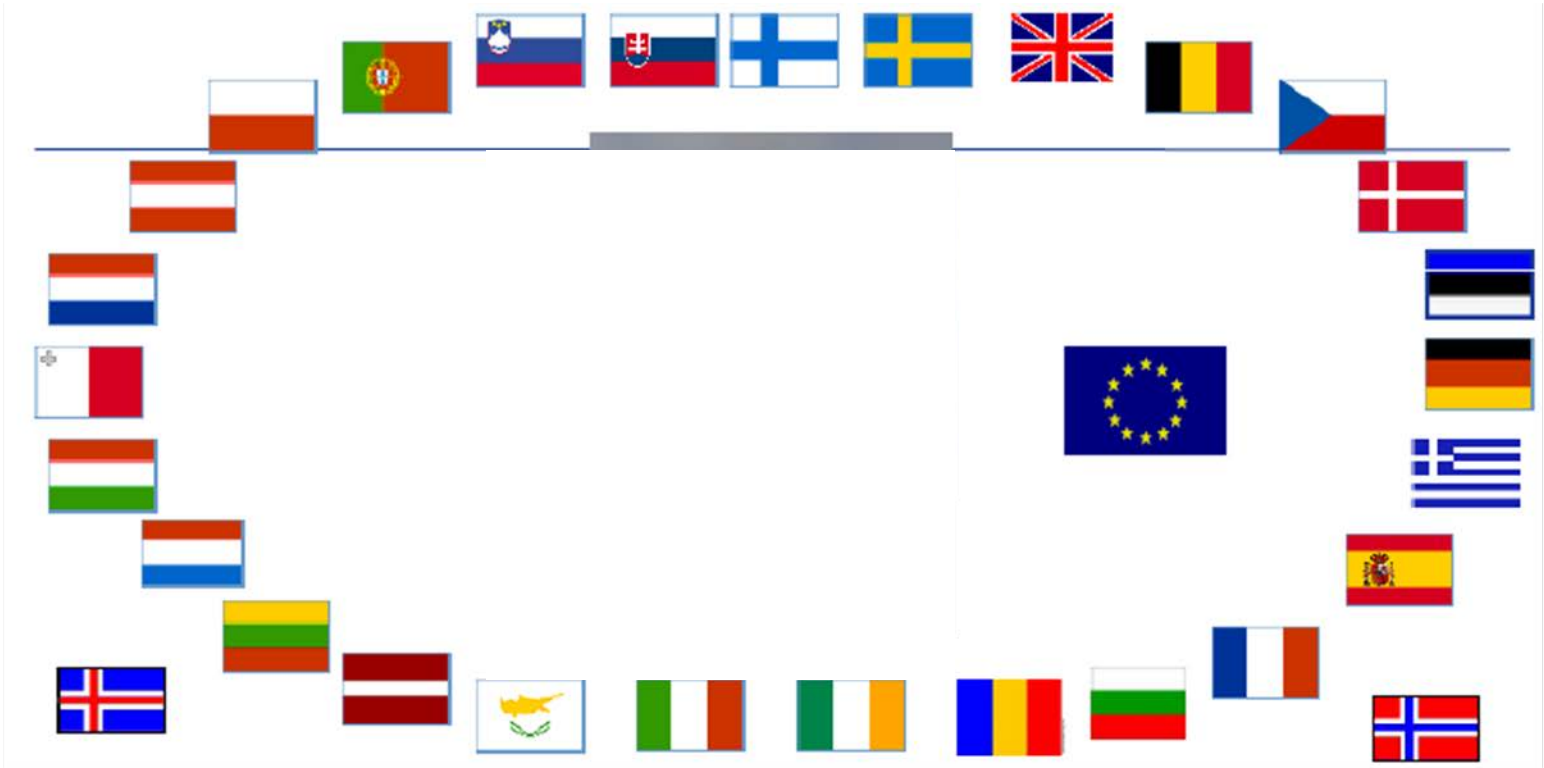
- A medicinal product, which constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation is in the interest of patients at Community level (Article 3(2)b), e.g. “old” substances for new:

  - therapeutic indications e.g. *Thalidomide Celgene for the treatment of multiple myeloma*

  - pharmaceutical forms e.g. *Adasuve (loxapine) inhalation powder for rapid control of agitation in adult with schizophrenia or bipolar disorder*

- Generic/Hybrid of centralised medicinal product applications (Article 3(3))

CHMP - Human Medicines



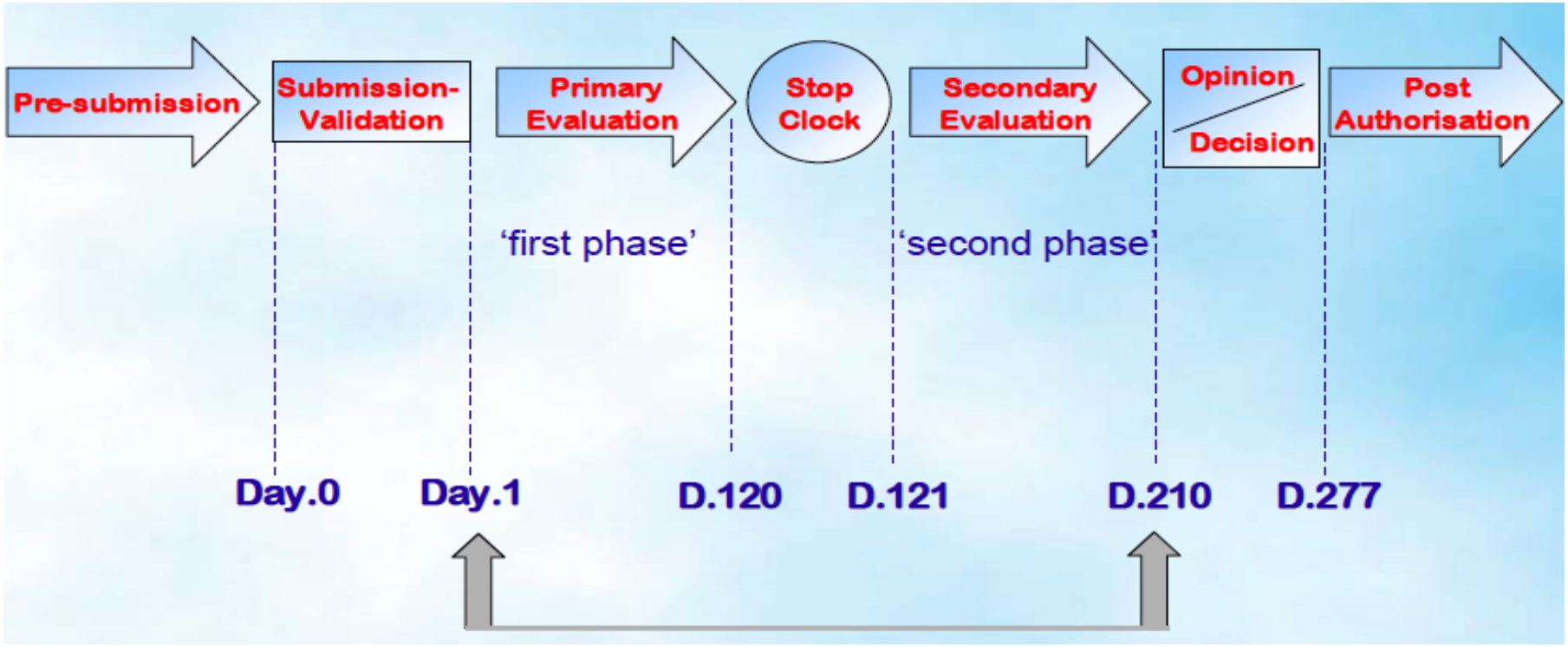
1 scientific expert member + 1 alternate nominated by each of 28 MSs
1 scientific expert member from NO and IS and 1 alternate (observers)
5 co-opted members as appointed by Management Board
1 chairman + 1 vice chairman + supportive staff
4-day monthly meetings


Committee on Advanced Therapy CAT (since 2008)
Committee on Orphan Medicinal Products COMP
Pharmacovigilance and Risk Assessment Committee PRAC (since 2012)
Paediatric Committee PDCO
Committee on Herbal Medicinal Products HMPC
Ad-hoc Inspections (GMP, GCP, GVP)
Quality Review of Documents
Invented Names Review Group
Scientific Advice WP (Stand)
Safety WP (Stand)
Biologics WP (Stand)
Patients' and Consumers' Organisations WP (Stand)
Joint CHMP/CVMP Quality WP (Stand)
Pharmacogenomics WP (Temp)
Vaccine WP (Temp)
Biostatistics WP (Temp)
Biosimilar WP (Temp)
Blood Products WP (Temp)
CHMP Working Parties (WP) and other Committees
Other Temporary WPs:
- Cardiovascular
- Central Nervous System
- Infectious diseases
- Oncology
- Pharmacokinetics
-Rheumatology/Immunology
Drafting Groups:
- Gastroenterology
- Radiopharmaceuticals
- Respiratory
- Urology
SAGs:
- Anti-Infectives
- Neurology
- Psychiatry
- Psychiatry
- Diabetes/Endrocrinology
- HIV/Viral Diseases
- Oncology
- Cardiovascular issues
- Vaccines

Centralised procedure – presubmission phase

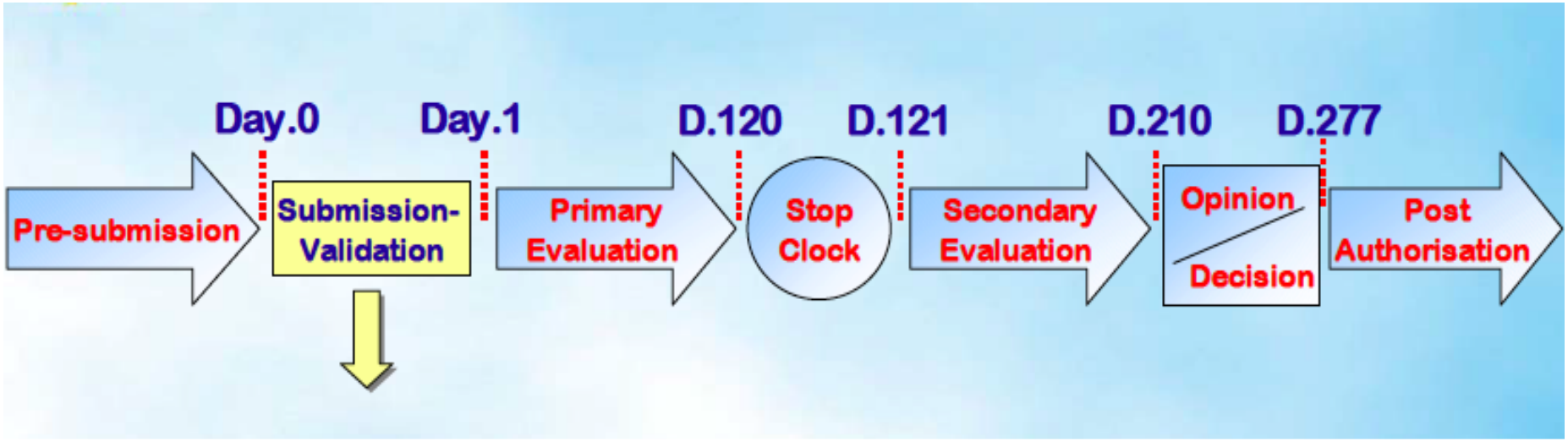
- Appointment of 1 Rapporteur and 1 Co-Rapporteur (CHMP/PRAC/CAT)
- Appointment of 1 Peer-Reviewer
- Nomination of the assessor team (staff of the NCA and external from academic world) with no or low level of conflict of interests, and inform EMA accordingly
- Pre-submission meetings between applicants and the EMA/(Co-) Rapporteur (several months prior to the anticipated date of submission of the application)
- Preparatory aspects of the dossier and scientific viewpoint

Centralised Procedure-Overview



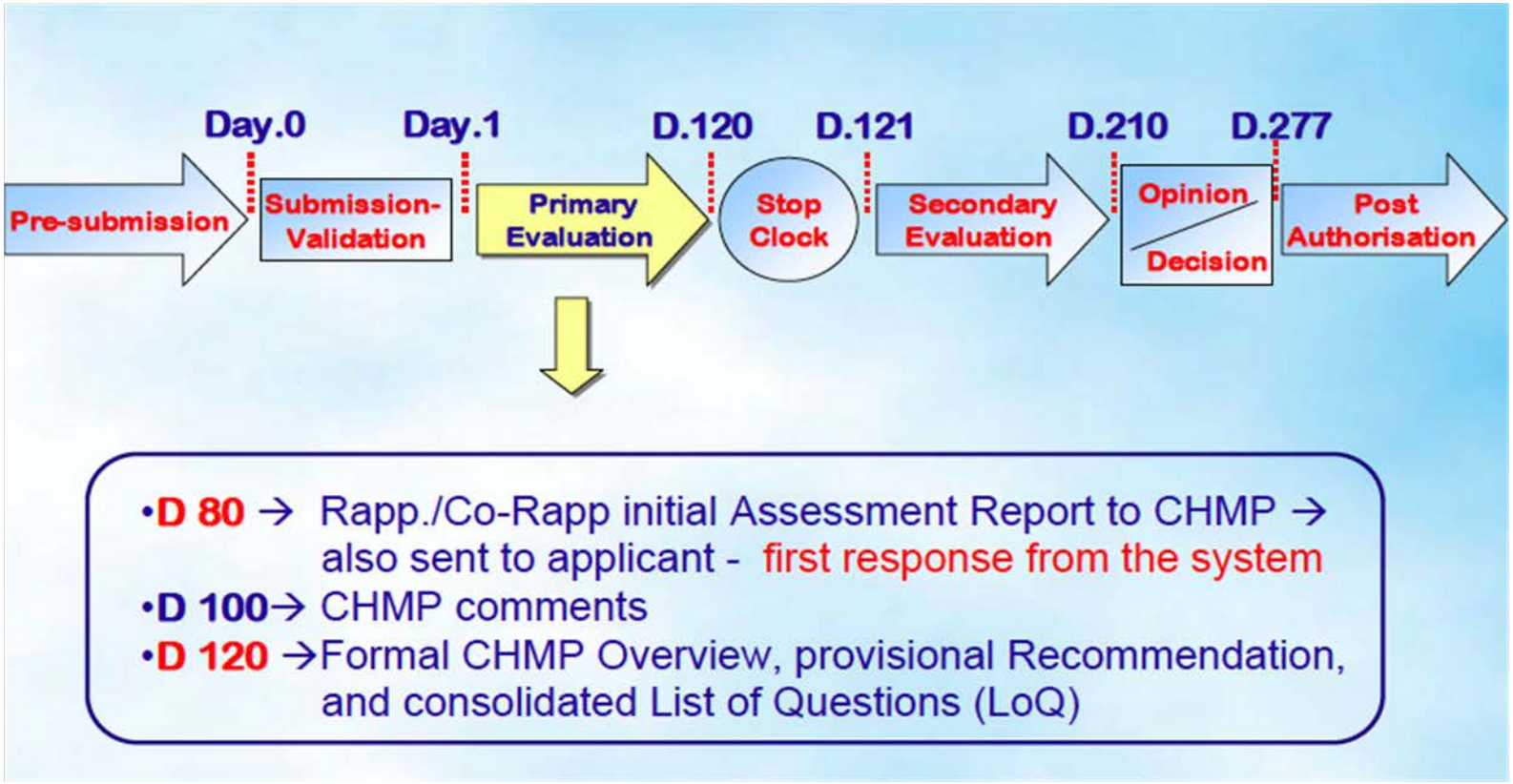
CHMP OPINION WITHIN 210 DAYS: LEGAL REQUIREMENT

Submission-Validation Phase

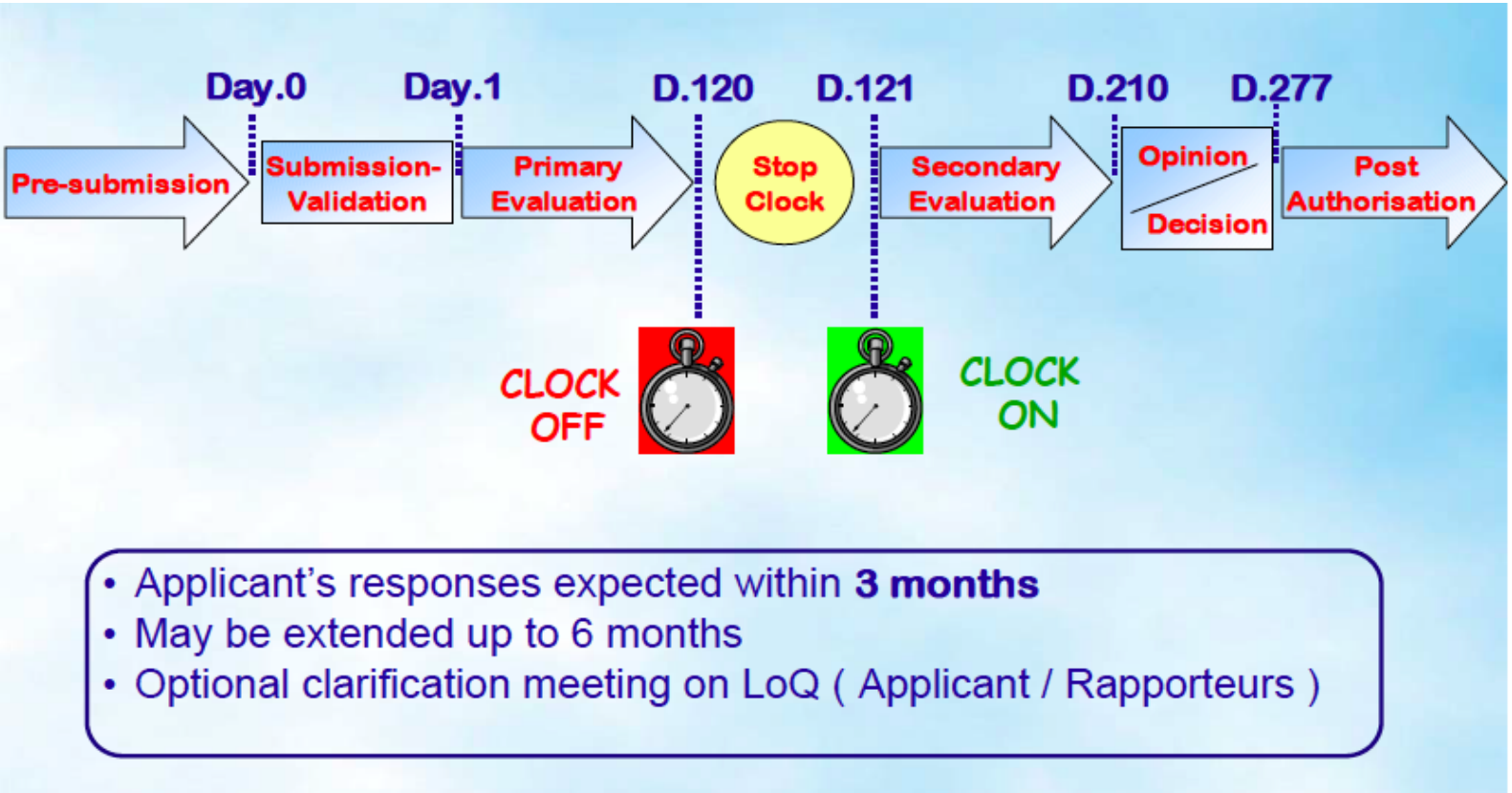


Submission:	Validation:
Applicant submits the dossier Dossier requirements are defined in the legislation and in relevant guidelines	Performed by EMA 10 working days from submission date No scientific evaluation, at this point Only check of: 1) completeness of the dossier 2) compliance with legal/regulatory requirements

Primary Evaluation Phase

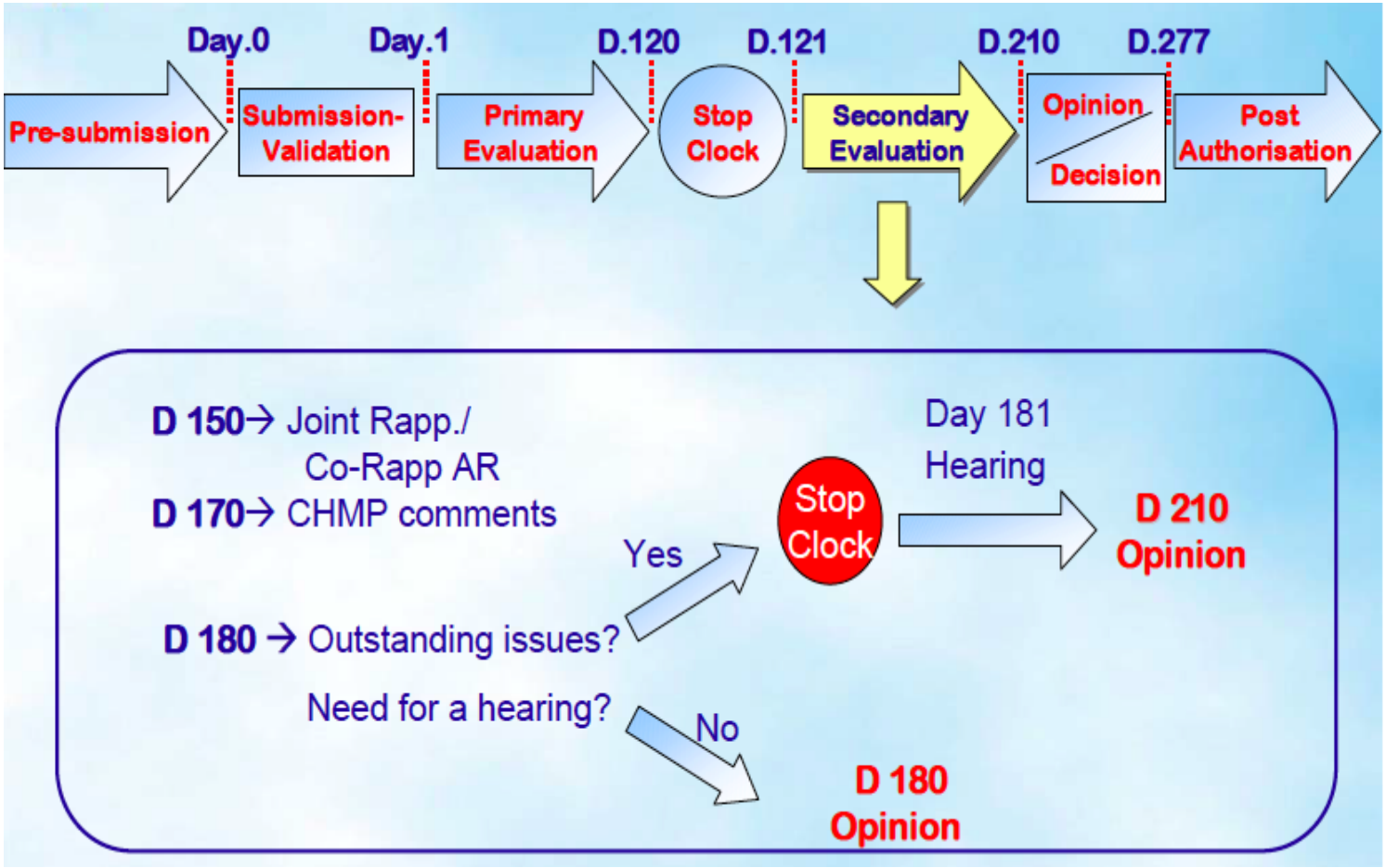


Clock-Stop



- Applicant's responses expected within **3 months**
- May be extended up to 6 months
- Optional clarification meeting on LoQ (Applicant / Rapporteurs)

Secondary Evaluation Phase



Types of Opinion

CHMP reaches an Opinion on the Benefit/Risk ratio involving evaluation of all Quality/Safety/Efficacy aspects:

- by consensus
- by majority (divergent positions reported in the Opinion)

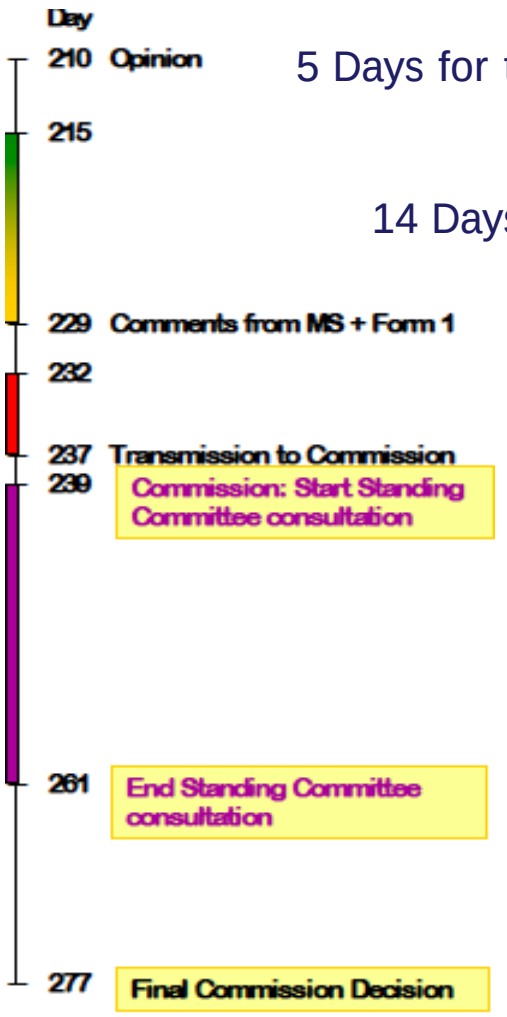
- Positive
- Negative (15 days to appeal, 60 days to submit grounds for appeal)
- Under Exceptional Circumstances
  - Comprehensive data cannot be provided
  - Reviewed annually to reassess the Benefit/Risk balance
- Conditional
  - Additional data is required, however the benefit to public health of immediate availability outweighs risk
  - Authorisation valid for one year, on a renewable basis
  - Once the pending studies are provided, it can become a “normal” marketing authorisation

Negative Opinion

In case of negative opinion: re-examination procedure

- the Applicant has 15 days to appeal and 60 days to submit grounds for appeal (no new data);
- the CHMP has 60 days to re-examine

Post-opinion Phase: 67 days



5 Days for the MAH to translate the labelling

14 Days to check translation

Implementation of corrections by the MAH (3 Days) and final check by the EMA (5 Days)

EC Decision Making Process
Preparation of EPAR: scientific assessment report w/o information of commercially confidential nature

Publication on EU Official Journal

EPAR- European Public Assessment Report

= CHMP Assessment Report after deletion of information of commercially confidential nature

Summary = All readers

Authorised presentations = All readers

Package leaflet = Patients

Summary of Product Characteristics = Health professionals

Labelling = Pharmacists/patients

Authorisation Scientific Basis = Scientific community/Health prof.

Steps taken for the assessment = Anyone interested

Steps taken after granting the MA = Anyone interested

 available in all EU languages

 available in English

Accelerated procedure

"Major public health interest" = addressing the "greater unmet medical needs" (Opinion in 150 days):

-Serious, chronically debilitating, or life-threatening conditions
-Alternatives are not available
-Expectation of exceptionally high benefit (dramatic effect)

Items to be addressed:

- the unmet needs and the available methods of prevention, diagnosis or treatment
- the extent to which the medicinal product is expected to have major impact on medical practice, its major added value, and/or how it addresses the greater unmet needs
- a brief outline of the main available evidence on which the applicant bases its claim of major public health interest

Approvals subject to post-approval specific obligations/commitments - 1

Conditional Marketing Authorisation	Marketing Authorisation under Exceptional Circumstances
Authorisation before the availability of comprehensive data in order to address unmet medical needs. Comprehensive data are still being generated post authorisation in agreed timelines.	Authorisation when comprehensive data on the efficacy and safety cannot be obtained, but it is still appropriate to grant the authorisation due to exceptional circumstances.
Medicinal products without comprehensive data belonging to at least one of the following categories: • Seriously debilitating diseases or life-threatening diseases, • Emergency situations, • Orphan medicinal products • and fulfilling all of the following criteria:	Medicinal products without comprehensive data on the efficacy and safety under normal conditions of use, because: • Indications encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or • In the present state of scientific knowledge, comprehensive information cannot be provided, or

Approvals subject to post-approval specific obligations/commitments - 2

Conditional Marketing Authorisation	Marketing Authorisation under Exceptional Circumstances
• Positive risk-benefit balance • Applicant likely to be able to provide comprehensive data • Fulfilment of unmet medical need. • Benefits of immediate availability outweigh the risks that additional data are still required	• It would be contrary to generally accepted principles of medical ethics to collect such information
Authorisation valid for one year, to be renewed annually based on reconfirmation of the benefit-risk balance	Authorisation initially valid for 5 years (renewable), but the status of fulfilment of the specific obligations and the impact of the specific obligations' data on the benefit / risk balance is to be reassessed annually
Once the comprehensive data are provided, it can become a "standard" marketing authorisation	Will normally not lead to the completion of a full dossier and become a "standard" marketing authorisation

PROCEDURE NAZIONALI

LA DETERMINAZIONE DI AIC

E' autorizzata l'immissione in commercio del medicinale: “XXXXX", nelle forme e confezioni: "4 mg compresse masticabili" 28 compresse, alle condizioni e con le specificazioni di seguito indicate, a condizione che siano efficaci alla data di entrata in vigore della presente determinazione:

TITOLARE AIC: XXX S.r.l. con sede legale e domicilio fiscale in 00100 - ROMA, Via aaaaa, 59, Codice Fiscale 000000000.

Confezione: "4 mg compresse masticabili" 28 compresse

AIC n° 045342019

Forma Farmaceutica: Compressa masticabile

Validità Prodotto Integro: 2 anni dalla data di fabbricazione

Produttore del principio attivo: NOME e INDIRIZZO

Produttore del prodotto finito:

a) NOME e INDIRIZZO (produzione, confezionamento, controllo e rilascio lotti);

b) NOME e INDIRIZZO (confezionamento primario e secondario);

c) NOME e INDIRIZZO (applicazione bollino ottico).

continua .....

LA DETERMINAZIONE DI AIC

.... segue

Composizione: Una compressa masticabile contiene:

Principio attivo: zzzzz sodico 4,152 mg equivalente a 4 mg di zzzzz

Eccipienti: mannitolo (E421) 172,8 mg; cellulosa microcristallina 48,0 mg; croscarmellosa sodica 9,6 mg; ferro ossido rosso (E172) 0,288 mg; idrossipropilcellulosa 0,72 mg; aroma ciliegia 0,792 mg; aspartame (E951) 1,2 mg; magnesio stearato 2,4 mg.

NB: la composizione quantitativa in termini di eccipienti è confidenziale e non può essre pubblicata.

Indicazioni Terapeutiche: .....

continua .....

LA DETERMINAZIONE DI AIC

Le confezioni del medicinale devono essere poste in commercio con etichette e fogli illustrativi conformi al testo allegato alla presente determinazione.

E' approvato il **riassunto delle caratteristiche del prodotto** allegato alla presente determinazione.

In ottemperanza all'art. 80 commi 1 e 3 del decreto legislativo 24 aprile 2006, n. 219 e s.m.i. il foglio illustrativo e le etichette devono essere redatti in lingua italiana e, limitatamente ai medicinali in commercio nella provincia di Bolzano, anche in lingua tedesca. Il Titolare dell'AIC che intende avvalersi dell'uso complementare di lingue estere, deve darne preventiva comunicazione all'AIFA e tenere a disposizione la traduzione giurata dei testi in lingua tedesca e/o in altra lingua estera. In caso di inosservanza delle disposizioni sull'etichettatura e sul foglio illustrativo si applicano le sanzioni di cui all'art. 82 del suddetto decreto legislativo.

Allegato D.Lgs. 219/2006

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO (1)

1. Denominazione del medicinale seguita dal dosaggio e dalla forma farmaceutica.
2. Composizione qualitativa e quantitativa in termini di sostanze attive ed eccipienti la cui conoscenza sia necessaria per una corretta somministrazione del medicinale. Sono utilizzate la denominazione comune usuale o la descrizione chimica.
3. Forma farmaceutica:
4. Informazioni cliniche:
   - 4.1 Indicazioni terapeutiche;
   - 4.2 Posologia e modo di somministrazione per adulti e, qualora necessario, per bambini;
   - 4.3 Controindicazioni;
   - 4.4 Avvertenze speciali e opportune precauzioni d'impiego e, per i medicinali immunologici, precauzioni speciali per le persone che manipolano detti medicinali e che li somministrano ai pazienti, nonche' eventuali precauzioni che devono essere prese dal paziente;
   - 4.5 Interazioni con altri medicinali e altre forme di interazione;
   - 4.6 Gravidanza ed allattamento;
   - 4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari;

Allegato D.Lgs. 219/2006

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO (2)

4.8 Effetti indesiderati;

4.9 Sovradosaggio (sintomi, procedure di primo intervento, antidoti).

5. Proprietà farmacologiche:

5.1 Proprietà farmacodinamiche;

5.2 Proprietà farmacocinetiche;

5.3 Dati preclinici di sicurezza.

6. Informazioni farmaceutiche:

6.1 Elenco degli eccipienti;

6.2 Incompatibilità;

6.3 Periodo di validità, all'occorrenza specificare il periodo di validità dopo la ricostituzione del medicinale o dopo che il confezionamento primario sia stato aperto per la prima volta;

6.4 Speciali precauzioni per la conservazione;

6.5 Natura del confezionamento primario e contenuto della confezione;

6.6 Eventuali precauzioni particolari da prendere per l'eliminazione del medicinale utilizzato e dei rifiuti derivati da tale medicinale.

Allegato D.Lgs. 219/2006

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO (3)

7. Titolare dell'AIC.
8. Numero dell'AIC o numeri delle AIC.
9. Data della prima autorizzazione o del rinnovo dell'autorizzazione.
10. Data di revisione del testo.
11. Per i radiofarmaci, dati completi sulla dosimetria interna della radiazione.
12. Per i radiofarmaci, ulteriori istruzioni dettagliate sulla preparazione estemporanea e sul controllo di qualità della preparazione e, se occorre, il periodo massimo di conservazione durante il quale qualsiasi preparazione intermedia, come un eluato, o il radiofarmaco pronto per l'uso si mantiene conforme alle specifiche previste.

D.Lgs. 219/2006
FOGLIO ILLUSTRATIVO (1)

Art. 77

Contenuto del foglio illustrativo

1. Il foglio illustrativo e' redatto in conformità al riassunto delle caratteristiche del prodotto; esso contiene, nell'ordine seguente:

a) per l'identificazione del medicinale:

1) la denominazione del medicinale, seguita dal dosaggio e dalla forma farmaceutica, ed eventualmente se esso e' indicato per prima infanzia, bambini o adulti; quando il medicinale contiene un'unica sostanza attiva e porta un nome di fantasia, deve figurare la denominazione comune;

2) la categoria farmacoterapeutica o il tipo di attività, redatte in termini facilmente comprensibili per il paziente;

b) le indicazioni terapeutiche;

D.Lgs. 219/2006
FOGLIO ILLUSTRATIVO (2)

c) una lista delle informazioni da conoscere prima di assumere il medicinale:

1) controindicazioni;
2) appropriate precauzioni d'uso;
3) interazioni con altri medicinali e altre forme di interazione (ad esempio con alcool, tabacco, alimenti), che possono influire sull'azione del medicinale;
4) avvertenze speciali;

d) le istruzioni necessarie e consuete per un uso corretto e, in particolare:

1) posologia;
2) modo e, se necessario, via di somministrazione;
3) frequenza della somministrazione, precisando, se necessario, il momento appropriato in cui il medicinale può o deve essere somministrato, e all'occorrenza, in relazione alla natura del prodotto;
4) durata del trattamento, se deve essere limitata;

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FOGLIO ILLUSTRATIVO (3)

5) azioni da compiere in caso di dose eccessiva (ad esempio: descrizione dei sintomi di riconoscimento e dell'intervento di primo soccorso);
6) condotta da seguire nel caso in cui sia stata omessa l'assunzione di una o più dosi;
7) indicazione, se necessario, del rischio di effetti conseguenti alla sospensione del medicinale;
8) specifica raccomandazione a rivolgersi al medico o al farmacista per ottenere opportuni chiarimenti sull'uso del medicinale;

e) una descrizione degli effetti indesiderati che si possono verificare con il normale uso del medicinale e, se necessario, delle misure da adottare; il paziente dovrebbe essere espressamente invitato a comunicare al proprio medico o farmacista qualsiasi effetto indesiderato non descritto nel foglio illustrativo;

D.Lgs. 219/2006
FOGLIO ILLUSTRATIVO (4)

f) un riferimento alla data di scadenza che figura sull'etichetta, seguito dagli elementi sottospecificati:

1) un'avvertenza contro l'uso del medicinale successivamente a tale data;
2) all'occorrenza, le precauzioni speciali da prendere per la conservazione del medicinale;
3) all'occorrenza, un'avvertenza relativa a particolari segni visibili di deterioramento;
4) la composizione qualitativa completa, in termini di sostanze attive ed eccipienti, nonche' la composizione quantitativa in termini di sostanze attive, fornite impiegando le denominazioni comuni, per ogni presentazione del medicinale;
5) la forma farmaceutica e il contenuto in peso, in volume o in unità posologiche, per ogni presentazione del medicinale;
6) il nome e l'indirizzo del titolare dell'AIC;
7) il nome e l'indirizzo del produttore;

g) quando il medicinale e' autorizzato ai sensi del capo V del titolo III con nomi diversi negli Stati membri della Comunità europea interessati, un elenco con il nome autorizzato in ciascuno degli Stati membri;

h) la data in cui il foglio illustrativo e' stato revisionato l'ultima volta.

Guideline on the readability of the labelling and package leaflet of medicianal products for human use

Il foglio illustrativo è stato pensato per essere uno strumento informativo indirizzato all'utilizzatore al fine di consentire un uso corretto e consapevole del medicinale.

Per questo, il coinvolgimento diretto dei consumatori/pazienti nella verifica della leggibilità può essere considerato un aspetto importante per attestare la qualità informativa del foglio.

A questo proposito il codice comunitario introduce l'obbligo di condurre dei test di leggibilità e stabilisce che "il foglio illustrativo deve riflettere il risultato di indagini compiute su gruppi mirati di pazienti al fine di assicurare che esso sia leggibile, chiaro e di facile impiego".

Per questo dovrà essere testato sia nel suo aspetto grafico (il layout e la reperibilità delle informazioni nel testo) sia nel contenuto e nel linguaggio utilizzato.

Per condurre questi test le aziende hanno a disposizione la linea guida, con precisi requisiti da rispettare che sono poi gli elementi che l'autorità regolatoria valuta per approvare o respingere il test e il relativo foglio illustrativo.

Il fine è quello di trasformare il foglio illustrativo in un vero strumento di educazione al momento dell'assunzione del farmaco.


QUEL FARMACO CHE MI HA DATO PER DORMIRE E' UNA MERAVIGLIA !
QUINDI SEGUE CORRETTAMENTE LA MIA CURA...
NO, BASTA LEGGERE IL FOGLIETTO ILLUSTRATIVO PRIMA DI ANDARE A LETTO...

CONCLUSIONI

PROCEDURA	STATI MEMBRI COINVOLTI	TEMPI DI DEFINIZIONE	ORGANISMI INTERESSATI
CENTRALIZZATA	TUTTI GLI STATI DELL'UE	210 giorni	EMA COMMISSIONE UE STATI MEMBRI
NAZIONALE	Solo lo Stato in cui è presentata la domanda	210 giorni	AUTORITÀ NAZIONALE
MUTUO RICONOSCIMENTO	RMS CMSs	90 giorni	RMS CMSs – CMD (referral) EMA (arbitrato)
DECENTRATA	RMS CMSs	210 giorni	RMS CMSs – CMD(referral) EMA (arbitrato)

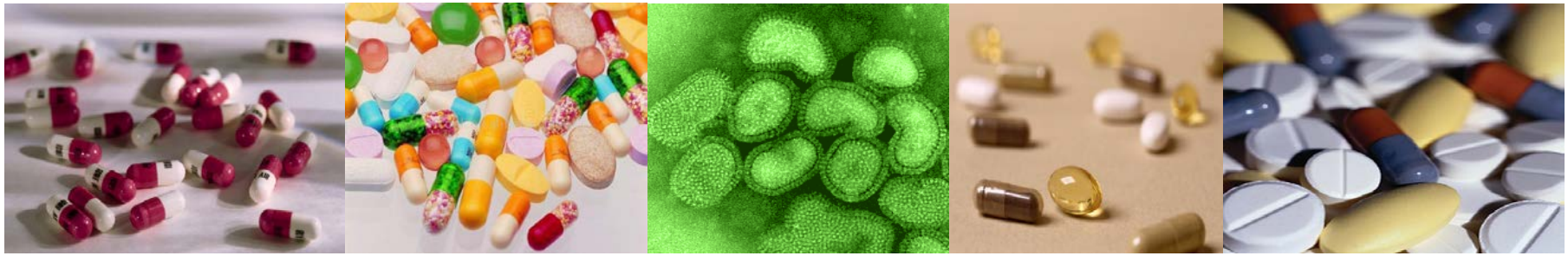
- Diverse tipologie di procedure autorizzative
- Medesimi requisiti: qualità, sicurezza ed efficacia
- Medesimo approccio: risk/benefit 
- Medesimo scopo: salute dei pazienti  

Useful addresses

EUROPEAN COMMISSION
http://ec.europa.eu/health/index_en.htm

EMA home page
http://www.ema.europa.eu/

EDQM Home page
http://www.edqm.eu/en/Homepage-628.html



Thanks

Any questions?
....but not too many!

Contact details
a.proietti@aifa.gov.it
http://www.aifa.gov.it/