Benefit-risk assessment for initial marketing authorisations and standard of evidence

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

March 9th 2018

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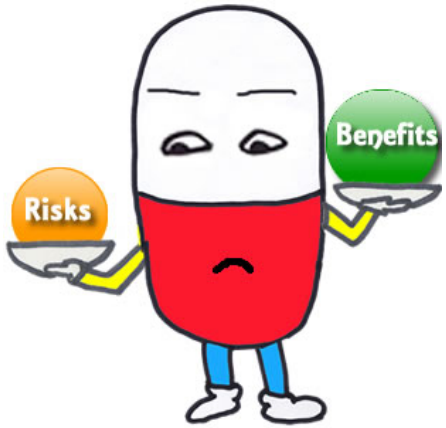
CHMP member SE



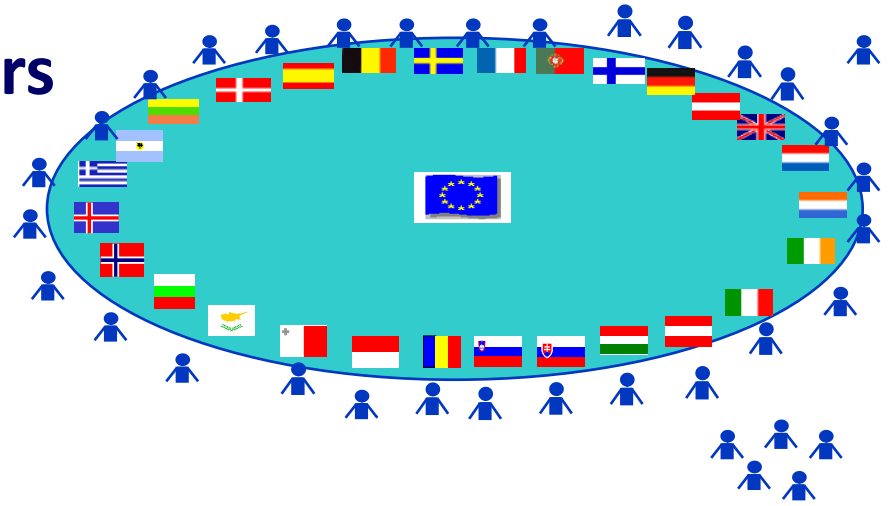
LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Assessment of Benefit Risk Balance of a medicinal product

- **Why do we do it and why is it important?**
- **How to do it?**
- **How to communicate and who are the recipients?**

Who is doing it? The CHMP

- 1 member/member state
- 1 alternate /member state
- 1 member from Iceland, Norway
- 5 (6) coopted members



Why do we do it and why is it important?

- **Final reflection/conclusion of our assessment of the data submitted**

- **Identify the condition, population(s), (conditions for use) for which it is established that benefits outweigh the risks**
  - BENEFITS MUST ALWAYS OUTWEIGH THE RISKS

How to do it?

- **Continuous process during the assessment procedure**
  - Day 80 (rapp and corapp), Day 120, D 180, end of procedure (CHMP)
- **Template and guidance to aid assessors**
- **Not easy!**

How to do it; challenges

- **Which results are most important?**
  - Scientific guidelines specify preferred primary and secondary enpoints
  - Obejctive vs subjective endpoints?
  - Surrogate endpoints?

- **How to decide the ”value” of a certain benefit or risk?**

- **How to weigh benefits against risks?**
  - Qualitative or quantitative analysis?

- **Absolute or relative benefit/risk assessment?**
  - Do we have to compare the new product to already available alternatives?

Therapeutic Context; what do we need to consider up front?

Disease or condition

- Applicants proposal for indication
- Aims of therapy (e.g. to prolong survival) and key efficacy endpoints

Available therapies and unmet medical need

- Be aware of main available treatment options
- Unmet need?

Main clinical studies

- Randomisation, blinding, control, dosing and study size

How to do it; structure of the B/R Section of our assessment reports

- **Benefits**
- **Benefits; uncertainties/limitations**
- **Risks**
- **Risks; uncertainties/limitations**
- **Benefit-risk assessment and discussion**

  Importance of favourable and unfavourable effects

  Balance of benefits and risk

  Additional considerations

Benefits

- **Describe key favourable effects** (primary and most important secondary endpoints)
  - Objective, subjective endpoints?

- Strive for clarity, e.g., a difference in median overall survival of 6.8 months was observed for treatment X compared to treatment Y, HR=0.8 (95% C.I.: 0.6, 0.9; log rank P=.001); use **quantitative data**

- Describing key effects in **important subgroups** (e.g. as defined by age, sex, ethnicity, organ function, disease severity, or genetic polymorphism)

- **Avoid interpretation and value judgements** (e.g., it was convincingly shown that overall survival was greatly improved for treatment X)
  - **Important that the Reader can understand the data and draw own conclusions**

Benefits; uncertainties and limitations

- Focus on important uncertainties that have an **impact in terms of benefit-risk** assessment or on **relevant parts of the SmPC**
  - Too small sample size, too broad confidence intervals, insufficient statistical significance,
  - Withdrawal patterns that may impact on the interpretation of the results
  - Appropriateness of statistical model, assay sensitivity
  - Representativeness of the target patient population
  - Choice of comparator
  - GCP compliance issues
  - Any specific aspects of formulation (composition or development) which impact the safe and effective use of the product
  - Inconsistent findings in important subgroups or in comparison to other products in the field

Risks

- **Describe key risks/ unfavourable effects** (incidence, severity, duration, reversibility, dose response relationship; incidence of adverse events leading to withdrawals and/or hospitalisations)

- Unfavourable effects in important **subgroups** (e.g. as defined by age, sex, ethnicity, organ function, disease severity, or genetic polymorphism)

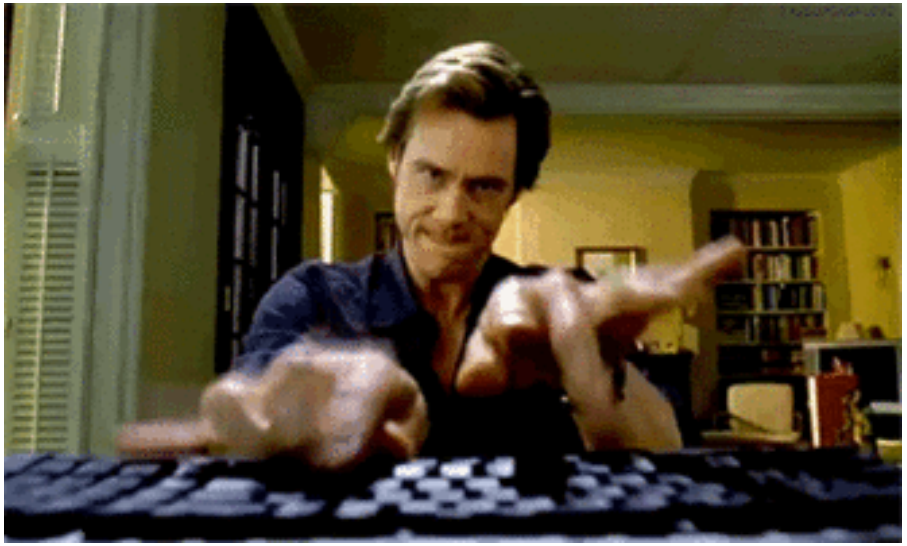
- **Quantitative and comparative data (**e.g., treatment X was associated with nauesa in 30% of patients, the incidence in the placebo group was 15%)

Risks; uncertainties and limitations

- Describe any important uncertainties and limitations about the knowledge of risks that is **important for the benefit-risk balance**
  - Sample size, duration of follow up
  - Type of control group
  - Missing data, discontinuations
  - Adequacy of monitoring

Benefit-risk assessment and discussion

This is where we use value judgements! Interpretation of the results; possibility to be creative!!



Importance of benefits and risk

- **Clinical relevance** of the **benefits**
  - Is the magnitude of the effect of clinical relevance?; what knowledge is this judgement based on (literature, clinical experience, previous approvals, expert meetings, patient consultations)
  - If **surrogate endpoints** have been used, what could be the expected outcome on the clinical endpoint?
- Importance of the **risks** for the patients with respect to severity, reversibility, treatment withdrawals ("what will it mean for the patient?")
  - Relation to severity of disease?
- **Impact of uncertainties and limitations** associated with benefits and risks; how will uncertainties be handled; eg warnings, restricted indication, follow up studies
- Do favourable and unfavourable effects differ between **subgroups** of the proposed target population?

Balance of benefits and risks

- **Describe the tradeoffs** – do the benefits outweigh risks given the current state of knowledge, uncertainties and limitations?
  - Today; based on knowledge from assessors, CHMP, experts, patients
  - Could other analyses be helpful? ”Quantitative analyses”

- **Describe the condition, population, condition for use for which the benefit/risk balance is positive**
  - Is the population broader or more restricted compared to the study population?
  - If so; how did we come to that conclusion?

- **Relative assessment of benefit and risks?**
  - New product compared to other alternatives in the submitted studies
    - Does a new product have to be “better” than what is already approved?
  - Sometimes only compared to placebo
    - Comparison to previous studies with alternative treatments?

How to communicate /Who are the recipients?

- **How do we communicate?**
  - SmPC; Summary of Product Characteristics
  - SmPCs are a key part of the marketing authorisation of all medicines authorised in the European Union and the basis of information for healthcare professionals on how to use a medicine safely and effectively.
  - EPAR; European Public Assessment Report
  - The EMA publishes an EPAR for every medicine granted a central marketing authorisation by the European Commission
  - Press releases etc on EMA website and national authorities
- **Different recipients may have different preferences concerning the description/assessment of the benefit/risk balance**
  - Prescriber
  - Patient
  - HTA, payers

Conclusion

- **Why:**
  - BENEFITS MUST ALWAYS OUTWEIGH THE RISKS
  - Identify the condition, population(s), (conditions of use) for which it is established that benefits outweigh the risks
  - Benefit-risk assessment final reflection/conclusion of our assessment of the data submitted
- **How;**
  - Describe the key findings;
    - Of importance to patients
    - Possible to evaluate
  - Assess the values of these findings
    - Integrate knowledge from experts, patients etc
    - Values may differ between different conditions, also within a condition
- **Communication**
  - Communicate in a way that provides relevant information to different stake holders

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assuring scientific and regulatory quality through pre-submission guidelines and use of experts

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

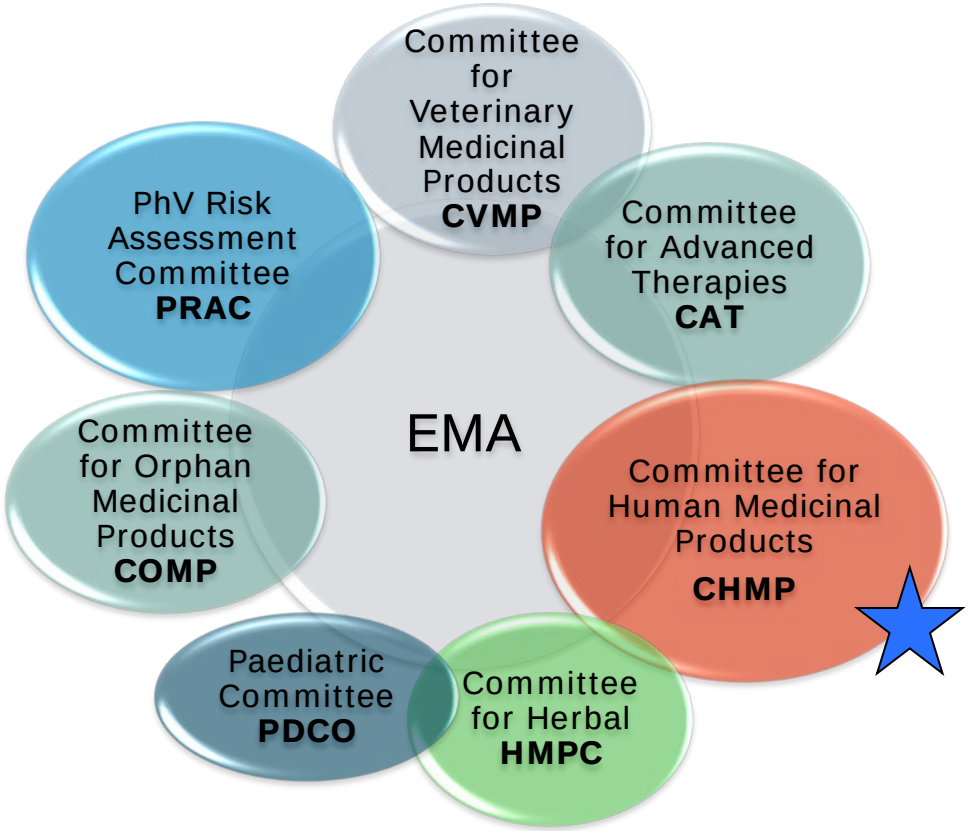
Presented by Andrea Taft on 9 March 2018
Guideline Consistency Group Coordinator
Scientific and Regulatory Management Department

Content

- CHMP - best scientific expertise in the EU system
- Working Parties and Scientific Advisory Groups
- Guidelines, EMA scientific guidelines
- Process of drafting
- Role of the Guideline Consistency Group
- Other supportive documents

EMA Committees

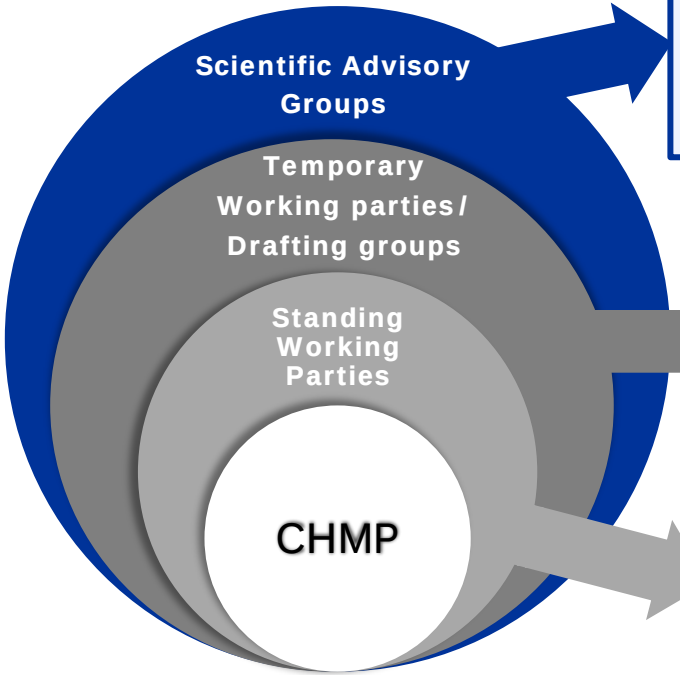
- Member States have **pooled their sovereignty** for authorisation of medicines



Main tasks of the CHMP

- Deliver **scientific opinions to the EC** and **WHO**
- Determine whether products meet **Quality, Safety** and **Efficacy** requirements and have a **positive benefit-risk balance**
- Prepare of **EU guidelines / policies**
- Give **Scientific Advice** and protocol assistance
- Establish and work with **Working Parties, Scientific advisory groups**
- Interact with **international regulators** (e.g. ICH)

Scientific expertise across the EU network



- Psychiatry
- HIV/ Antiviral
- Diabetes
- Anti-infectives
- Oncology
- Vaccines
- Cardiovascular
- Neurology

- Pharmacogenomics
- Biosimilar
- Biostatistics
- Gastroenterology
- Vaccines
- Rheumatology /Immunology
- Respiratory
- Excipients
- Infectious Diseases
- Oncology
- Pharmacokinetics
- Cardiovascular
- Blood Products
- Central nervous system
- Radiopharmaceuticals

- Patients & Consumers
- Healthcare Professionals
- Scientific advice
- Quality
- Biologics
- Safety

Working Party and Scientific Advisory Group

- **Working Party** (WP):
  - Experts in a **particular scientific field, irrespective of MSs**.
  - Advice to CHMP on **scientific evaluation** of marketing authorisation applications or drafting and revision of **scientific guidance documents**.
- **Drafting group** (DG):
  - Review or development of **guidelines that do not fall within the remit of the existing WPs**.
- **Scientific advisory group** (SAG):
  - Specific scientific advice on medicines or treatments. Experts are selected based on therapeutic expertise.

European experts

- Policy on handling of competing interests of scientific committees' members and experts
- Public list of EU experts

Users can browse the list in two ways:

- **Browse A-Z**: searches by the first letter of the expert's family name.
- **Browse by country**: searches by the nominating authority in the Member States. Experts nominated by the Agency are listed under 'European Union'.

On request, EMA makes publicly available details of the specific areas of expertise and previous declarations of interests of individual experts. Please submit requests via Send a question to EMA.

Browse A-Z | Browse by country

Select a letter to view a list of scientific experts by first letter of family name

A B C D E F G H I J K L M N O P Q R S T U
V W X Y Z View all

First name	Surname	Country	Nominating authority	Interest level	Declaration of interests	Curriculum Vitae
Birgit	Gadatsch	Germany	Federal Institute for Drugs and Medical Devices	No interests declared	DoI	CV
Marie	Gadeyne	France	French National Agency for Medicines and Health Products Safety	Direct interests declared	DoI	CV
Andrea	Gaggioli	Italy	Italian Medicines Agency	No interests declared	DoI	CV
Elma	Gailite	Latvia	Latvian State Agency of Medicines	No interests declared	DoI	CV

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/experts.jsp&mid=WC0b01ac058043244a

Guideline definition

- **Guideline:** A document with explicit legal basis referred to in the legislative framework as intended to fulfil a legal obligation laid down in the Community pharmaceutical legislation*.

- Aimed to give advice to applicants or marketing authorisation holders, competent authorities and/or other interested parties
- **Scientific guidelines** usually relate to specific scientific issues reflecting a harmonised EU approach and based on the most up-to-date scientific knowledge.

*https://ec.europa.eu/health/documents/eudralex_en

Legal status of guidelines

- **Guidelines are "soft law",** i.e. do not have legal force
- However, guidelines are to be considered as a **harmonised EU position** on how to interpret and apply requirements to demonstrate quality, safety and efficacy set out in the directives.
- Guidelines are to be followed to **facilitate development, assessment, approval and control** of medicinal products in the EU.
- Alternative approaches must be duly justified in the dossier at the time MA submission.

EMA scientific guidelines

- Quality
- Biologicals
- Non-clinical
- Clinical pharmacology and pharmacokinetics
- Clinical safety and efficacy
- Multidisciplinary
- Herbal medicinal products
- ICH

Procedure for writing a guideline

EUROPEAN MEDICINES AGENCY

Procedure for EU guidelines and related documents within the pharmaceutical legislative framework, March 2009 (EMEA/P/24143/2004 Rev. 1 corr):

1. • Selection of topic and inclusion in the relevant work programme
2. • Appointment of rapporteur
3. • Development of concept paper
4. • Adoption and release for public consultation of concept paper
5. • Preparation of initial draft guideline
6. • Release for public consultation of draft guideline
7. • Collection of comments
8. • Preparation of final version of guideline
9. • Adoption of final guideline for publication
10. • Implementation

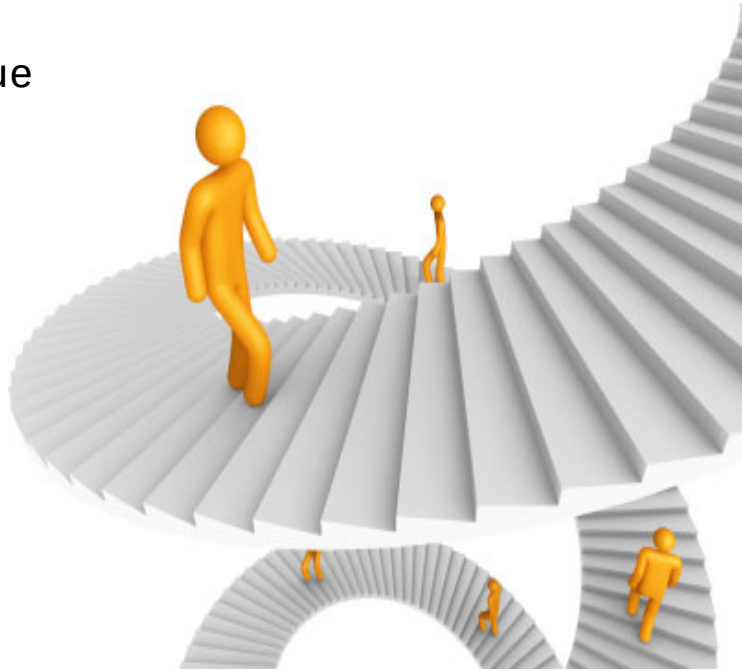
Selection of topics, inclusion in WP's annual work programme, appointment of a Rapporteur

- **Topics:**
  - EU Commission, legislative requirements
  - Technical and scientific developments
  - International activities (ICH guidelines)
  - Other regulators, member states, scientific committees, learned societies

- **Rapporteur (and Co-Rapporteur):**
  - From relevant working party, scientific advisory group
  - Lead for drafting concept paper and subsequent guidelines

Concept paper development, adoption for consultation

- CP conveys the need for discussion of a specific issue but does not elaborate on the solutions
- Standard template
- Adopted for public consultation, usually 2-3 months



Initial guideline preparation, release for public consultation

- Rapporteur drafts the guideline
- Comments from public consultation on CP
- Standard template
- Section “Scope” – precise purpose of the guideline

- Agreed by the WP, adopted by Committee for public consultation (~ 6 months)
- Proactive consultation with learned societies, academia, patients, physicians

Comments - example

London, 26 February 2015
EMA/37217/2015
Rheumatology Immunology Working Party (RIWP)

Overview of external comments received on the "Guideline on clinical investigation of medicinal products for nephritis" (EMA/CHMP/5

Interested parties (organisations or indivi
consultation.

Stakeholder no.	Name of
1	EFPIA
2	Technolo
3	TEVA
4	Lupus Re
5	Pfizer, Inc

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 379 - 384	1	Comment: It is not clear from the preceding sentences why a minimum 18 month trial duration is needed for damage to occur or progress and to stay present for another 6 months. Potentially one could demonstrate that in a study of 12 months duration given that lupus is diagnosed at study entry. In addition, SLICC/ACR measures damage in a 6-month period. Two 6-month periods of measurement is sufficient, three seems excessive. It is thus suggested to change the requirement of damage measurement from 18 months to 12 months. Proposed change: "Therefore to measure the damage that has accrued during the clinical trial, the trial has to be long enough (for at least ~~18~~ ***12*** months for damage to occur and remain present for 6 months."	Accepted – text changed. Damage items are usually recorded if the clinical item has been present over 6 months or associated with immediate pathological change indicative of damage. Therefore to measure the damage that has accrued during the clinical trial, the trial has to be long enough (for at least 12 months) for damage to occur and remain present for 6 months.

http://www.ema.europa.eu/docs/en_GB/document_library/Overview_of_comments/2015/03/WC500184890.pdf

Preparation, adoption and implementation of final guideline

- Final guideline is agreed by the WP, adoption by the Committee

- Publication on the external EMA website
- Implementation: 6 months post publication

- Training for assessors/experts, workshops
- Revisions – to be considered on annual basis
- Communication – under “what’s new” section of EMA website

Guideline Consistency Group (GCG)

- Scientific and regulatory peer review of concept papers, draft/final guidelines and reflection papers before adoption by CHMP
- Ensuring clinical and methodological guidelines follow regulatory and scientific consistency
  - Lack of contradiction, i.e. alignment with recent scientific advice, other CHMP scientific opinions as well as with other guidelines
  - Any deviation has to be duly justified
  - Template adherence

How long does it take?

Publication of a CP → publication of final guideline:

Normally **~ 2-3 years**

Shorter if urgent for public health, e.g.:

"*Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products*" **1 year**

Other supportive documents

- **Public statement**: important immediate information, e.g. withdrawal of a product
- **Reflection paper**: current status of scientific discussion, invitation to comment/discuss in areas where scientific knowledge is limited
- **Question & Answer**: additional clarity on particular aspects, guideline/product
- **Addendum to guideline**: usually specific topic, e.g. paediatric
- **Recommendations / procedural advice**: technical and regulatory documents

Any questions?

Further information

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Types of approvals and commitments

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Malgorzata Zienowicz on 9 March 2018
Procedure Management Department

Outline of the presentation

- EMA opinion and EC decision
- Types of approvals – non-standard vs standard Marketing Authorisation
- Post-approval commitments

EMA Committee issues Opinion and EC issues Decision to grant Marketing Authorisation

- The EMA Committee/s issue/s Opinion following assessment of data:

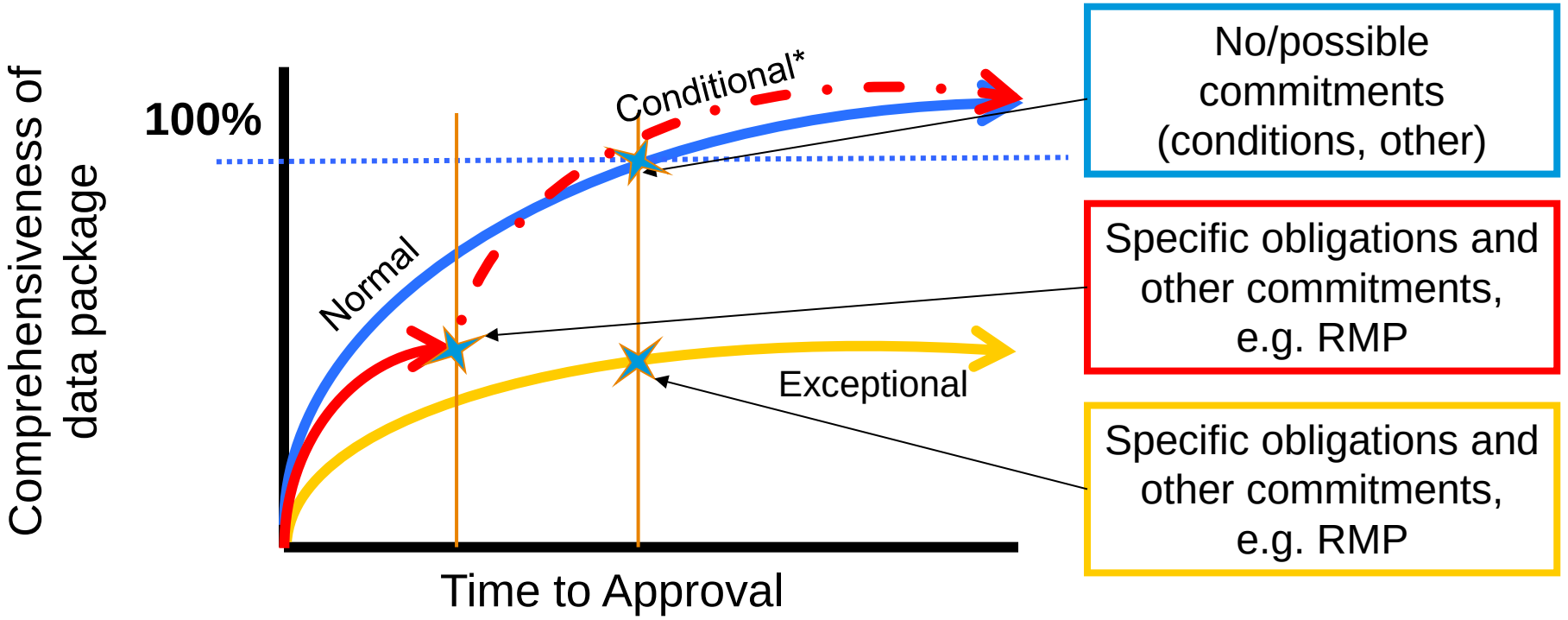
  ➢medicinal products must have a **positive benefit-risk balance** based on scientific assessment of the **quality**, **safety** and **efficacy** data

- European Commission makes decision based on EMA Committees' opinion in a process called Decision Making Process which lasts approximately 2 months

Post-approval commitments / obligations to address uncertainties

- Commitments in Risk Management Plan
  - Studies as part of Pharmacovigilance plan
  - Risk minimisation measures
- Conditions imposed to the Marketing Authorisation
  - Post-authorisation efficacy study
  - Post-authorisation safety study
- Specific obligations (only for MA under exceptional circumstances and conditional MA)

Types of MAs and post approval commitments



*Tool for EARLY ACCESS, see also PRIME

MA under Exceptional Circumstances*

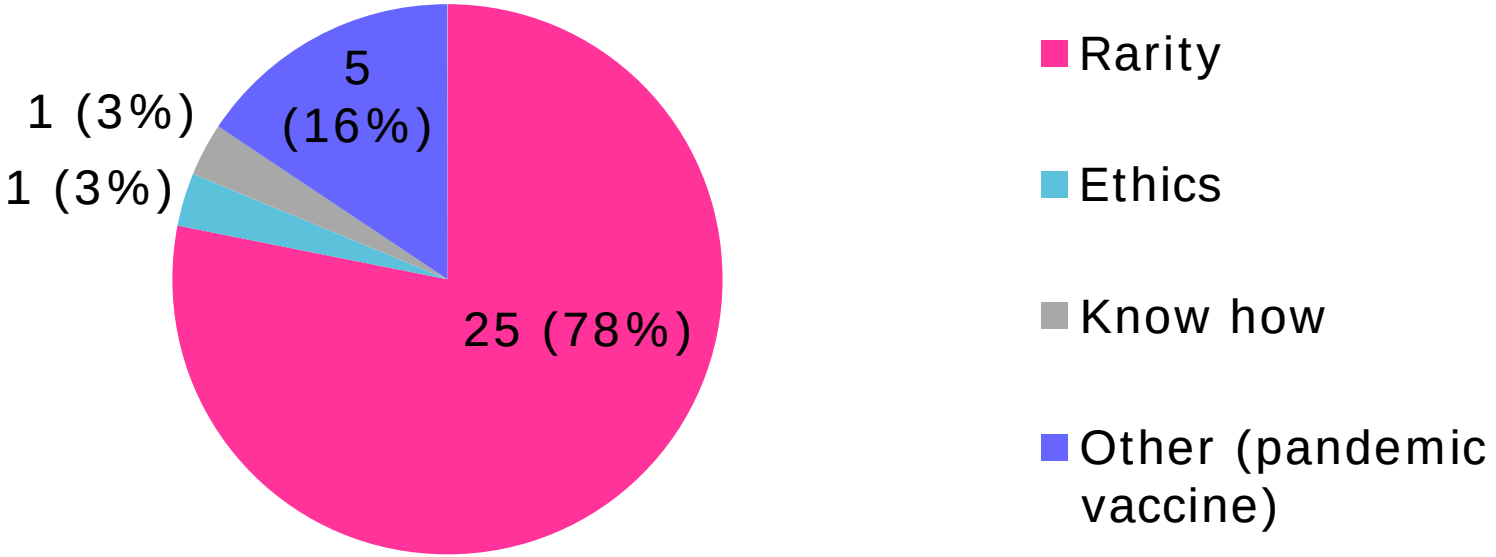
Collection of comprehensive data is not possible because

- The **indications** for which the product in question is intended are encountered **rarely**
- The **present state of scientific knowledge does not allow it**
- It would be **contrary to** generally accepted principles of medical **ethics**

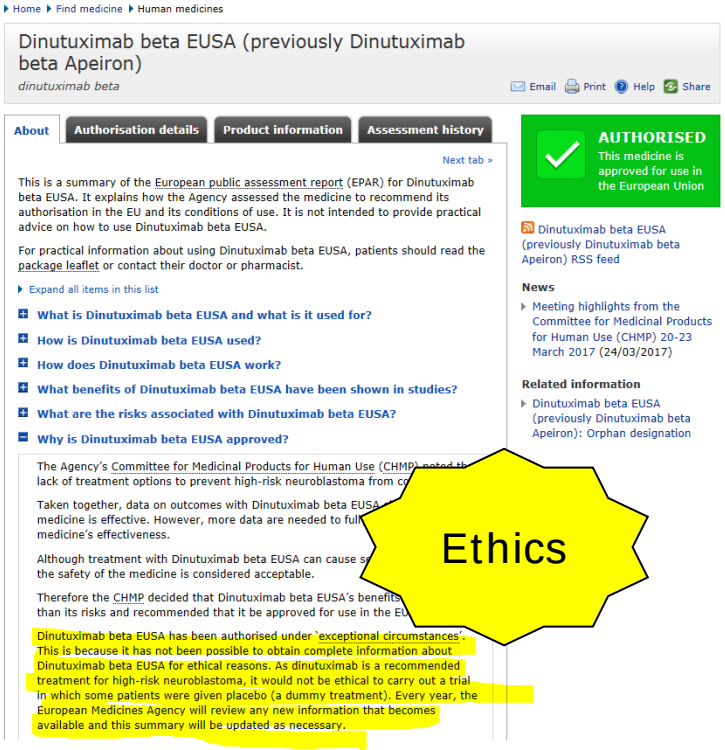
hence, switch to full MA not foreseen

*Legal basis - Art. 14(8) Reg. EC 726/2004; criteria Annex I to Directive 2001/83/EC

Number of MAs under exceptional circumstances and reasons for approval (2002-2017)



MA under exceptional circumstances – examples



Specific obligation example – Brineura for Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) disorder

Clinical Data

Study 190-201, Phase 1/2, single arm, open-label, dose escalation study (N=23)

Study 190-202, an ongoing Phase 1/2 open-label extension study (N=22)

Uncertainty

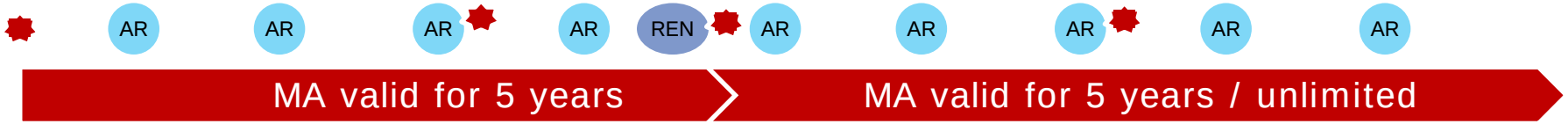
Long term safety, no/ limited data in children below 2 and above 8 years

Obligation

E/S study (ongoing study 203 including children <2 and >8 yrs; end - 2020)

Safety study (PASS - registry; reports annually)

MA under EC - Annual Reassessments



- **Annual Reassessment** to be **submitted annually**
- Scope: re-assessment of the **benefit-risk** profile based on **data from specific obligations**
- **Submission of annual re-assessment** a **condition for validity of the MA**
- **Standard** duration of **MA validity**

EC decision REN Renewal AR Annual Reassessment

Conditional MA*

Scope

- seriously **debilitating or life-threatening** diseases
- to be used in **emergency situations**, in response to public health threats
- **orphan** medicinal products

*Legal basis - Art. 14(7) of Reg. (EC) No. 726/2004

Criteria

- the **risk-benefit balance is positive**
- **unmet medical needs** will be fulfilled
- the **benefit** to public health of the immediate availability […] **outweighs** the **risk** […]

expected that comprehensive data will be provided to switch to full MA

10-year report on CMA highlights (2006-June 2016)

30 CMAs

- 24 Target debilitating or life-threatening conditions
- 14 Are orphan medicines
- 3 Address emergency situations linked to a public health threat

By therapeutic area

- 17 Oncology
- 9 Infectious diseases
- 3 Neurology
- 1 Ophthalmology

107 post-authorisation obligations

(of these, 57 obligations were fulfilled before June 2016)

Categories of specific obligations imposed to companies

- 78 Final results from clinical studies or pool of studies
- 9 Interim results of a clinical trial
- 8 Additional analysis
- 3 Quality data
- 9 Other measures

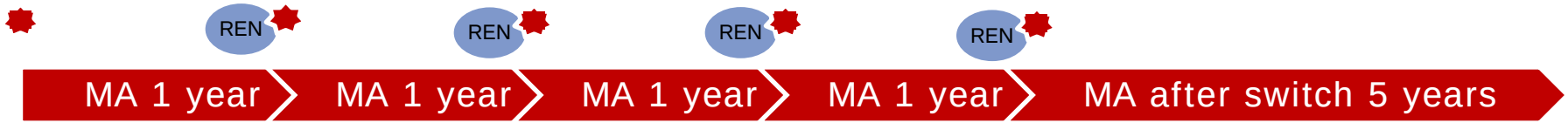
How timely was the submission of specific obligation results?

- 33 Due date +/- 1 month
- 15 Early (1-6 months)
- 4 Early (6-12 months)
- 1 >1 year early
- 2 Late (1-6 months)
- 2 Late (6-12 months)

>90% of completed specific obligations did not have major changes to their scope

≈70% of specific obligations were completed within specified timelines

CMA - Annual Renewals



- **MA valid for 1 year** – renewal applications to be submitted annually

- **Renewal application to contain (interim) report** on fulfilment of specific obligations

EC decision

REN Renewal

Switch to ‘full/standard’ MA

- When **comprehensive data results submitted** (all specific obligations completed) **confirming positive B/R**

- Based on a CHMP Opinion the **EC to issue a ‘full’ Marketing Authorisation** *(not subject to specific obligations)* with standard **5 year renewal cycle validity**

Full/standard Marketing authorisation

Full MA with Annex II conditions (~ 30% of full MA 2012-2016)

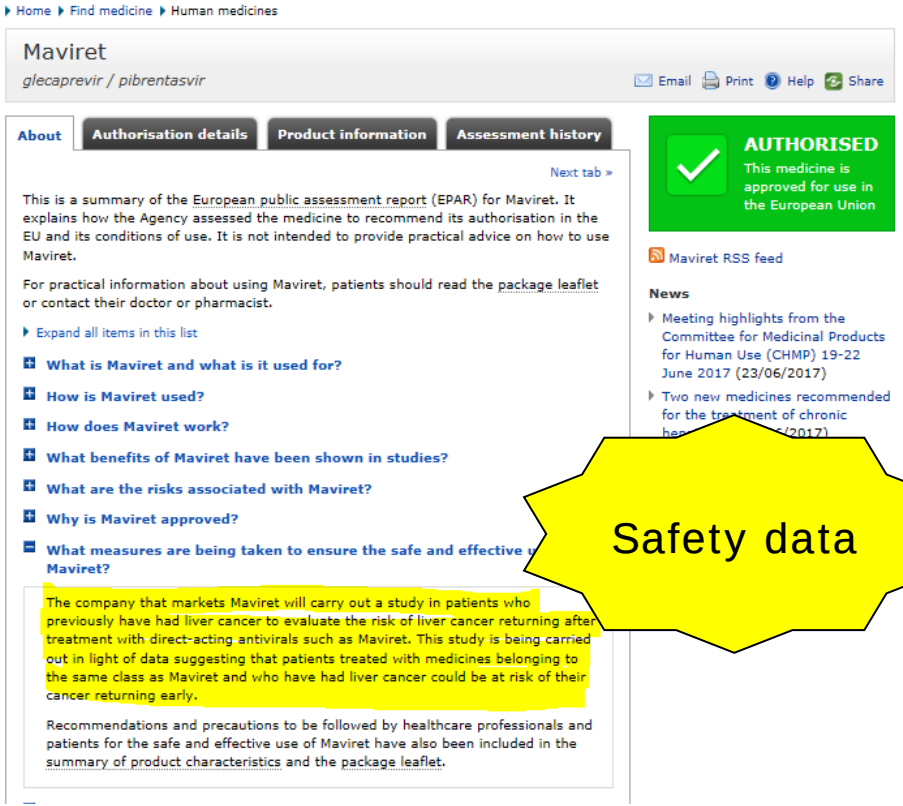
- Full MA at approval
- Comprehensive data available
- Condition well substantiated – data key to benefit risk
- Normal validity of MA (5 years)
- Reasonable timeline for fulfilment of condition

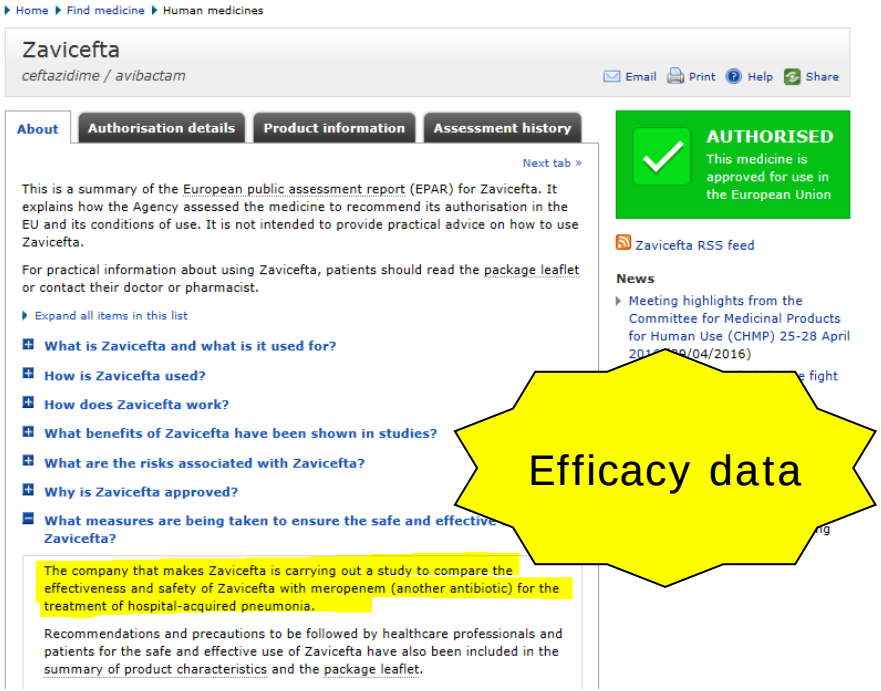
Full MA with/without commitments

- Full MA at approval
- Comprehensive data available
- No condition*
- Normal validity of MA (5 years)

*Other commitments possible

Full / standard MA with Annex II condition - examples





Annex II condition example – Zavicefta for cIAI; cUTI; HAP/VAP; infections due to aerobic Gram(-) organisms

Clinical Data

RECLAIM – RCT in cIAI

RECAPTURE & REPRISE – RCTs in cUTI and resistant GRAM(-) infections

Uncertainty

Efficacy, safety and tolerability in **nosocomial including ventilator-associated pneumonia** in hospitalised adults

Condition

Efficacy study (PAES - ongoing at time of approval; fulfilled in 2017)

Types of Marketing Authorisations – recap

MA under exceptional circumstances

- MA granting based on a *less comprehensive* data package
- Comprehensive clinical data *not expected*
- Post approval commitments (studies) *always*
- *5 year validity* with annual reassessment of MA
- Standard MA not envisaged

Conditional MA

- MA granting based on a *less comprehensive* data package
- Comprehensive clinical data *expected within defined timeframe*
- Post approval commitments (studies) *always*
- *1 year validity* with annual renewal of MA
- Switch to standard MA envisaged

Standard MA

- MA granting based on *comprehensive* data package
- Post approval commitments (studies) *possible*
- *5 year validity*
- Standard MA at approval

17

Take home message

- Comprehensiveness of data package will determine the type of the approval/MA

- Post-approval commitments are related to uncertainties remaining after the initial assessment of the benefit/risk of the product

Glossary

EMA - European Medicines Agency

EC – European Commission

CHMP/CAT – EMA committees

DMP – Decision Making Process

MA – Marketing authorisation

B/R – Benefit risk (balance)

cIAI – Complicated intraabdominal infections

cUTI – Complicated urinary tract infections

HAP/VAP – Hospital acquired/ventilation associated pneumonia

References

Reg. EC 726/2004, Directive 2001/83/EC and other legislation
https://ec.europa.eu/health/human-use/legal-framework_en

10-year report on CMA
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/01/WC500219993.pdf

Dinutuximab beta EUSA EPAR
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003918/human_med_002104.jsp&mid=WC0b01ac058001d124

Brineura EPAR
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004065/human_med_002111.jsp&mid=WC0b01ac058001d124

Xigrid EPAR
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000396/human_med_001160.jsp&mid=WC0b01ac058001d124

Maviret EPAR
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004430/human_med_002151.jsp&mid=WC0b01ac058001d124

Zavicefta EPAR
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004027/human_med_001993.jsp&mid=WC0b01ac058001d124

Any questions?

Further information

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EUROPEAN MEDICINES AGENCY
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Benefit-risk assessment throughout the medicinal product lifecycle

07 - Benefit Risk assessment and good regulatory practice

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Carlos Aicardo Muñoz on 08th March 2018
Procedure Management Department – Human Medicines Evaluation Division

Knowledge on the benefit/risk of medicinal products

Source of image: wikipedia

At the time of marketing authorisation…

Positive benefit/risk balance based on:

- Sufficient evidence of the efficacy in the controlled population
- Good evidence on the most common adverse reaction

Approval decision based on acceptable levels of uncertainty

Risk Management Plan

What happens after approval?

During the lifecycle of the medicinal the following activities will or may take place

Periodic evaluation of the benefit risk

⇩

Legal and regulatory requirements

Development and maintenance of the product

⇩

New solutions for patients

Ad-hoc evaluation of the benefit risk of the product

⇩

Concerns on the safety, efficacy and quality of medicinal products

Sources of evidence during the life cycle of the product

- Randomised controlled trials
- Uncontrolled clinical trials
- Spontaneous adverse event reports
- Registries
- Observational studies
- Expert committee reports, opinions of respected authorities/experts, publications

Build knowledge on the quality, safety and efficacy of the medicinal product

The European regulatory system to ensure that a positive benefit risk is maintained

Development and maintenance of the medicinal product

Variations

Periodic evaluation of the benefit risk

Annual Renewals

PSURs PSUSA

Annual Re-assessment

PAMs

Renewals

Ad-hoc evaluation of the benefit risk of the product

Urgent Safety Restriction

Referrals


Periodic evaluation
of the benefit risk

PSURs – Periodic Safety Update Reports

Comprehensive, concise and critical analysis of the benefit-risk balance

Takes into account new or emerging information in the context of cumulative information on benefit and risk

List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

Related Information:

Introductory cover note to the List of European Union reference dates and frequency of submission	http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133157.pdf
Requests for amendments of the EU reference dates list	http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2012/10/WC500133160.xls
The PSUR assessment procedure will start according to the Timetables published on EMA website	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000330.jsp&mid=WC0b01ac05803d8b9c

Single Assessment Reports of PSURs are shared among all Marketing Authorisation Holders involved in the concerned procedure.

Active substances and combinations of active substances	European Union reference date (EURD) Not Available* = EURD not provided during the consultation phas	PSUR Submission Frequency	DLP	Submission date (According to the timelines defined in GVP Module VII, Section A)	Next DLP (For active substances or combination of active substances with a PSUR frequency of less than one year)	Next Submission date (According to the timelines defined in GVP Module VII, Section A - For active substances or combination of active substances with a PSUR frequency of less than one year)
fludeoxyglucose (18f)	14/11/1994	3 years	30/11/2017	28/02/2018		
1,3-butanediol / cinchocaine hydrochloride / dexamethasone	23/09/1983	13 years	15/05/2025	13/08/2025		

Renewals / Annual Renewals / Annual re-assessment

The European legislation requires the renewal or reassessment of the license depending on the type or marketing authorisation

The difference is based on the uncertainties around the benefit/risk at the time of authorisation and the need to further supervise the benefit risk on a regular basis

	Full MA	MA except. Circ.	Conditional MA
Renewal	5-year	5-year	1-year Then 5-yr from the date of switch to standard MA
Specific Obligations review	Not applicable	Annual Re-assessment	Annually = 1-yr renewal

Supervise the progress of studies to address the uncertainties identified at the time of authorisation

Post-authorisation studies (PASS / PAES) & Post Authorisation Measures (PAMs)

Regulators can require studies to be conducted at any time

Consolidate /fill the gaps of the benefit risk

Legally binding (SOBs, ANX, MEA)

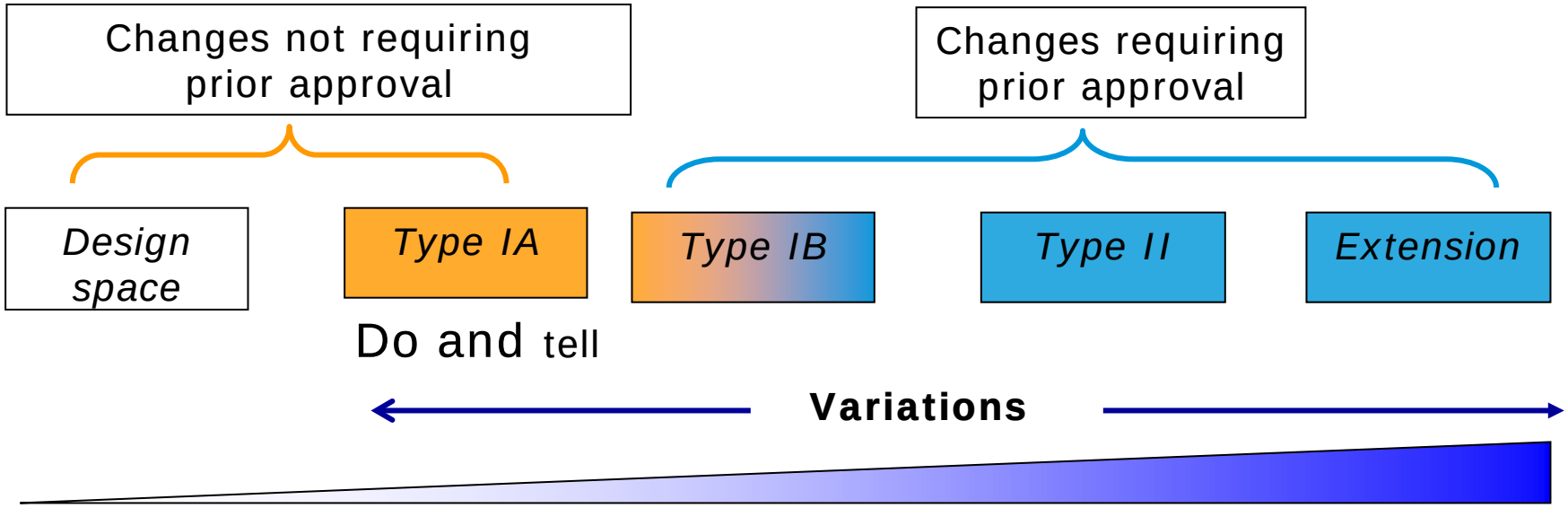
Recommendations

Protocol and final study results are submitted for evaluation by EMA


Development and maintenance of the product

Variations

Introduction of changes to the terms of the marketing authorisation



An evaluation procedure adapted to the level of risk

Examples of Variations

New solutions for patients

- New indications
- New strengths/ pharmaceutical forms
- Changes in posology

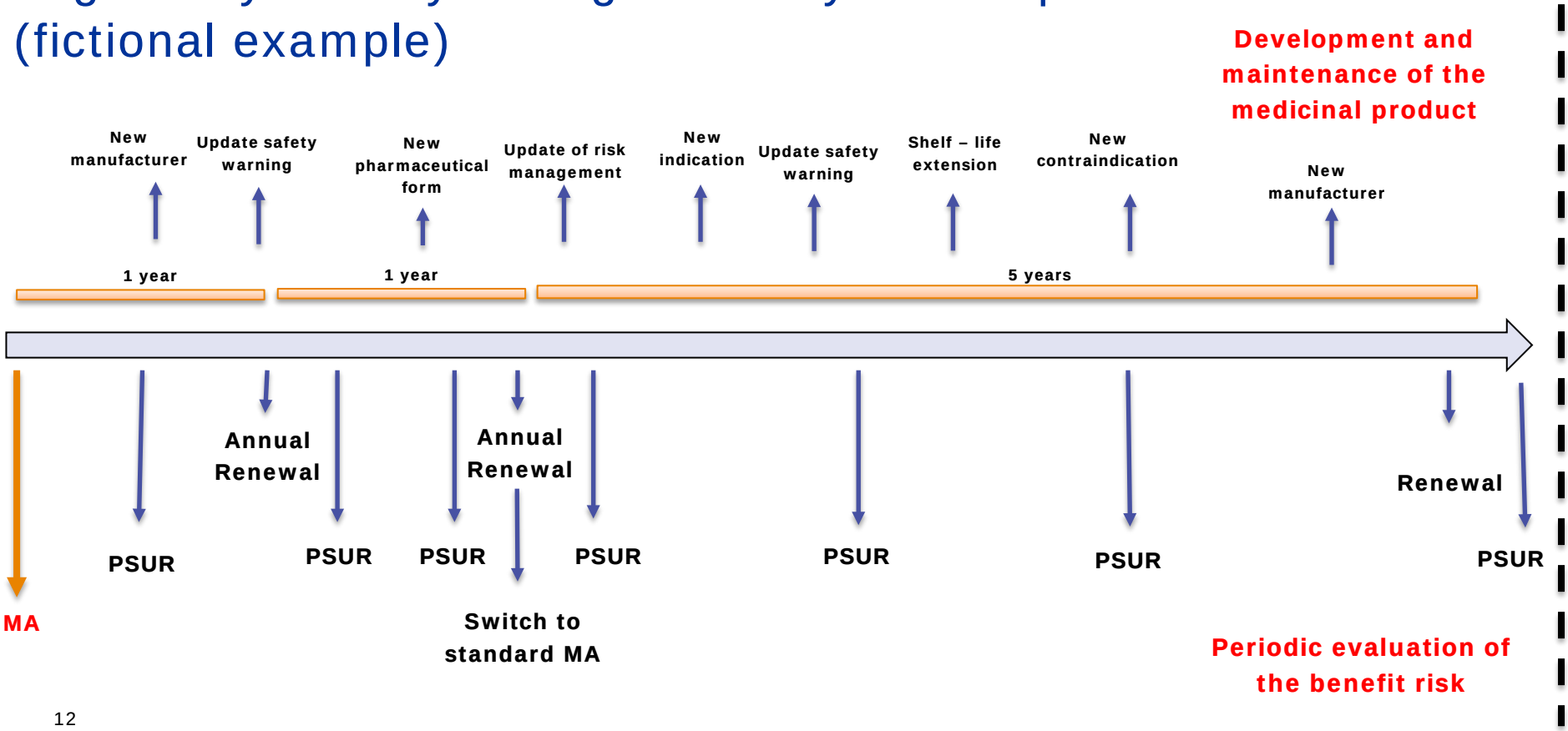
New safety and efficacy data

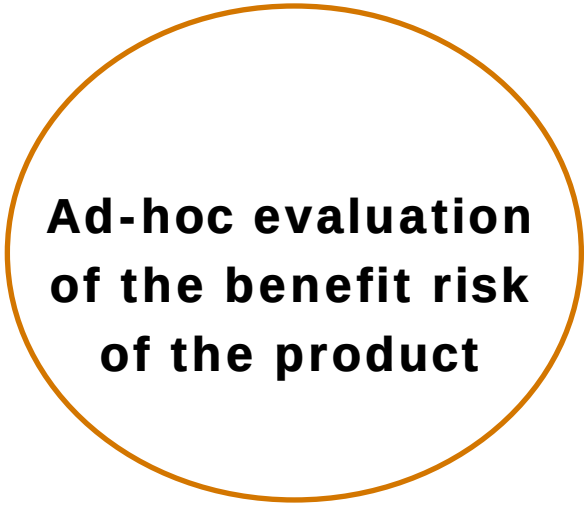
- Update of PD/PK data
- Update of safety warnings
- Updates in Risk management
- Introduction of contraindications

Maintaining the supply of medicinal products

- New or changes to Manufacturing sites
- Extension of shelf-life

Regulatory activity during the lifecycle of a product (fictional example)




Ad-hoc evaluation
of the benefit risk
of the product

Referrals

- To assess issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines that requires immediate action.
- The referrals differentiate from variations in a sense that have a component of urgency and are mainly initiated by member states and European commission. MAHs can also initiate a referral
- EMA and its Committees conduct a scientific assessment on behalf of the European Union and make a recommendation for a single outcome across the Member States.
- Different type of referrals depending on the urgency, the issue (quality, safety, efficacy, particulars)

✓ Article 107i – Dir 83/2001/EC	Safety issues
✓ Article 20 (centrally authorised products only) – Reg 726/2004/EC ✓ Article 31 – Dir 1234/2008/EC ✓ Article 13 – Variation Reg 1234/2008/EC	Safety, quality, manufacturing, efficacy issues or overall benefit-risk balance
✓ Article 29(4) – Dir 83/2001/EC ✓ Article 30 - 83/2001/EC	Harmonisation for national authorised products

Referrals - examples

- Suspension of marketing authorisations due to concerns on the reliability of clinical studies (e.g. data manipulation revealed after inspection of clinical sites)

- Restrictions on the use of the medicinal product due to serious and life-threatening liver problems

- Review of the information to patients on the safety concern risk of Venous Thromboembolism for a group of prescription only and over the counter medicinal products

Other activities Post Authorisation

Take home message

Knowledge on the quality, safety and efficacy is built throughout the lifecycle of medicinal products

The benefit-risk balance of any medicinal product is re-evaluated at different stages through different regulatory activities

Any questions?

Further information

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