EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

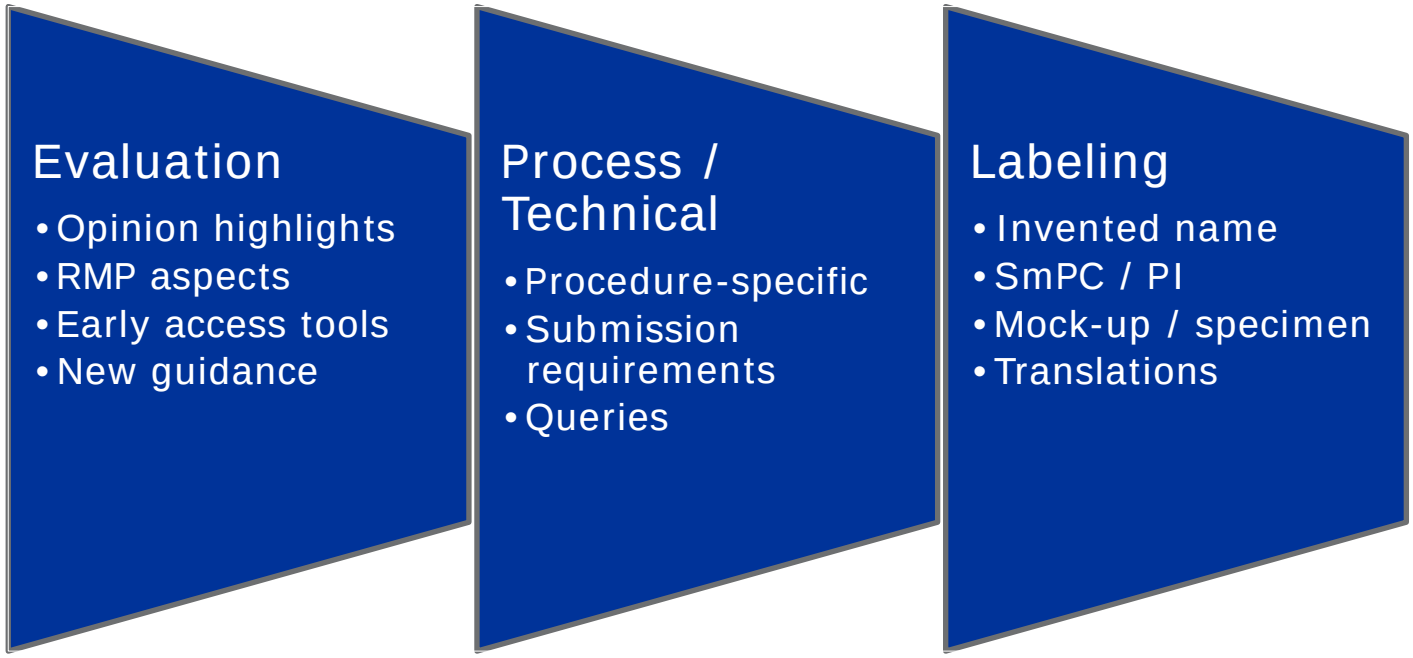
Overview of recent changes in the centralised procedure

2nd Industry stakeholder platform, 9 November 2015

Presented by: Michael Berntgen
Head of Scientific & Regulatory Management Department

Topics to be addressed

Objective: Overview of key developments and changes in the centralised procedure in 2015 so far



Industry stakeholder platform on the operation of the centralised procedure

Purpose: to promote awareness about the changes in the centralised procedure, to have an open dialogue and exchanges of views, and to discuss ideas and proposals for continuous improvement

- New platform in addition to the ones on PhV and on Paediatrics
- First meeting held on 24 April 2015
  - Agenda, all EMA presentations as well as the meeting highlights are available on the EMA website

Highlights from the EMA industry platform meeting held on 24 April 2015 on the operation of the centralised procedure

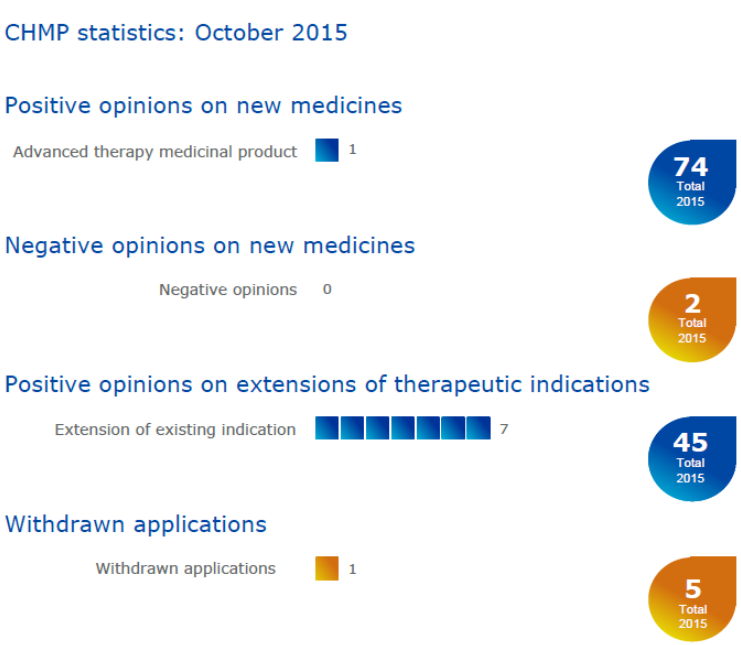
EMA/290883/2015

Topic area:

Evaluation

- Opinion highlights
- RMP aspects
- Early access tools
- New guidance

Medicines evaluation highlights so far in 2015



- PCSK9 inhibitors for treatment of hypercholesterolemia
- New treatment option for ADHD
- Treatments for orphan metabolic diseases
- First treatments for rare sleep-wake disorder
- Several new cancer treatments
- GLP-1 agonist for weight management
- First malaria vaccine
- Neprilysin inhibitor (in combination with an ARB) for the treatment of heart failure
- Antidote to the anticoagulant dabigatran
- First oncolytic immunotherapy medicine

Until October 2015, 4 recommendations for marketing authorisation have been adopted following accelerated assessment and 2 positive Opinions concerned conditional marketing authorisations.

Revision of guidelines on Early Access tools

News

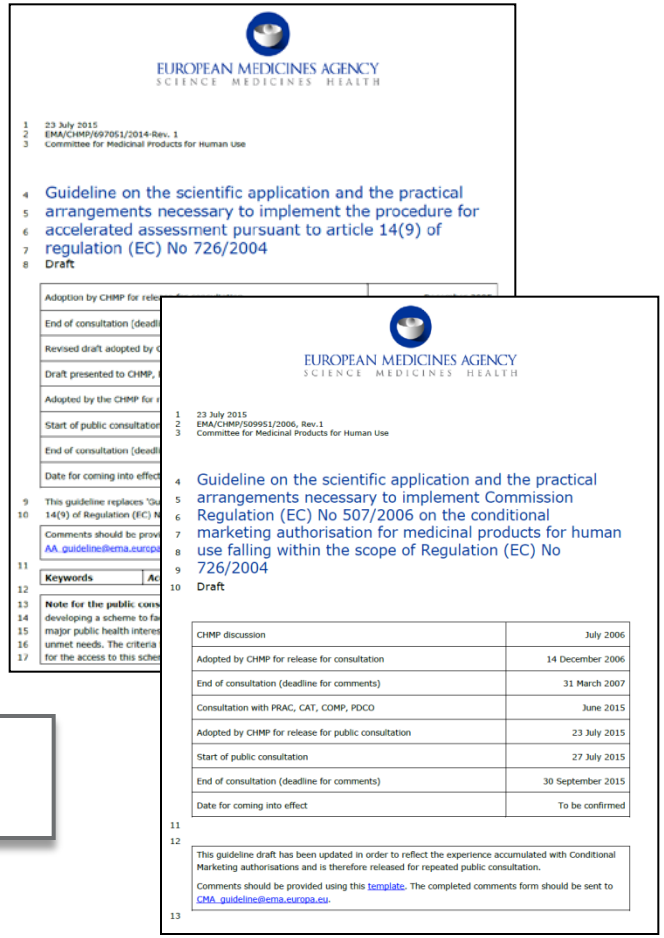
27/07/2015

Fast track routes for medicines that address unmet medical needs

Launch of two-month public consultations on revised guidelines on accelerated assessment and conditional marketing authorisation

The European Medicines Agency (EMA) has revised its guidelines on the implementation of accelerated assessment and conditional marketing authorisation, two key tools in the European legislation to accelerate patients' access to medicines that address unmet medical needs.

EMA/CHMP/697051/2014 Rev. 1
EMA/CHMP/509951/2006 Rev. 1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23 July 2015
EMA/CHMP/697051/2014-Rev. 1
Committee for Medicinal Products for Human Use

Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to article 14(9) of regulation (EC) No 726/2004
Draft

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23 July 2015
EMA/CHMP/509951/2006, Rev.1
Committee for Medicinal Products for Human Use

Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004
Draft

CHMP discussion	July 2006
Adopted by CHMP for release for consultation	14 December 2006
End of consultation (deadline for comments)	31 March 2007
Consultation with PRAC, CAT, COMP, PDCO	June 2015
Adopted by CHMP for release for public consultation	23 July 2015
Start of public consultation	27 July 2015
End of consultation (deadline for comments)	30 September 2015
Date for coming into effect	To be confirmed

This guideline draft has been updated in order to reflect the experience accumulated with Conditional Marketing authorisations and is therefore released for repeated public consultation.

Comments should be provided using this template. The completed comments form should be sent to CMA_guideline@ema.europa.eu.

Draft revisions of these guidelines have been published for public consultation until 30 September 2015

Benefit / risk methodology

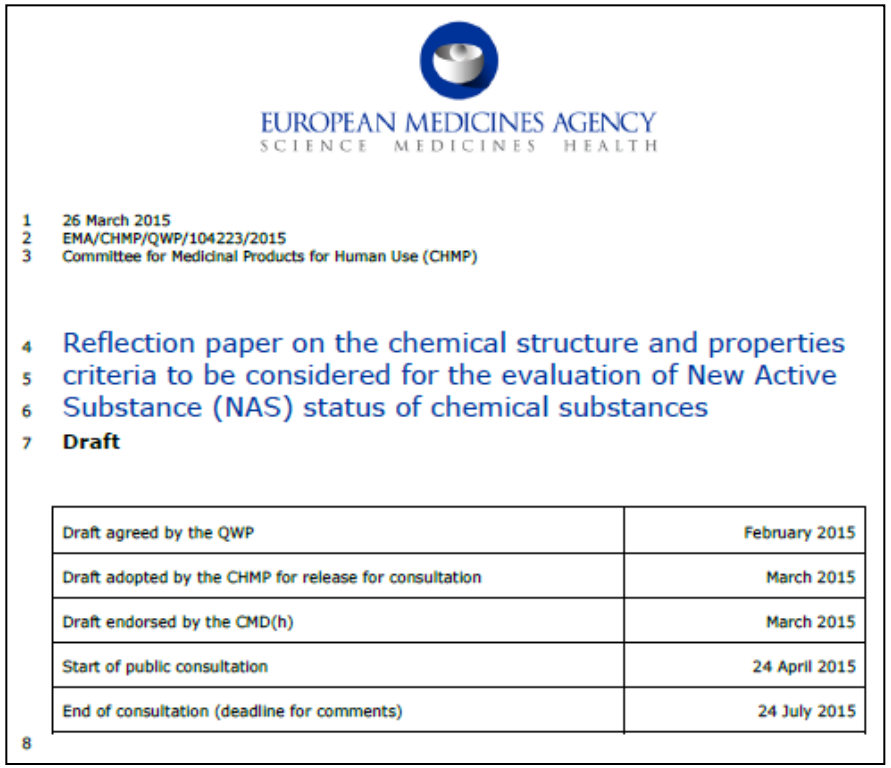
Development of the Effects Table as part of the CHMP's project on Benefit/risk methodologies:

	Effect	Short Description	Unit	Placebo	Vandetanib	Uncertainties/ Strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
Favourable	PFS (median)	Weibull model	Mo	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
Favourable	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	No clear effect on PRO/QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short *vs.* the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
Unfavourable	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointe?	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
Unfavourable	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

- Pilot phase completed in 2014
- Implementation of the Effects table routinely for MAAs / extensions of indications starting **since February 2015**
- Collaboration with other committees and HTA bodies

Evaluation of the “New active substance” claim

- Draft reflection paper on chemical structure and properties to be considered for the evaluation of new active substance status
- Focus on active substances that are structurally related to an already approved active substance
- Public consultation ended in July 2015



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1 26 March 2015
2 EMA/CHMP/QWP/104223/2015
3 Committee for Medicinal Products for Human Use (CHMP)

4 Reflection paper on the chemical structure and properties
5 criteria to be considered for the evaluation of New Active
6 Substance (NAS) status of chemical substances
7 **Draft**

Draft agreed by the QWP	February 2015
Draft adopted by the CHMP for release for consultation	March 2015
Draft endorsed by the CMD(h)	March 2015
Start of public consultation	24 April 2015
End of consultation (deadline for comments)	24 July 2015

8

EMA/CHMP/QWP/104223/2015

Change to the RMP review process during the assessment of initial MAAs

Key aspects:

- Roles and responsibilities of Rapporteurs clarified (CHMP: safety specification; PRAC: prospective risk management planning);
- Timing of detailed PRAC plenary discussion
- Practical arrangements (business process and assessment template) currently being put in place, in collaboration with PRAC and CHMP

➔ Implemented for MAAs that started in May 2015

Ongoing revision of the GVP Module V – Risk management systems

Revision based on almost three years of experience:

1. Defined the purpose of the RMP (prospective planning, fit-for-purpose, reducing the size in the life cycle of the product)
2. Provided clarity on risk definitions, aligned with ICH E2E / E2C
3. Evidence based risk identification -> reshaped module SVII
4. Guidance on post-authorisation removal of safety concerns
5. Provided detailed guidance on requirements for all types of initial MAAs (GVP V and RMP template)
6. Data driven RMP updates! RMP submission is required only at initial MAA and/or when SS, PhV or RM activities change
7. Provided further PASS guidance on imposed & required studies
8. Cleaned annexes; clarified role and content

Revision will be released for public consultation in 2H15.

Latest publications: New guidance on Post-authorisation efficacy studies (PAES)

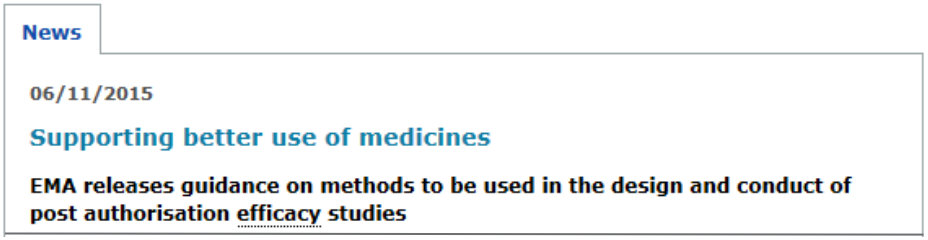
Draft Scientific guidance on post-authorisation efficacy studies

- Provide scientific guidance for MAHs and for competent authorities regarding PAES in the EU on the general need for such studies, on general methodological considerations, on specific situations and on study conduct.

Regulatory and procedural Q&A on PAES

- Provides detailed guidance on regulatory and procedural aspects on the imposition of PAES imposed in accordance with the Commission Delegated Regulation (EU) No 357/2014 and protocols and final study results submission and assessment

Public consultation on the draft scientific guideline until 31 January 2016.


News

06/11/2015

Supporting better use of medicines

EMA releases guidance on methods to be used in the design and conduct of post authorisation efficacy studies

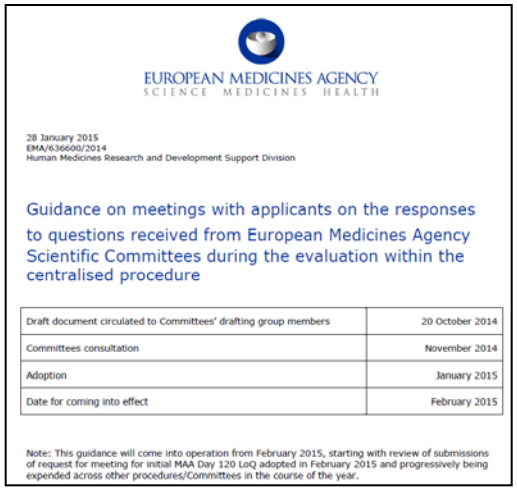
Topic area:

Process / Technical

- Procedure-specific
- Submission requirements
- Queries

MAA evaluation: Revised guidance on clarification meetings

➔ New guidance applicable for CHMP/PRAC/ CAT published in January 2015



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28 January 2015
EMA/636600/2014
Human Medicines Research and Development Support Division

Guidance on meetings with applicants on the responses to questions received from European Medicines Agency Scientific Committees during the evaluation within the centralised procedure

Draft document circulated to Committees' drafting group members	20 October 2014
Committees consultation	November 2014
Adoption	January 2015
Date for coming into effect	February 2015

Note: This guidance will come into operation from February 2015, starting with review of submissions of request for meeting for initial MAA Day 120 LoQ adopted in February 2015 and progressively being expended across other procedures/Committees in the course of the year.

Objectives of the meeting:

- Clarify scientific rationale behind questions in LoQs/LoOIs/RSIs
- Discuss Applicant's proposed responses' strategy taking into account regulatory context
- To clarify specific questions providing opportunity to applicant to better target their responses (clarification component)
- To prevent incomplete or premature responses leading to prolongation of the procedure
- Discuss Timeline's implications

Type II variations: additional submission dates for applicants

- Weekly procedure start dates for Type II variations which
  - do not involve multiple committees (PRAC, CAT)
  - do not require plenary discussion
  - do not lead to immediate EC Decision
- Certain weeks of the year are excluded
- Linguistic review remains monthly and sweeps all procedures finalised during the month

Main goals

- More flexibility to MAHs for initial submission and response submission

Experience so far is that approximately 35% of II and WS variations start on the rolling TT and approximately 25% are finalised outside CHMP.

Renewals: new procedural management

- New process for 5-year renewals implemented in September
  - Single Joint Assessment Report => living document updated from submission to final opinion
  - Systematic involvement of CHMP and PRAC Rapporteurs
  - Target for finalisation => Day 90 (Opinion at Day 120 exceptional)
  - Minor amendments to the dossier possible at Day 60 without LoOI
  - Procedure Manager = Primary Contact Point
- Q&A document on renewals in preparation for publication

- In progress: procedural alignment for annual re-assessment and renewal of conditional MAs procedures (expected finalisation end of the year)

Other recent updates of the post-authorisation guidance

- Guidance on changes to presentations that trigger new EU numbers (April 2015)
- Guidance on editorial changes that can be submitted in post authorisation procedures (May 2015)
  - *Description of changes that can be considered as editorial in Modules 3,4,5 and in the PI, practical aspects for the submission and acceptability for inclusion in a type IA, IB or II.*
- Publication of validation checklist for Type IBs (Nov 15)
- In progress: update of EMA guidance on ASMF submissions and Q&A on consultation on ancillary substances in medical devices.

New Q&A's on the Pre-submission Queries Service (July 2015)

- 1. What is the pre-submission queries service? NEW July 2015
- 2. How should I send queries to the pre-submission queries service?NEW July 2015
- 3. How will my query be handled by the pre-submission queries service? NEW July 2015
- 4. When can I expect to receive a response to my query? NEW July 2015

- The Agency endeavours to provide a response within 5 working days
- With the response the MAH is notified of the contact details of the PM dealing with the request in case follow-up/clarification via e-mail or telephone is required

Submission requirements and other technical aspects

- Mandatory use of the electronic application forms for all submission to the EMA as of 1st July 2015
- Mandatory use of common repository for human centralised procedures as of 1st July 2015
- Mandatory use of the XML delivery file for all (CAPs and NAPs) PSUR submissions to the EMA via the eSubmission Gateway and/or the Web Client from 1st September 2015
- No longer “wet signature” on CHMP opinions. Procedure-related correspondence (e.g. notifications for variations, opinion letters, etc.) from the Agency is signed electronically

Topic area:

Labeling

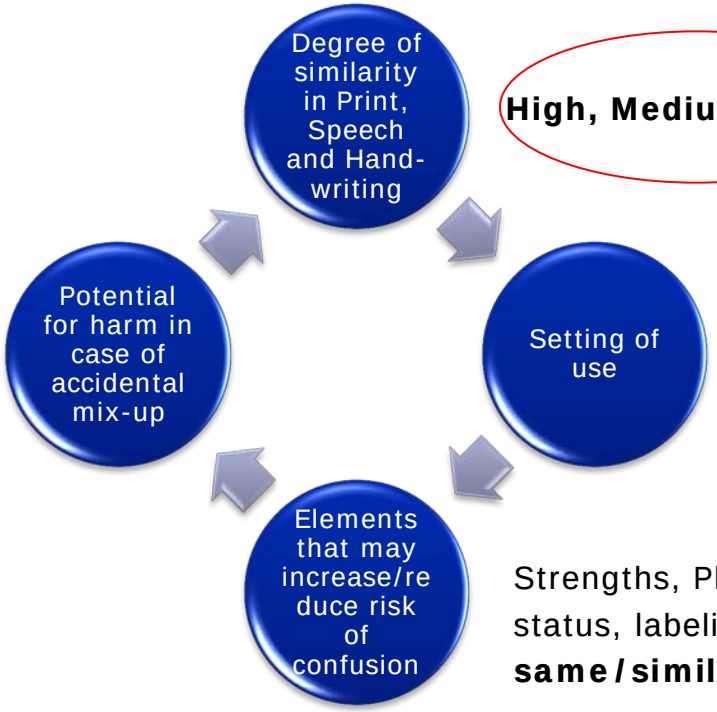
- Invented name
- SmPC / PI
- Mock-up / specimen
- Translations

Revision 6 of the "NRG guideline"* – effective since January 2015

- Eligibility to the centralised procedure is a requirement
- Any name proposed for a centralised procedure requires NRG review
- Up to 2 names can be accepted per marketing authorisation application; up to 2 names can be proposed per meeting
- Additional review of names may be allowed on a case by case basis on duly justified grounds
- Further clarification of review criteria, e.g. linking packaging and labelling design to the overall acceptance of invented names, in particular for OTC
- Modification of the product profile after acceptability of names may trigger further review of the name.
- 'Conditional' acceptability

* Guideline on the acceptability of names for human medicinal products processed through the centralised procedure (EMA/CHMP/287710/2014 – Rev. 6)

Increased transparency of the NRG decision making process in case of name similarity



High, Medium, Low?

Challenge!

High, medium, low?

Prescription
Dispensing
Preparation
Administration

Any medicines management controls that may reduce risk?

Strengths, Ph. forms, RoA, Legal status, labeling, Orphan status – **same / similar / different?**

With more detailed information available it is expected that applicants can better judge on the likelihood of success of a justification and – if submitted – that applicants provide justifications that better address the specific concerns.

Quick Response (QR) codes in the labelling and Package leaflet

- **Potential use of the QR code:** additional format to provide information to patients and healthcare professionals.
- Legal basis – Article 62 of Directive 2001/83/EC
  "the outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of product characteristics which is useful to the patient, with the exclusion of any element of a promotional nature".
- Guidance and request/declaration form recently published

Quick Response (QR) codes in the labelling and package leaflet of centrally authorised[1] medicinal products

General principles of acceptability and rules of procedure

Labelling exemptions – New recommendations

Recommendations for the implementation of the exemptions to the labelling and package leaflet obligations in the centralised procedure

Quality Review of Documents (QRD) group

EMA/276177/2015 rev.2

1. Orphan medicinal products [Article 63 (1)]
2. Medicinal products not intended to be delivered directly to patients or severe problems in the availability of the medicinal product [Article 63(3)]

- Exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet.
- Translation exemption of labelling and package leaflet

New policy on “Combined SmPCs”

Allow combined SmPCs for **different** strengths of the **same** pharmaceutical form for all languages **after the adoption** of the opinion.

- SmPCs must be completely **identical**, except for the few strength-specific details (e.g. if the **indications are different** for the different strengths, the SmPCs cannot be combined).
- In case of combined terms, only the primary pharmaceutical form should be considered, e.g. *solution for injection in vial* and *solution for injection in pre-filled syringe* can be combined.
- **Different** pharmaceutical forms will **always** be presented in **separate** SmPCs.

Revised labeling review process during MAA evaluation

1st evaluation phase: Initial EMA PI technical check to be carried out before Rapporteur Day 80 assessment report is produced => allow Rapporteurs to introduce their scientific comments in the same file

2nd evaluation phase: PI review (ex-D165 QRD comments) by Day 140 => for Rapporteur's to consider for their Day 150 assessment

Expected benefits from applicant's perspective:

- Early flagging of PI issues
- Only one set of comments on PI sent to the applicants at D120 and D180 => No more parallel documents
- Optimised workflow => improved clarity
- Better support to ensure consistency => throughout the evaluation, across therapeutic class, between SmPC and Package Leaflet

Interactions with patients and HCP during mock-up and specimen review

- Significant improvements to the labelling/packaging as result of collaboration with healthcare professionals, patients and patient safety and safe medication practice organisations
- Examples for reports from Patient safety and safe medication practices organisations (post-marketing):
  - Dosing errors reported due to expression of strength
  - Dosing errors reported due to active substance expressed as base rather than salt
- Intensification of interactions with patients and HCP in product specific consultations (insulins, oncology products etc.) to address potential risk of medication errors
- Consultation outcomes have been incorporated in assessment reports and were relevant for the final labeling

Translation of labelling changes following signal assessment

Since January 2015 translations in all official EU languages, as well as Norwegian and Icelandic, will be made available three weeks after publication in English.

18/02/2015

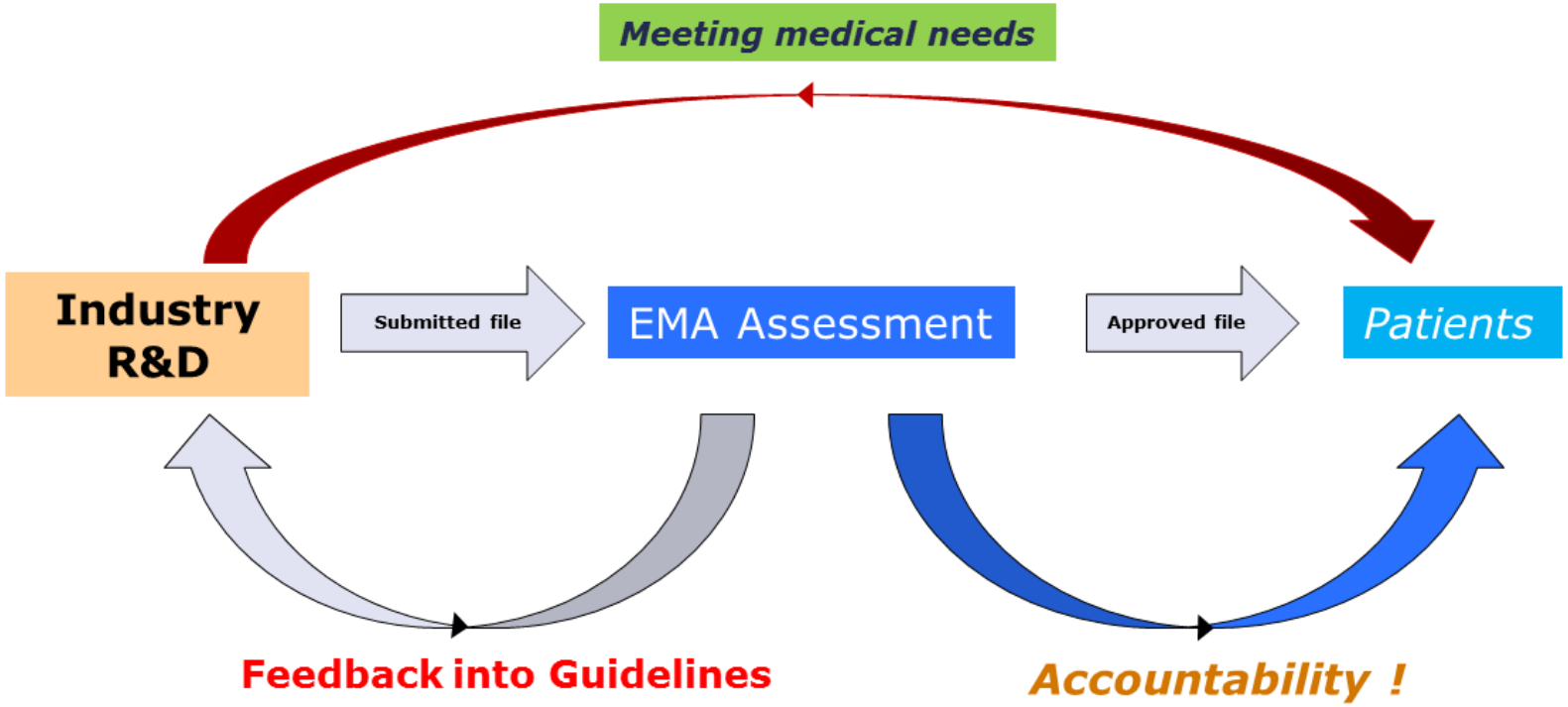
Safety signals: recommendations now available in all EU languages

Translations will facilitate consistent implementation of product-information changes across the EU and reduce administrative burden for stakeholders

The European Medicines Agency (EMA) has started to translate its recommended changes to product information based on the assessment of safety signals into all official languages of the European Union (EU). The translations should be used by pharmaceutical companies to update the product information of their medicines.

Acceleration of the implementation of changes to product information, ensuring consistency across EU countries, and reduction of administrative burden and costs.

Concluding remarks: “Raise the game” in the interest of the patient



Enrica Alteri at the 1st meeting of the Industry stakeholder platform on the operation of the centralised procedure on 24 April 2014

Thank you for your attention

Further information

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