CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

Adapting to Community referrals

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Why do we need referrals?

- Legal framework is important-binding decision
- Harmonisation of information
- Discussion at EU level on safety signals
- Same timetable for implementation
- No repetition of discussions on same topic

Referral procedures

- A referral is a procedure used to resolve disagreements and address concerns at EU level
- The EMA (CMDh) is asked to conduct scientific assessment of a particular medicine or class of products
- CHMP makes a recommendation
- European Commission issues a decision to all Member States
- Member States have to implement Commission decision in 30 days

Art 29 (4) of Dir 2001/83/EC

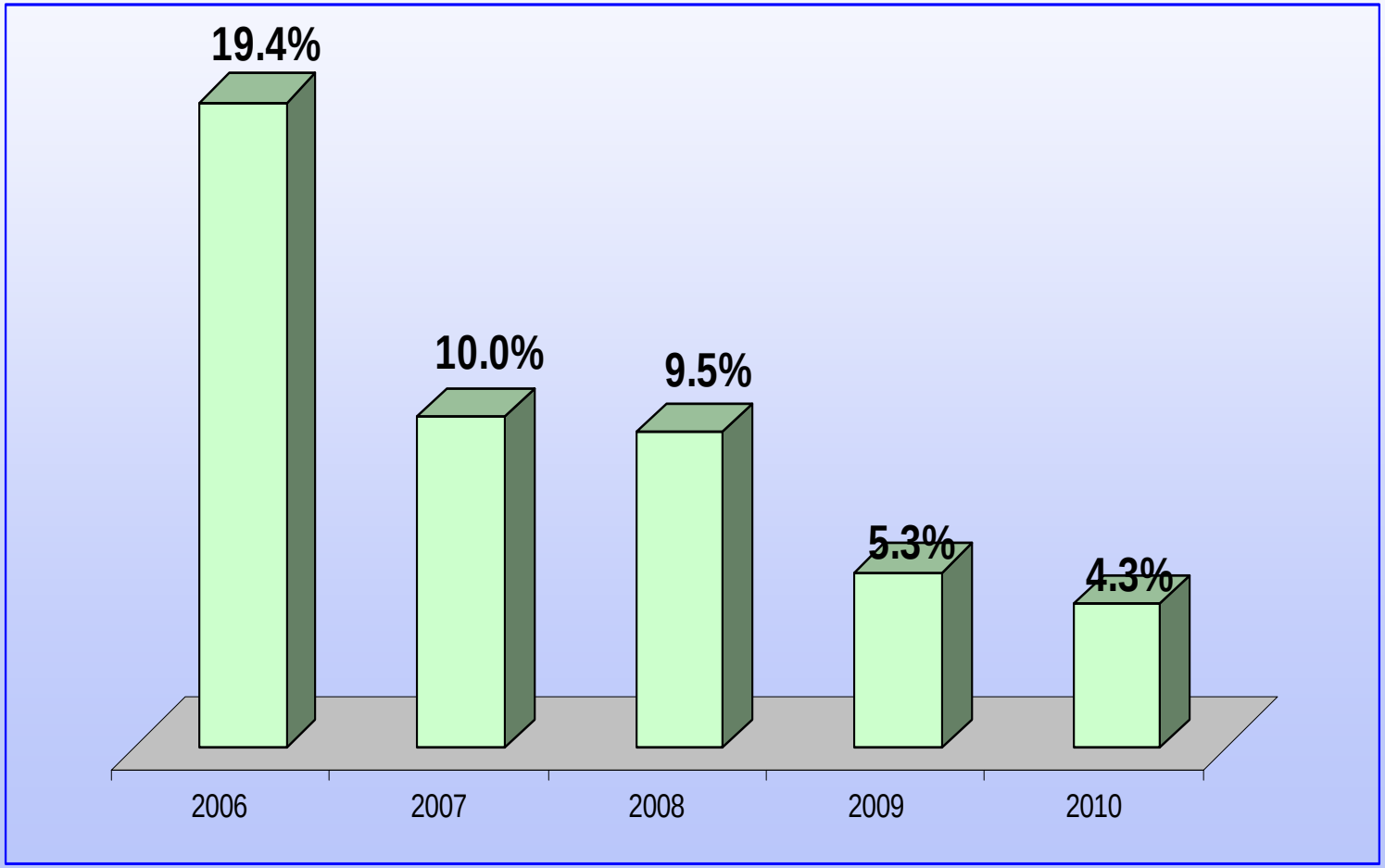
- This referral is triggered when there is a disagreement between CMSs and RMS regarding a medicine being evaluated during a ‘mutual recognition’ or ‘decentralised’ procedure, on the grounds of potential serious **risk to public health (**raised by CMS)
- First discussion in CMDh; 60 days timetable
- If there is no consensus between CMS and RMS in CMDh discussion, referral to CHMP

Commission guideline

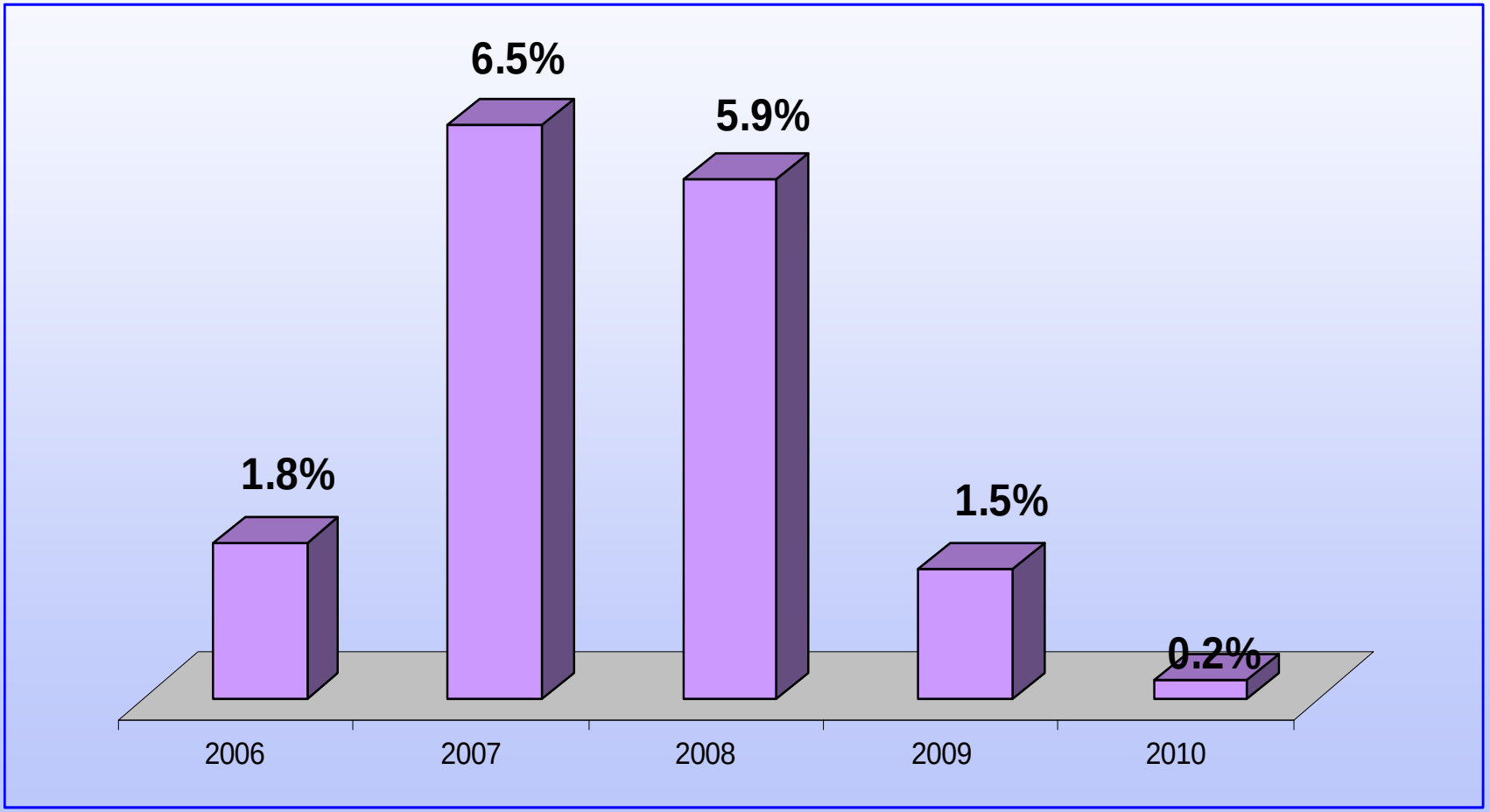
EC Guideline on the definition of PSRPH

- Efficacy not demonstrated, no adequate proof of bioequivalence
- Safety not sufficiently demonstrated
- Quality, major defects in quality
- Overall risk-benefit considered negative
- Product information: misleading, incorrect

Percentage of procedures referred in MRP since 2006



Percentage of procedures referred in DCP since 2006

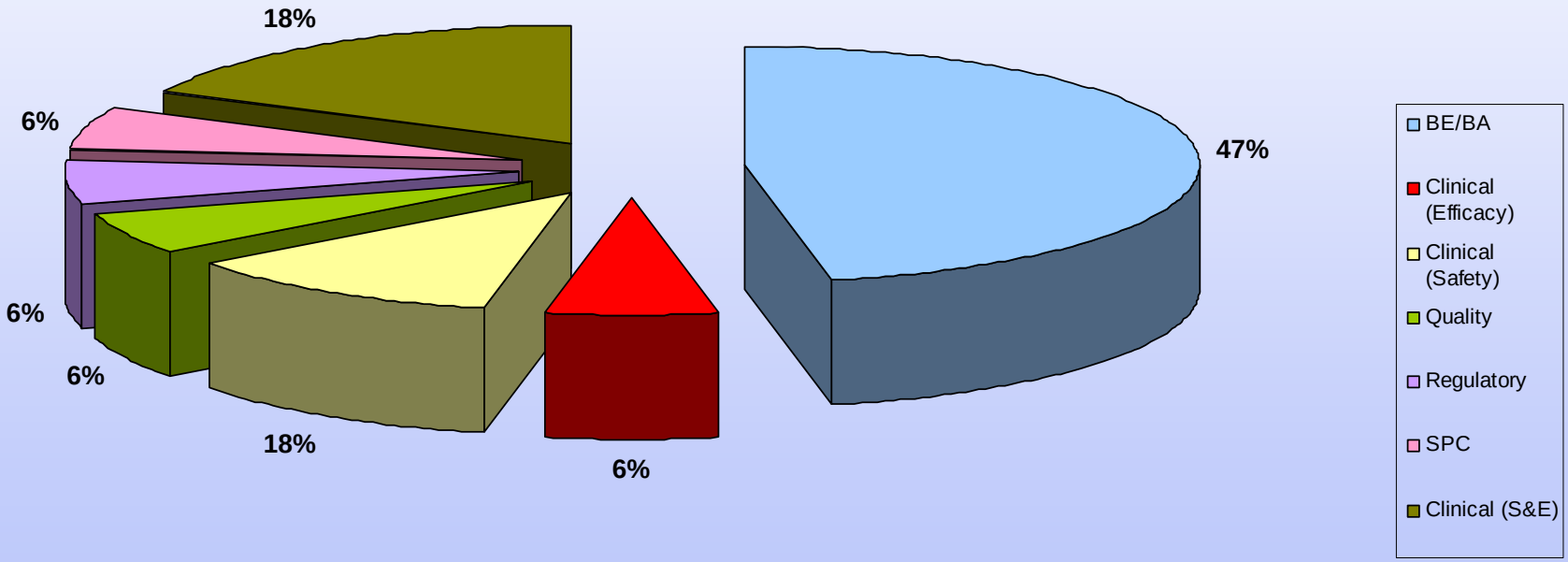


CMDh 60-day Referral Procedures
1st January to 31st December 2010

Per Grounds**

Procedures referred to CMDh in 2010*

** The numbers include **2** procedures (MRP) referred to the CMDh on identical grounds*



*** one procedure may be referred on more than one ground*

Experience CMDh referrals

- CMD(h) referrals are important to agree on common standards in assessment
- It is in the CMD(h) mandate to aim for consensus and avoid referrals to CHMP
- Recommendations to reduce the number of **unjustified** referrals should be followed in national agencies
- No repetion of discussions on the same topic
- Discussions should start earlier in DCP
- Pro-active approach needed for consistent assessment for same active moiety

Transparency on referrals art 29 (4)

- On website CMDh tracking table with overview of products referred to CMDh
- Overview of grounds for referral and outcome of procedure

- For specific questions on interpretation Bioequivalence guideline WG of PK assessors have been involved

- Publication of Q and A’s op website EMA

Art 30 of Dir 2001/83/EC

Divergent decisions

Who may start?

- Each MS, European Commission, applicant

Which Member States are involved?

- Each MSs where a marketing authorisation has been granted, suspended, refused, withdrawn

In which situation?

- If national authorities have taken divergent decisions with regard to one medicinal product, esspecially on Indications, Contra-indications and Posology

Experiences (1)

- This procedure has mainly been used to harmonise SPC's of innovators with major differences in Section 4.1, 4.2 and 4.3.
- Reason- Generics in Mutual recognition procedures meant harmonisation SPC/PL at EU level, but disharmonisation at national level
- Started before 2005, but has been used in a more systematic way after 2005
- CMDh got legal mandate to create an annual list of products for SmPC harmonisation

Experiences (2)

- 35 products have been referred on the basis of CMDh-annual list
- CMDh publishes each year draft list
- After some reluctance companies are also interested to initiate Art 30 referral procedure to harmonise their SmPC and PL
- Tracking table and overview on CMDh-website under Product information

Finalisation Art 30

- After Commission Decision implementation of SmPC and patient leaflet in 30 days
- After finalisation Art 30 procedure, Medicinal Products follow Mutual Recognition rules, no longer national variations allowed
- MAHs should contact future RMS after CHMP opinion before EC decision
- Module 3 can be harmonised during Art 30 procedure, otherwise afterwards in agreement with RMS
- Generics follow SPC and PL of innovator

Implementation (1)

Innovators

- MAH should contact RMS before Commission decision
- Further guidance is given in “ CMDh recommendations for MRP after finalisation of a referral procedure with a positive decision”
- If RMS has not all strenghts and pharmaceutical forms it can be necessary to appoint more than 1 RMS, but 1 lead RMS

Implementation (2)

- Commission decision is only applicable to products mentioned in annexe of decision
- MRP Repeat use procedure must be followed for new applications
- MRP Repeat use procedures can also be followed to bring national approved products into the Mutual recognition procedure after accession

Implementation

Generics:

- After finalisation of Art 30 procedure in CMDh press release a link is published to Commission decision
- Generic companies are encouraged to contact the RMS to harmonise product information if authorised via MRP/DCP through Type IB variation

Art 31 of Dir 2001/83/ERC

Community interest

Who can start procedure?

- Member States, Commission, MAH

In which situation?

- Community interest
- Community interest is : single market, public Health interest, especially used for safety reasons

Scope Art 31

- 1 product
- All medicinal product with same active substance
- Group (class) of products

- Art 31 (2) question can be limited to 1 aspect of registration; in that case no full harmonisation of SmPC .Mainly used for class of products, Products stay in national procedures
- Art 31 (1) : full harmonisation SmPC; mainly used for particular product. Products fall under the scope of MRP after finalisation procedure

Example of Art 31(2) referral

Modafinil

- Modafinil is used to promote wakefulness
- In 2007 PhVWP reviewed safety of modafinil containing medicines because of concerns that medicines were associated with serious psychitric disorders
- After discussion in PhVWP the UK medicines agency asked CHMP to carry out full assessment of the benefit-risk balance
- Conclusion CHMP:limited efficacy, risk odfserious side effects

Examples of Art 31(2) referral

Modafinil

Recommendation: Art 31

- Modafinil is only indicated to treat narcolepsy
- Modafinil should **no longer** be used to treat
  - obstructive sleep apnoea
  - Shift work sleep disorder
  - idiopathic hypersomnia
- Docters should be aware of the safety profile and they should monitor their patients appropriately

Future 107 referrals/Role PRAC

Urgent Union Procedure – art. 107i, 107j, 107k:

"…urgent action is considered necessary as a result of the evaluation of data resulting from pharmacovigilance activities"

- PRAC: 60 days to issue a recommendation, including wording in SmPC/PL if necessary and implementation timetable.
- CHMP/Coordination Group: 30 days to reach a position.

No Commission Decision in case of agreeement at the Coordination Group

Union procedures

- Art 107i shall be initiated by MS or Commission in any of the following cases:
  a) it considers suspending or revoking a marketing authorisation
  b) it considers prohibiting the supply of a medicinal product
  c) it considers refusing the renewal of a marketing authorisation
  d) is informed by MAH that, on the basis of safety recommendations, he has interrupted the placing on the market,.
  e) it considers that a new contraindication, a reduction in dose, or a restriction in indications is necessary

Art 107j (2):

The PRAC shall assess the matter which has been submitted to the Agency in accordance with Art 107i. The rapporteur shall closely collaborate with the rapporteur appointed by the CHMP and the RMS for the medicinal products concerned

Implementation of safety recommendations (2)

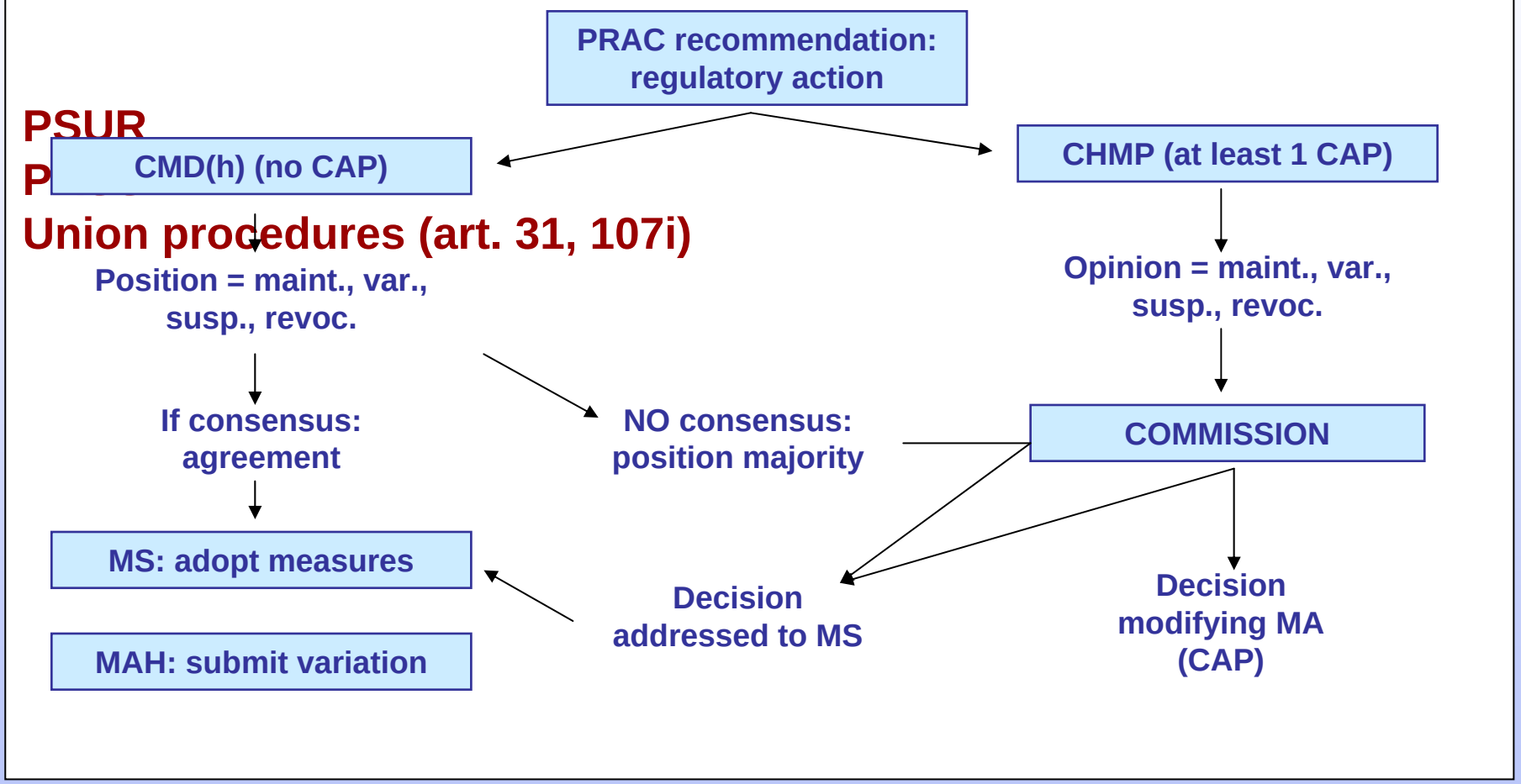
Future situation with recommendations PRAC

Reg no 1235/2010 Art 26 is about European medicines Webportal

i) the initiation of the procedure provided for in Art 107i to 107 k of Dir 2001/83/EC , the active substances or medicinal products concerned and the issue being addressed, any public hearings pursuant to that procedure and information on how to submit information and to participate in public hearings.

j) Conclusions of assessments, recommendations, opinions, approvals and decisions taken by the Committees referred to in points (a) and (aa) of Art 56(1) of this Regulation and by the coordinationgroup, the national competent authorities and the Commission in the framework of the procedures of Art 28, 28a and 28b etc.

Decision making



Implementation of safety recommendations (1)

Current situation

- Safety signals for nationally approved products are discussed in PhVWP, formal referrals are exceptions
- PhVWP sends report for national approved products (including MRP/DCP) to CMDh
- CMDh agrees on timetable for publication on CMDh website, with agreed wording
- Summary of Assessment report will be published on CHMP website in PhVWP press release
- Same situation for group of products, including centralised approved products
- Recommendations for centrally approved products go to CHMP

Recommendations for phasing in (1)

- All procedures before accession are national procedures
- EC decisions are only binding for those being addressed EU Mss

However:

- Harmonisation should not be lost with accession
- Preaccession harmonisation is preferable
- No repetition of discussions on safety issues

Recommendations for phasing in (2)

Where can information be found on referrals?

- The EMA announces the start of referral procedures in CHMP press release of the meeting when referrals are officially started
- In the same way, the EMA announces their conclusion in the CHMP press release of the meeting during the opinion is given

Recommendations for phasing in (3)

Information on the outcome of referrals;

Once the European Commission had issued its decision on the referral the following information is published:

- a list of all products affected by the referral
- the conclusion of the Committee
- SmPC/PL/other information

Transparency CMD(h)

Website: http://www.hma.eu/cmdh

- CMD(h) press release, every month
- Guidance Documents, Q and A's
- List of products referred to CMD(h) and CHMP
- Paediatrics, including PARs
- PhVWP recommendations with timetable for implementation
- Products approved in MRP/DCP:

  - MRI Product index includes SPC, PL and public assessment reports

CMDh
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Thank you

Any questions?

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