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CMD Best Practice (European aspect) on the new Variation Regulation

Dublin 22nd January 2010

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Overview of presentation

- Involvement of the Coordination Group for Mutual Recognition (MRP) and Decentralised Procedures (DCP)(CMD) in the new Variation Regulation
- New roles for the CMD
- The CMDh / CMDv (human & veterinary) BPG (Best Practice Guide): the application of variation procedures in MRP
- Work-sharing
- Article 5 procedure for the classification of 'unforeseen' variations

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Involvement of the CMD in the New Variation Regulation

- Regulation (EC) 1234/2008: effective since 1st January 2010, replacing 1084/2003 EC and 1085/2003 EC
- Concerns variations in the Mutual Recognition procedure (MRP), Decentralised procedure (DCP) and Centralised procedure (CP)
- CMDh Best Practice Guide updated (revision 6 published 26th October 2009 on the CMDh website)
  http://www.hma.eu/96.html

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New roles for the CMD

- Work-sharing (Article 20): to prevent duplication of assessments done by National Competent Authorities (NCA)
- Unforeseen variations (Article 5)
- Arbitration (Article 13) – 60 day CMD referral procedure: if no consensus – CXMP

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CMDh Best Practice Guide (BPG) (1)

- Intended to facilitate the handling of MR variations outlined in Notice to Applicants (NtA) Volume IIA, Chapter 5
- Provide details on the actions undertaken by the Reference Member State (RMS), Concerned Member State (CMS) and the applicant at each step of the variation process
- Provide detail on the involvement of the CMD, where applicable
- To ensure that a consistent approach is maintained and that variations are processed in an efficient manner

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CMDh Best Practice Guide (2)

Structure

Updates to:

- Chapter 1: Allocation of the MR variation number for Type I notifications, Type II variations, Grouping and Work-sharing
- Chapter 2: Procedure for automatic validation of MR procedures for variations
- Chapter 3: Processing of Type IA minor variations (notifications) in the MR procedure
- Chapter 4: Processing of Type IB minor variations in the MR procedure
- Chapter 5: Handling of Type II variations in the MR procedure

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CMDh Best Practice Guide (3)

New Chapters

- Chapter 6: Processing of Grouped applications in the MR procedure
- Chapter 7: Work-sharing
- Chapter 8: CMDh recommendations on unforeseen variations

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Chapter 1: Allocation of MR variation number for MRP (1)

- Veterinary medicinal products: vetinfo@imb.ie
- Human medicinal products: mostly in hands of the Marketing Authorisation Holder (MAH): responsible for allocating the number for all MR products
- Exceptions:

  1) Grouping Type IA notification affecting more than 1 marketing authorisation (MA)

  2) Work-sharing procedure
- These procedure numbers can only be allocated by the RMS or Reference Authority and must be obtained prior to submission of variation: Receipt&Validation@imb.ie
- If in doubt, contact the RMS or Reference Authority

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Chapter 1: Allocation of MR variation number for MRP (2)

- No changes in principle for Type IA, IB & II

CC/D/nnnn/sss/QQ/vvvv

where:

CC: two letter country code of RMS

D: is 'H' for medicinal products for human use and 'V' for medicinal products for veterinary use

nnnn: is the medicinal product number

sss: is the speciality number characterising the strength and / or pharmaceutical form of a medicinal product

QQ is either IA or IB for Type I notifications or II for Type II variations or X for extension applications

vvv: is a chronological number

eg: for a Type IA: IE/H/218/001/IA/001, for a Type IB: IE/H/218/001/IB/002 & Type II : IE/H/0218/001/II/003

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Chapter 1: Allocation of MR variation number for MRP (3)

- A grouped application or a work-sharing application is a single procedure for the variation
- For the purposes of handling grouping of variations and work-sharing the definition of a MA is **'all strengths and pharmaceutical forms of a certain product of one MAH '** (does not affect the national definition of a MA)
- Only for Type IA variations, is it allowed to group variations over more than one MA…if Type IB or Type II variations are applicable to more than one MA, then work-sharing has to be followed.

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Chapter 1: Allocation of MR variation number for MRP (4)

- Scheme for numbering of grouped variations:
  CC/D/nnnn/QQ/vvv/g

where: **CC** and **D** are as detailed in slide 10

nnnn: product counter (if 1 MA) and **xxxx** (if > 1 MA)

QQ: procedure qualifier (IA, IB, II, X)

vvvv: chronological number: if 1 MA: next available sequential variation counter and if > 1 MA: new sequential variation grouping counter (for Type IA only)

g : Grouping qualifier (G)

Examples: DE/H/0450/IB/0070/G (for 1 (same) MA)
DE/H/xxxx/IA/0004/G (for > 1 MA)

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Chapter 1: Allocation of MR variation number for MRP (5)

- Scheme for numbering of Work-sharing procedures

  CC/D/nnnn/QQ/vvvv where:

  CC and **D** are as before

  nnnn: the product counter is replaced by the placeholder: xxxx (literally is xxxx)

  QQ: procedure qualifier for the work-sharing procedure: WS

  vvvv: sequential work-sharing counter (new counter starting from 1 for each Reference Authority)

  example: DE/H/xxxx/WS/002
- Number is not product related
- A decision tree has been included in Annex II of Chapter 1 of the BPG

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Chapter 2: Procedure for automatic validation (1)

- Validation remains an administrative procedure
- Type IA notifications: within 5 calendar days of receipt of Type IA as annual reports and grouping and Type IA_{IN}, the RMS completes the Communication Tracking System (CTS)
- Type IB notifications: within 7 calendar days of variation application and supporting documentation (listed in the Classification guideline, Article 5 recommendation), the RMS creates the CTS record

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Chapter 2: Procedure for automatic validation (2)

- Where Type IB variations are not listed in the Classification Guideline or have been agreed following an Article 5 procedure…possibility of upgrading to a Type II
- Where RMS considers that the proposed change could have significant impact on the quality (Q), safety (S) and efficacy (E) of the medicinal product…additional 7 calendar days to give the RMS and CMS time to discuss before the final decision taken
- If upgrade to Type II is considered, the MAH has 21 days to update the application form for a Type II variation, pay the corresponding fee and submit any supplementary documentation

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Chapter 2: Procedure for automatic validation (3)

- Type II: the CMS should inform the RMS within 14 calendar day period of acceptance of a valid application and update CTS….unchanged
- Grouped applications: handled according to the highest variation type within the application
- Work-sharing: handled as for the Type II procedure with the Reference Authority taking the responsibilities of the RMS
- Flowcharts for automatic validation in Annex II of Chapter 2 BPG

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Chapter 3: Processing of Type IA minor variations (notifications) (1)

"Do and Tell"

- For MRP products, the RMS submission: list of dispatch dates, declaration re fees and application form should specify the MR variation number
- For grouped variations with > 1 MA: common cover letter and application form but separate supportive documentation and revised product information (PI), if applicable
- In MRP, the RMS is responsible for reviewing the variation
- CMS may only comment in the case of non receipt of documentation or non payment of fees
- Annex II of Chapter 3 BPG includes a flow chart for the procedure

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Chapter 3: Processing of Type IA minor variations (notifications) (2)

- Acceptable notification: the RMS will inform the MAH on behalf of the CMS and a letter of 'Acknowledgement of an acceptable Notification' will be issued. CMS informed of the outcome : updated CTS record
- Unacceptable notification: the RMS informs the MAH in writing, providing reasons and a course of action. CMS informed: updated CTS record stating the reasons for non acceptance
- Examples of letters: Annex I of Chapter 3 BPG
- Grouped variations: each variation in the group may have a different outcome: some accepted and some rejected (see Chapter 6 of BPG)

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Chapter 4: Processing of Type IB minor variations (notifications) (1)

"Tell, Wait and Do"

- RMS submission should include the list of dispatch dates and the declaration regarding fees
- For MRP products, if a MAH has not been sent an unfavourable opinion within 30 days of validation by the Competent Authority (CA), then it can be **assumed** that the variation is acceptable
- In MRP, the RMS is responsible for the review of the application, however, in the cases of change in the product name (category A2) and change in pack size (category B.II.e.5), input is needed from the CMS
- Annex II of Chapter 4 BPG has flowchart of procedure

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Chapter 4: Processing of Type IB minor variations (notifications) (2)

- Approval: the RMS will inform the MAH that the variation is acceptable together with the date of approval. CMS informed via updated CTS record
- Refusal: the RMS will inform the MAH and CMS reasons for refusal and will update CTS also stating the reasons for refusal
- Examples of letters in Annex I of BPG Chapter 4

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Chapter 5: Handling of Type II variations (1)

"Tell and Wait – requiring prior approval"

- RMS submission should include the list of dispatch dates and declaration regarding fees
- MAH may implement the change 30 days after the RMS approval
- Implementation of safety issues to be agreed between the MAH and the NCA
- NCAs implement the change within 2 months of approval or within 30 days if the variation results in an extended period of data protection (paediatric regulation, new indication)

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Chapter 5: Handling of Type II variations (2)

- Acceptance: RMS informs the MAH and CMS and if applicable, the MAH should send the national translations within 5 days of the end of the procedure (EOP)
- Rejection: RMS informs the MAH and CMS and provides reasons by e-mail and updates the CTS
- **Disagreement on grounds of a potential serious risk to public health (PSRPH) between Member States at the end of a procedure will result in a referral which will now be initiated at the CMD (60 day referral procedure), rather than the CXMP**
- To avoid arbitration, the MAH may withdraw the application from RMS and all CMS
- In the case of a rejection, the Regulation does not foresee a MAH appeal
- Flowcharts provided for the procedures in the BPG Chapter 5 Annex II

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Chapter 6: Grouped applications (1)

- Article 7 (Regulation 1234/2008/EC) and Annex III of the Regulation allow for the combination of several changes in to 1 application (grouping)
- For the purposes of grouping, it has been agreed that a MA can be considered to consist of all strengths and pharmaceutical forms of a medicinal product eg AT/H/1234/001-n
- Grouping can only be carried out by a single MAH
- MAHs recommended to inform RMS at least 2 months in advance: grouping not listed in Annex III, together with justification
- CMD is currently recommending that for MRP products, grouping should be confined to products with the same RMS

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Chapter 6: Grouped applications (2)

- For the purposes of grouping the definition of the same MAH applies according to EC communication 98/C 229/03:

  ”applicants belonging to the same mother company or group of companies have to be taken as one entity. Applicants which, (…) have concluded practices concerning the placing on the market of the relevant medicinal product in different MSs, also have to be taken as one”

- Not possible to include nationally authorised products (NAP) and MRP products together in grouped applications at the moment

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Chapter 6: Grouped applications (3)

- RMS introduces the outcome of the grouped variation in CTS

  1) approved if all single changes are approvable

  2) partially approvable if some of the single changes are refused or withdrawn (details in letter to MAH (stored in CTS)

  3) if the whole group is refused/withdrawn (details in letter to MAH (not stored in CTS)

- For MR products, if a group contains a Type II variation or line extension and if a CMS cannot approve the variation on the basis of PSRPH, then the RMS will refer the procedure to the CMD (unless the application is withdrawn by the MAH before the end of the procedure)

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Chapter 6: Grouped applications (4)

- Generally, the whole group of changes will not be approved until the referral is finalised. The CMD will only discuss the single issue and not the whole group
- If it is considered that one of the other changes in the group is very urgent and completely independent from the referred change, the MAH may request the RMS to implement this change in advance
- Procedures may only be referred to the CMD by the RMS and not by a MAH
- CMD intends to publish examples of grouping which are acceptable / non acceptable

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Chapter 7: Work-sharing (1)

- Article 20 (Regulation 1234/2008/EC) sets out the possibility for a MAH to submit the same Type IB or Type II variation or the same group of variations affecting > 1 MA from the same MAH, in 1 application – Work-sharing (optional procedure)

- This may also contain Type IA changes only if these are included in a group containing also Type IB or Type II variations

- Line extensions may not be included

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Chapter 7: Work-sharing (2)

- Nationally authorised products are currently excluded from WS procedures. However, NCAs can choose to take the outcome of any relevant WS procedures into account

- To be suitable for a WS procedure, it is expected that the same change(s) will apply to the different medicinal products, with either no or limited need for assessment of a specific product

- For WS, the same definitions of MA and MAH, as defined and discussed for grouping, will apply

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Chapter 7: Work-sharing (3)

- MAHs are advised to provide advanced notice (3 – 6 month) of an upcoming WS procedure, to the CMD:

  - a list of the concerned MAs
  - justification as to why all the MAs are considered to belong to the same MAH
  - description of the variation
  - preferred and justified Reference Authority
  - justification as to why a WS procedure is suitable
  - planned submission date

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Chapter 7: Work-sharing (4)

- Pre-submission information should be submitted to the CMD Secretariat via CMDhSecretariat@emea.europa.eu

  2 weeks in advance of the next CMDh meeting (list of CMDh meetings: http://www.hma.eu/115.htm)
- At the latest, 2 weeks after the CMDh meeting: MAH will be informed by the CMDh if the WS application has been accepted and which NCA will act as Reference Authority
- The CMDh may on it's own initiative, or if requested by the MAH, give advice on the suitability and/or practicability of the proposed WS procedure

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Chapter 7: Work-sharing (5)

- If there is a centrally authorised product (CAP) included in a WS procedure, the European Medicines Agency is automatically the Reference Authority

- For all other cases, the CMD will appoint the Reference Authority for the WS procedure.

- Where the chosen Reference Authority has not granted a MA for all the products in the application, the CMD on the request of that Reference Authority, may ask another relevant authority to assist

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Chapter 7: Work-sharing (6)

- Submitted as 1 integrated package covering all variations for all medicinal products:
  - a common cover letter
  - common application form (including the variation procedure number (requested from the Reference Authority))
  - details of the MA(s) concerned
  - details of the current situation and proposed changes for all products involved in the WS
  - separate supportive documentation and revised product information, if applicable, for each medicinal product

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Chapter 7: Work-sharing (7)

- The WS procedure will follow a standard Type II variation procedure of 60 days followed by a 30 day period for national implementation (even if the procedure only concerns Type IB changes)
- The 60 day procedure can be extended if supplementary information is required
- Advice may be sought from the CMD or a relevant CXMP Working party during the procedure
- No 'automatic' discussion of procedure at the CMD
- At the end of the WS procedure, the Reference Authority will issue a finalisation letter which will also list any parts of the application which were not considered approvable

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Chapter 7: Work-sharing (8)
Outcome procedure: Reference Authority : MS

- If at the end of the WS procedure there is a CMS who cannot approve the variation on the basis of a PSRPH, the Reference Authority refers the procedure to the CMD according to the same principles as discussed for grouping applications (except that in WS procedures Type IB changes can also be referred)

- A CMS raising a PSRPH must do so within 30 days of the distribution of the final opinion of the Reference Authority - practical agreement to do this within 10 days, to keep 20 days for amendment of MA

- If no request for CMD referral is sent within 10 days, variation is accepted

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Chapter 7: Work-sharing (9)
Outcome procedure: Reference Authority : MS

- As for grouping, the whole group of changes will be referred to the CMD and will not be approved until the end of the referral procedure. Only the single unacceptable change will be discussed

- CMS approve the final opinion of the Reference Authority, inform the Reference Authority and amend the MAs within 30 days

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Chapter 7: Work-sharing (10)
Outcome procedure: Reference Authority : EMA

- CMS to approve opinion, inform the European Medicines Agency and amend the MA concerned within 30 days
- Where a CMS cannot approve the final opinion, an Article 31 referral shall be initiated within 30 days – practical agreement to do this within 10 days, to have 20 days to amend the MA
- Variation is accepted if no request is sent within 10 days , for an Article 31 referral

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Chapter 7: Work-sharing (11) Implementation (as for Type II)

- If a change to the product information is part of the WS procedure, then the amended versions should be submitted in English and in the national translations within 5 days of the circulation of the finalisation letter from the Reference Authority and may be implemented 30 days after that if no comments are received
- Variations related to safety issues must be implemented within a time frame agreed between the reference authority and the MAH
- All other changes can be implemented 10 days following receipt of the finalisation letter from the Reference Authority, unless a CMDh referral or Article 31 referral is initiated within 10 days

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Chapter 8: Unforeseen variations (1)

- A MAH can choose to submit an ‘unclassified’ variation as either a Type IB or Type II variation, taking into consideration the general definitions included in the Regulation

- If a MAH submits such a variation as a Type IB, a CA can request that this be upgraded to a Type II (S, Q, E), during validation (7 (+7 (to consult with the CMS in the procedure)), if the IB classification is considered to be incorrect

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Chapter 8: Unforeseen variations (2)

- Article 5 of the Regulation provides the basis for a MAH or a CA to request CMDh, CMDv or the European Medicines Agency to provide a recommendation on the classification of a variation which is not listed in the Classification guideline or in the Annex (Type IB = default)
- 45 day procedure at the end of which the recommendations will be published….no appeal
- Recommendations to be used to update the Guideline at a later time by the EC
- Has been in force since 1st January 2009

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Chapter 8: Unforeseen variations (3)

- Recommendation request submitted to CMD Secretariat via:

  h-cmdhsecretariat@emea.europa.eu

  prior to the submission of the variation, at least 2 weeks before the start of CMD meeting
- MRP - <Product name> -Art. 5 variation classification request
- Application form published on CMDh website: http://www.hma.eu/265.html
- Detailed description of the product, proposed variation, details of any previously similar submitted variation and classification of same, why variation is considered to be unclassified

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Chapter 8: Unforeseen variations (4)

- CMDh Secretariat send proposal for a recommendation to CMDh members, secretariat CMDv, European Medicines Agency contact point and the EC via designated mailbox
- Rapporteur is appointed at CMD
- There is opportunity for comments by the Member States, European Medicines Agency and the relevant CXMP Working Parties
- No discussion at the CMDh meeting if no divergent opinions received from the MS
- Divergent opinions among the CMDh MS: voting according to the Rules of procedure (RoP) (no MAH participation)
- Divergent opinions between CMDh/CMDv/ EMA: recommendation sent to the EC, for information

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Chapter 8: Unforeseen variations (5)

- Recommendation: sent to MAH, EMA, NCAs and EC by Monday after the CMD meeting

- Recommendation includes conditions applicable but not required documentation

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Conclusions

- CMD BPG, a common interpretation of the Procedural Guideline, to ensure a consistent and efficient approach in the handling of variation applications
- Work-sharing now formalised (already happening upon request by a MAH)
- Q & As published on the CMD website
- Ongoing meetings of the Joint Variation Subgroup
- CMD BPG will be further updated after experience gained with the new Variation Regulation

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Thank you

- Thank you very much for your attention

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