EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA procedural updates

Regulatory ‘noticeboard’

EMA Veterinary Medicines Info Day 16-17 March 2017, London

Presented by Emily Drury on 17 March 2017
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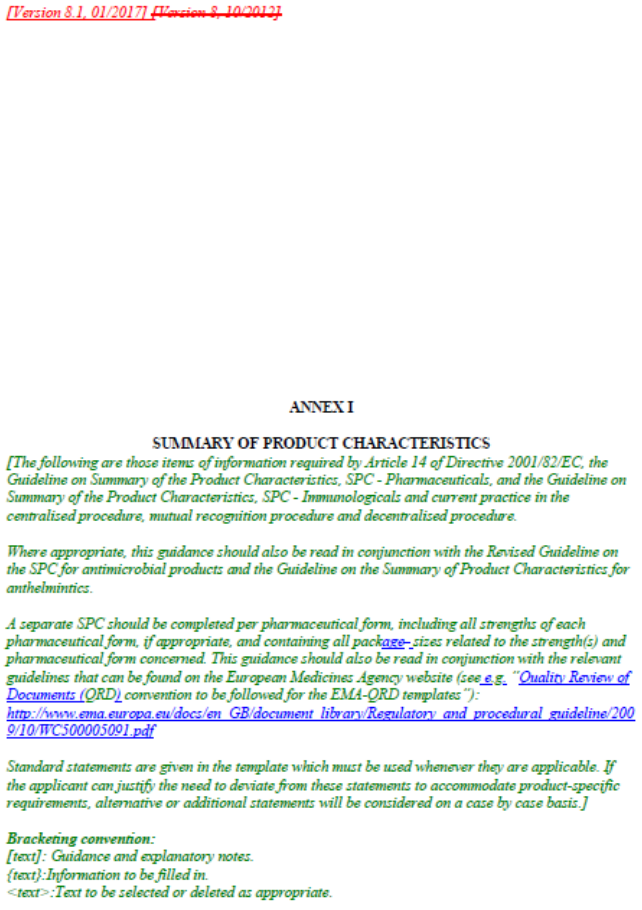
Overview of presentation

Areas of regulatory activity in 2016

- Local representatives
- Handling of new standard terms
- Variations: grouping, classification & worksharing
- New regulatory Q&As
  - Quality
  - Editorial changes within dossier
  - SPC content
  - Classification (prescription-status) of centrally-authorised products

Overview of presentation
Quality Review of Documents (QRD)

- Updated QRD template v.8.1
  - Implementation plan
- Combined label-leaflet template
- Draft pictogram guidance
- QR codes



[Version 8.1, 01/2017] ~~[Version 8, 10/2012]~~

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

[The following are those items of information required by Article 14 of Directive 2001/82/EC, the Guideline on Summary of the Product Characteristics, SPC - Pharmaceuticals, and the Guideline on Summary of the Product Characteristics, SPC - Immunologicals and current practice in the centralised procedure, mutual recognition procedure and decentralised procedure.

Where appropriate, this guidance should also be read in conjunction with the Revised Guideline on the SPC for antimicrobial products and the Guideline on the Summary of Product Characteristics for anthelmintics.

A separate SPC should be completed per pharmaceutical form, including all strengths of each pharmaceutical form, if appropriate, and containing all package sizes related to the strength(s) and pharmaceutical form concerned. This guidance should also be read in conjunction with the relevant guidelines that can be found on the European Medicines Agency website (see e.g. "Quality Review of Documents (QRD) convention to be followed for the EMA-QRD templates"): http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500005091.pdf

Standard statements are given in the template which must be used whenever they are applicable. If the applicant can justify the need to deviate from these statements to accommodate product-specific requirements, alternative or additional statements will be considered on a case by case basis.]

Bracketing convention:
[text]: Guidance and explanatory notes.
{text}:Information to be filled in.
<text>:Text to be selected or deleted as appropriate.

Local representatives

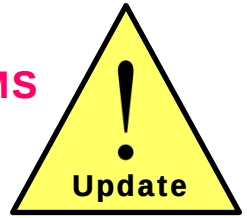
Definition

- A local representative, defined within Article 1(17a) of Directive 2001/82/EC, is the person “designated by the MAH to represent him in the Member State concerned”.
  - Should be able to respond in local language
- On the above basis, local reps can be included in section 15 of the package leaflet

Local representatives (2)

What has to appear in PI vs printed leaflet

- For CAP, product information (PI) = Annexes I, II, IIIA & IIIB
  - Package leaflet (PL) = Annex IIIB
- QRD template provides the content and format of these annexes
- If local reps are proposed, in section 15 of Annex IIIB **there must be one per MS**
  - Not possible to have designated local reps for only some MSs
  - NB a local rep may be designated for >1 MS
- On the actual printed leaflet, only the concerned local rep for that territory can be mentioned under section 15
- This is reflected in QRD template v.8.1 – see annotated version of PL



Local representatives (3)

Logos

- If local reps are mentioned in section 15 of the PL, they can be included within the blue-box of the outer pack only by name, phone no. /email and, if space permits, logo. The presence of the logo should not lead to reduced readability of the packaging text.

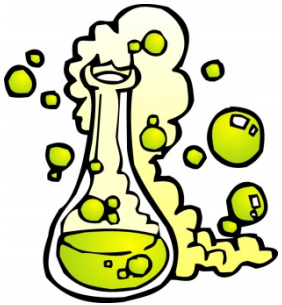
- Distributors or co-promoters cannot be shown on the outer pack unless they are equally nominated as local representatives in the PL (and able to fulfil that duty e.g. replying to enquiries in the local language of the requestor)

- This is to ensure that the entity responsible for placing the VMP on the market is readily identifiable

Standard terms (1)

What to do if you are proposing a new standard term

- New pharmaceutical form, route of administration, target species etc.



  - Inform EMA well in advance i.e. notification of intent to submit initial MAA (and let us know if the proposed term changes before submission)
  - Alerting EMA in advance allows for beneficial dialogue to construct the case for new term

Standard terms (2)
Continued

- EMA will ask applicant to complete ‘eAF term request form’
  - Specifically address why existing standard terms or combination of existing terms could not work
  - If standard term request not been initiated by applicant at least 10 days before submission, the proposed term will not be available in eAF drop-down menu
    - In this case, choose closest term in eAF and discuss with EMA during validation period
- QRD, CMDv and CVMP consideration of proposed term (ends here for target species)
- For quality terms, subsequent consideration by EDQM
- Ongoing collaboration with applicant to find best possible solution
- Must be solved by D180 or CVMP opinion, and therefore EC Decision, may have wrong terminology

Variations (1)

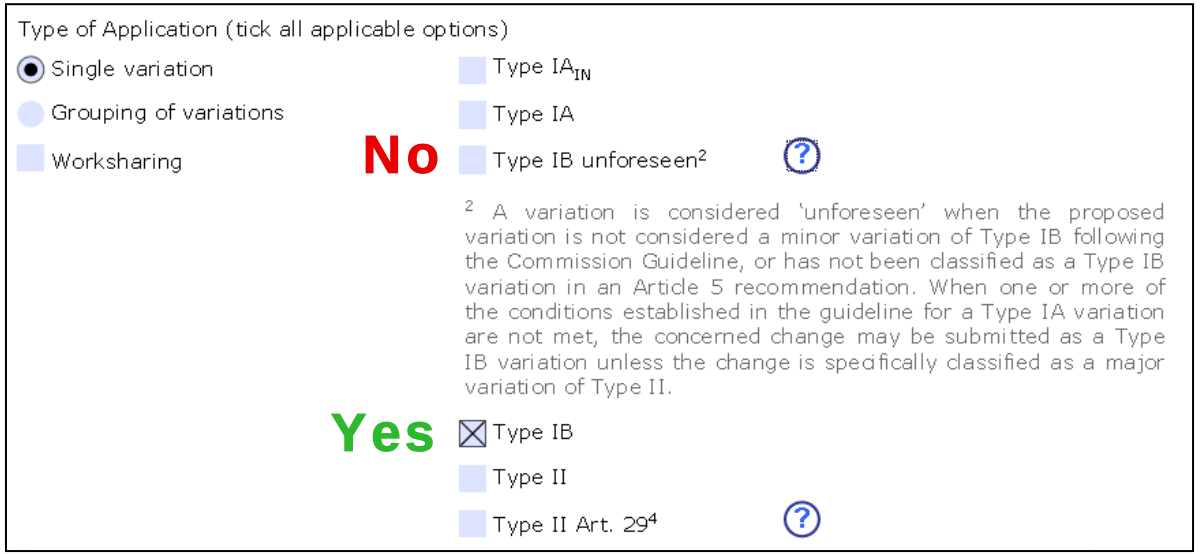
Some tips on grouping

- Reminder: EMA uses term ‘IG’s to refer to ‘internal groupings’
- ‘IGs‘ covered by Art. 7.2(a) of variations Reg. (EC) 1234/2008
- Grouped Type IAs/IA_{IN} applicable in the same way to several products, belonging to the same MAH and submitted to same relevant authority (i.e. the handling of that grouping across products is internal to that authority)
- On the eAF and cover Letter only select ‘grouping’ if there is > 1 variation scope.
- If only one scope affects > 1 product in an IG, do still select ‘single’ variation
  - i.e. on eAF ‘grouping’ refers to no. of scope, not no. products

Variations (2)

Upgrading of variations

- Upgrading still causes much confusion !
- If a condition of a Type IA/IA_{IN} is not met, upgrade to Type IB (or II) WITHIN SAME SCOPE
  - NOT unforeseen
  - NOT 'by default'
  - i.e. not 'z'



Variations (3)

Upgrading of variations continued

In variation eAF, explain which condition is not met

Always provide extract of classif. GL indicating which conditions are/are not met

B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in the manufacturing process	1, 2, 3, 4, 5, 6, 7	1, 2, 3, 4, 5, 6, 7, 8	IA
Conditions			
X 1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.			
2. Either the change relates to an immediate release solid oral dosage form / oral solution and the medicinal product concerned is not a biological /immunological or herbal medicinal product; or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form). Since the product concerned is an immunological product, this change becomes a type IB variation by default.			

IA

B.II.b.3	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	Procedure type		Top
☒ a)	Minor change in the manufacturing process	☐ IA	☒ IB[a]	☐ Art. 5 Implement. Date: + −

[a]If one of the conditions is not met and the change is not specifically listed as Type II.

Variations (4)

Unforeseen variations = Type IB 'by default'

- Only use Type IB unforeseen if change not classified at all in GL and no recommendation issued under art. 5 of variations Regulation
  - Check on CMDh website first (includes EMA art. 5 recommendations)
- No such thing as Type IA 'z' (unless this is outcome of EMA/CMDh/v art. 5 recommendation)
- If submitting an unforeseen variation i.e. a 'Type IB' by default, use higher, most relevant category and allocate 'z' as variation number e.g.
  - C.I.4.z used quite often for changes to SPC that do not need a Type II e.g. additional wording in PI due to outcome of PSUR
  - Change to in-process test(s) or limits applied during manufacture of the FP e.g. if not considered a critical parameter = unforeseen IB under B.II.b.5.z

Worksharing of variations (1)

Some tips

- Worksharing (of assessment across products) precludes any product-specific assessment
- Worksharing involving CAPs and NAPs (MRP/DCP/purely-national)
  - Letter of intent sent to EMA, EMA forwards to CMDv, discussed at next CMDv meeting, any comments forwarded to applicant for revised letter of intent (e.g. incorrect MA no.s, amended classification)
  - Clearly separate in letter of intent which products are authorised nationally via MRP/DCP and which are purely-national
  - Discuss any classification queries in advance with EMA (vet.applications@ema.europa.eu)
- If worksharing project is dependent on timings of national MAH transfers e.g. new/updated DDPS following a merger, it can be useful to engage in pre-submission dialogue with EMA/CMDv to avoid validation issues:
  - EMA will coordinate dialogue, please contact vet.applications@ema.europa.eu

Worksharing of variations (2)

CAP-NAP worksharing continued…

- Submit variation form + Annex B (NAP listing)
  - ‘Annex B’ available on EMA website under Q&As on worksharing
  - No need to submit Annex A (CAP listing) unless information there is actually affected by variation… if so, submit a tailored Annex A in tracked changes *showing only presentations affected by variation*
- For large CAP-NAP worksharings (record is 750 products!), EMA may kindly ask for an editable annex of all involved products that are authorised via MRP/DCP
  - Can just be a copy of working document that applicant is using to manage the project internally
  - Greatly facilitates the accurate entering of MAs into the Member States’ tracking database called ‘CTS’

New Q&As

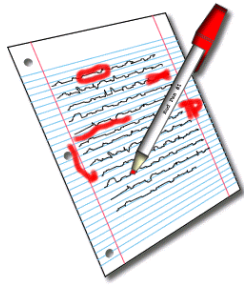
Quality variations (1) See vet post-authorisation Q&A for Type IIs, no. 15

- New handling of introduction of new FP manufacturing site
  - Agreed by CMDh/CMDv/EMA in July 2016
- Single ‘complex’ Type II
- Includes all changes to manufacturing process linked to the new FP manf. (site A), IPCs, changes in batch size etc. and also covers all the operations performed by the site (i.e. primary, secondary packaging or testing). However if, as consequence of the introduction of the new site A, a new external site B is introduced, where e.g. part of the product testing is performed, an additional scope would be needed for the site B.
- Changes to FP specifications not normally covered and should be submitted as grouped changes, even if they are consequential to the new site.

New Q&As

Editorial changes within the dossier

See vet post-authorisation Q&A for Type IAs, IBs or Type IIs, respectively



- A common example is editorial changes within manufacturing test methods / methods of analysis e.g. reference to SOPs, rearranging of same information, typographical errors
- All detail on how to handle editorial changes is given in the Q&A
- Key point is that editorial changes should be submitted at the same time as a variation
  - i.e. within an electronic submission, not just as an email attachment
- Improves traceability because we ask that the editorial changes are referred to in the precise scope of the variation, which is tracked in our SIAMED database
- Please only submit editorial changes with a variation affecting the same pharmaceutical form

New Q&As (1)

3 new Q&As when writing / updating the SPC

See EMA website: Product information/Reference and guidelines

1. Information contained in section 5.1 of the SPC on pharmacodynamics (pharmaceuticals)
   - Only elaborate PD properties directly related to the approved indication

2. Mentioning solvents in the product information, including trade names and scenarios when solvent packaged with product / separately

~~**Diluent**~~ **Solvent** ✓

3. How to express frequency of adverse events in line with convention of QRD template
   - Only give highest incidence, taking into account studies and PhV data (not both e.g. if AR incidence is higher in studies and lower in PhV data, the higher frequency only from studies should be given)

New Q&As (2)

Classification of CAPs

See EMA website: Post-authorisation procedural Q&A

New Q&A gives guidance on:

- which medicines required a prescription
- exemption criteria
- advertising
- different prescription status for different pharm. forms and target species
- what is the procedure to switch

QRD

Templates v.8.1 published on 15 Feb ‘17

- Main changes are:
  - SPC section 4.2, standard statements for onset/duration of immunity
  - SPC section 4.4, optional standard statement, ‘Vaccinate healthy animals only’
  - SPC section 4.6, amended to reflect CVMP Q&A on expressing frequency of adverse reactions
  - SPC section 4.11 (residues in eggs), current standard statement has been extended so that use is also forbidden in birds intended to produce eggs for human consumption where no MRL exists for eggs and where a safe {X} week period prior to start of laying cannot be calculated.
  - The term diluent is changed to solvent
  - Package leaflet section 6, revised advice on when/how to report side effects
- Separate implementation plans for CP/MRP/DCP/purely-national on EMA/CMDv websites
  - Implementation can affect currently-ongoing procedures so please check 

QRD

Combined label-package leaflet template

- Endorsed by CVMP & CMDv in Dec ‘16 and will shortly be published on EMA website
- Where applicant intends not to print a package leaflet and all labelling + leaflet information is printed on the immediate packaging, which is foreseen by Art. 61(1) of Directive 2001/82/EC.
- Objective is to harmonise existing initiatives at the national level and to ensure that critical elements are prominently located on these types of packs.
- Template can be introduced for an existing product using variation C.II.6.b (Type IB)
- A pilot phase of 18 months is proposed
- During this time, please use the template and send any feedback to qrd@ema.europa.eu using comments form on website
- After pilot, template will be incorporated into the full set of QRD templates (v.8.1)

QRD

Pictogram guidance

- Follows up on an industry-led proposal for a standard ‘catalogue’
- CMDv agreed to take forwards target species pictograms
- Brought under umbrella of QRD
- Draft guidance published for consultation in Nov ‘16 until end of Feb ’17 (if you have any late comments, let us know: qrd@ema.europa.eu)
- Outlines principles and mechanisms to introduce pictograms
  - Currently target species pictograms can only replace target species text on small, immediate labelling
  - Any other pictograms printed in addition to required text
- Feedback from consultation will be reviewed by QRD group in 1st half of 2017

QRD

QR codes

- Veterinary guidance for handling of QR codes to be progressed this year between EMA/CVMP/CMDv/QRD
- If applicant wishes to include a QR code in PI, please ask for a QR code request form from vet.applications@ema.europa.eu
- Request form to be submitted with Part 1 of MAA dossier
- Presence of QR code should also be indicated within product information and mock-ups
- Any material linked from the QR code (e.g. video) should included for assessment, at latest with D121 responses to questions

Thank you for your attention

Further information

vet.applications@ema.europa.eu

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