EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Variations for Centrally Authorised Products

What's changed?

2nd EMA Veterinary Medicines Info Day 2021

Presented by Catherine Griffin on 30 November 2021
National Expert, Veterinary Pharmaceuticals

Introduction

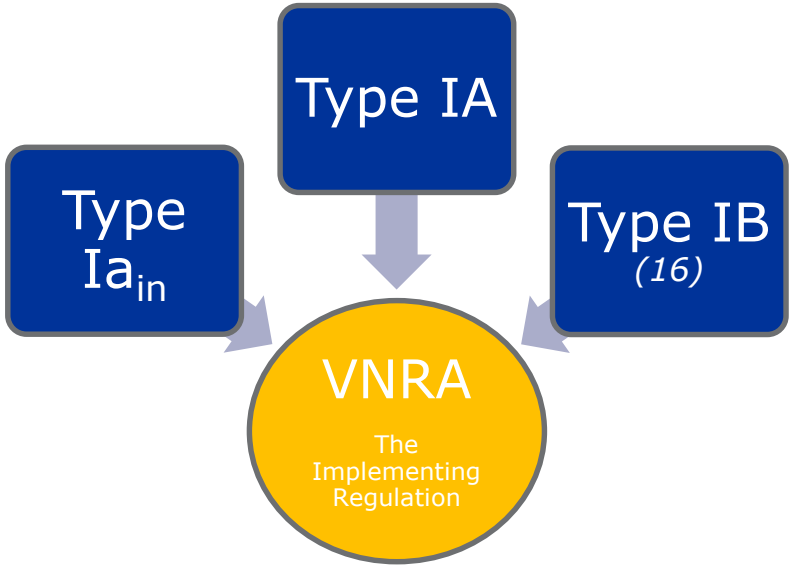
- Brief background
- Variations Not Requiring Assessment (VNRA)
  - Structure of the variations
  - Important points
- Variations Requiring Assessment (VRA)
  - Timetables
  - Important points

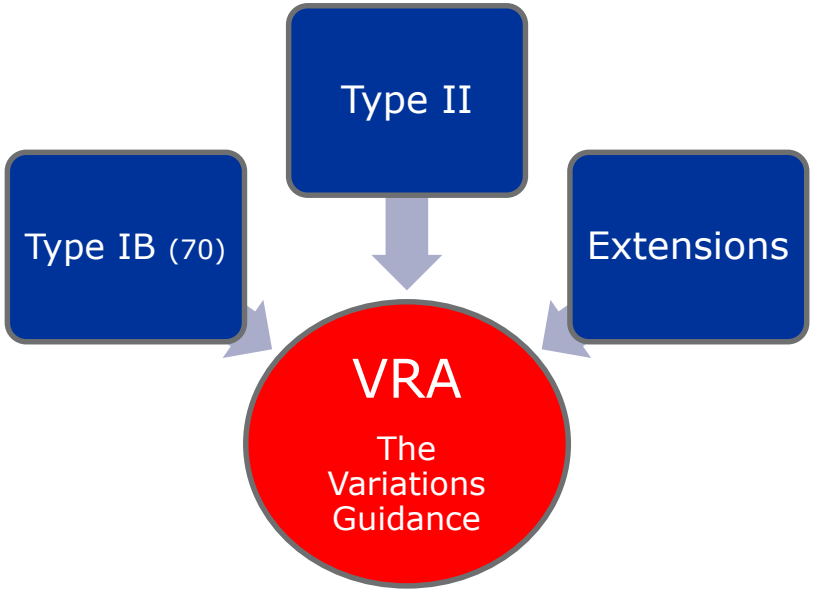
Brief Background- How we got here

- Articles 60-68 of Regulation (EU) 2019/6 specifies that there will be two types of variations- variations requiring assessment (VRA) and variations not requiring assessment (VNRA) and details the requirements for both.
- An expert group consisting of experts from the network and EMA representatives, formed in 2019, provided advice to the European Commission regarding a list of VNRAs that would not require scientific assessment.
- This advice was used by the Commission as the basis for the list of VNRAs included in the Implementing Regulation (EU) 2021/17 which will come into effect from 28 January 2022.

Evolution of the Implementing Regulation (EU) 2021/17 cont.

Where do the current variations fall now?





Variations Not Requiring Assessment (VNRA)

VNRA- Implementing Regulation (EU) 2021/17- Structure

- Divided into 4 main categories:
  - A. Administrative changes
  - B. Changes to the Quality part of the dossier
  - C. Changes to the Safety, Efficacy and Pharmacovigilance part of the dossier
  - D. Changes to the Vaccine antigen master file (VAMF) part of the dossier

Category	A	B	C	D
Number of variations	2	51	10	2

Example from the Implementing Regulation (EU) 2021/17

	Variation	Requirements	
Number		Conditions	Documents to be provided
B.27	*Change to in-process tests or limits applied during the manufacture of the finished product*	*The changes shall not relate to a commitment or to an un expected event during manufacture.* *The change shall not have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the finished product intermediates or in-process materials*	*Comparative table of former and new in-process limits*
a)	-tightening of in-process limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	Amendment of the relevant sections of the dossier.
b)	-addition of a new in-process test limits	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopeial microbiological method.	Amendment of the relevant section(s) of the dossier for method and validation, batch data and relevant comparative data.

What happens if the change does not meet the requirements for VNRA?

- If the proposed changes does not meet the requirements for a VNRA then **it is a Variation Requiring Assessment.**
- As such an application for the change needs to be submitted to the relevant CA.
- The Guidance on VRA has anticipated such situations and have provided for them though the use of “Z” variations.

What happens if the change is not listed anywhere?

- The Guidance on VRA also considers this scenario and has a procedure for the classification of a change.
- However, even if a change is classified as not requiring assessment it will not be possible to process it as such until the Implementing Regulation (EU) 2021/17 and consequently the Union Product Database (UPD) has been updated.

Other points

- Translations
  - *For CAP products submit all translations with the initial submission*
- UPD
  - *The UPD does not yet have a full functionalities. For example- until there is a specific field, the precise scope of the VNRA should be entered into the "comments" field in the UPD.*
- Commission decision
  - *Only VNRA that affect the PI will be sent for a commission implementing decision*

Other points Cont.

- Grouping
  - *Grouping is allowed with VNRA but not between VNRA and VRA*
- Approval on the UPD
  - *No notification of approval, MAH's can check the status of a VNRA in the UPD*
- Implementation dates
  - *Use actual implantation date*
- Grounds for rejection
  - *Will be entered into the comments field in the UPD*

A recording of the webinar held by the EMA on the UPD is available at:
https://www.ema.europa.eu/en/events/union-product-database-webinar-marketing-authorisation-holders

Variations Requiring Assessment (VRA)

VRA- The Variations Guidance

- The Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations was published in September 2021
- This is a joint document between EMA and CMDv
- Deals with classification of variations not already listed, general timetables and explains the Annex.
- The annex provides a classification for all VRA’s as well as document requirements

The Variations Guidance- Structure of the Annex

- The Annex divides the variations into 5 main categories:
  - E. Administrative changes
  - F. Quality changes
    - F.I. Active substance
    - F.II. Finished product
  - G. Safety, Efficacy, Pharmacovigilance changes
  - H. VAMF, PTMF Changes 1st Step
  - I. Changes of active substance(s) strength, pharmaceutical form, route of administration or food producing target species.

The Variations Guidance- categorisation of variations

- The legislation states that the assessment report or the opinion shall be prepared within 60 days with a further 30 days allowed for more complex procedures.
- The CMDv and EMA agreed that there should be different timetables dependant on the complexity of the variation.
- These are:
  - A Reduced timetable (R variations) of 30 days
  - A Standard timetable (S variations) of 60 days
  - An Extended timetable (E variations) of 90 days
  - How does the new structure look?

Example

F.I.e.2 Changes to a post approval change management protocol related to the active substance	Documentation to be supplied	Timetable
a) Introduction of a post approval change management protocol related to the active substance	**1, 2**	**S**
b) Major changes to an approved change management protocol		**S**
c) Implementation of changes foreseen in an approved change management protocol		
1. The implementation of the change requires further supportive data	**3, 4, 5**	**R**
2. Implementation of a change for a biological/immunological medicinal product	**3, 4, 5, 6**	**R**
Documentation		
1. Detailed description for the proposed change.		
2. Change management protocol related to the active substance.		
3. Reference to the approved change management protocol.		
4. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.		
5. Results of the studies performed in accordance with the approved change management protocol.		
6. Copy of approved specifications of the active substance.		

- Similar layout, similar numbering system, TT indicated
- No IB, so no requirements!
- R variations can only run on a reduced TT if the documents specified are supplied. If one is missing its an S TT.
- Blank spaces under “Documentation” doesn’t mean no documents required!

The timetables

- All VRA have to be completed within 90 days
- Why not align CAP, MR/DCP and national procedural timetables?
  - Article 66 specifies that an opinion, or assessment report, shall be prepared.
  - So an opinion has to be adopted by CVMP for every centrally authorised procedure.
- As a result there will be different procedural steps for VRA though the centralised procedure.

Procedural steps for the Variations- CAP only R timetables

Day	Step
	First phase
D0	Start of procedure
D16	Rapp AR due
D20	CVMP members comments due
D28	Circulation of RSI or opinion to CVMP members
D30	Adoption of RSI or opinion
	Second phase
D31	Clock re-start
D46	Revised Rapp AR
D50	CVMP comments
D58	Circulation of opinion to CVMP members
D60	Adoption of opinion

R VRA- Weekly submission dates (illustration purposes only only)

Submission	D1 start	Rapp AR	CVMP comments	Updated Rapp AR	Circulate opinion/RSI	Adoption opinion/RSI
31/01/2022 VRA with Linguistic review	16/02/2022	03/03/2022	07/03/2022	09/03/2022	15/03/2022 CVMP	17/03/2022 CVMP
07/02/2022	23/02/2022	10/03/2022	14/03/2022	16/03/2022	22/03/2022	24/03/2022
14/02/2022	02/03/2022	17/03/2022	21/03/2022	23/03/2022	29/03/2022	31/03/2022
21/02/2022	09/03/2022	24/03/2022	28/03/2022	30/03/2022	05/04/2022	07/04/2022
28/02/2022 VRA with Linguistic review	14/03/2022	31/03/2022	04/04/2022	06/04/2022	11/04/2022 CVMP	13/04/2022 CVMP
07/03/2022	23/03/2022	07/04/2022	11/04/2022	13/04/2022	19/04/2022	21/04/2022

Procedural steps for the Variations- CAP only S timetables

Day	Step
	First phase
D0	Start of procedure
D30	Rapp AR
D37	Co-Rapp critique
D43	CVMP/EMA comments
D50	Revised AR including draft RSI, if applicable
D60	Adoption of CVMP RSI or opinion, if applicable
	Second phase
D61	Clock re-start
D74	Revised Rapp AR
D79	CVMP/EMA comments
D83	Revised Rapp AR
D89	Adoption of CVMP AR and opinion

Procedural steps for the Variations- CAP only E timetable

Day	Step
	First phase
D0	Start of procedure
D39	Rapp AR
D45	Co-Rapp critique
D50	CVMP/EMA comments
D53	Revised Rapp AR including draft LoQ, if applicable
D60	Adoption of Rapps AR and RSI or CVMP AR and opinion, as applicable
	Second phase
D61	Clock re-start
D74	Revised Rapp AR
D79	CVMP/EMA comments
D83	Revised Rapp AR
D89	Adoption of CVMP AR and opinion

The E VRA

- The E variations consist of "I" variations and "Non-I" variations and will be treated a bit differently
- I variations are the I category variations to cover the former extension procedures and are changes of active substance(S), Strength, Pharmaceutical form, route of admin or addition of food producing target species.
- Non-I variations are other safety and efficacy variations which are not extension procedures. These include changes to the indication (G.I.7), addition of a non-food producing species (G.I.10), variations requiring submission of clinical, non-clinical and BE studies (G.I.9), variations to change serotype, strain, antigen for a vaccine based on a multi-strain dossier (G.I.13) and finally, replacement of a strain for a vaccine against equine influenza (G.I.14).

The E VRA cont.

- The reduction of the timelines associated with I Variations has presented a major challenge.
- There is concern that it will not be possible to get a meaningful assessment within 90 days and that this will lead to an increase in negative opinions.
- As such the following has been agreed for E variations

E variation	**Non I variations**	**I variations**
Grouping	Can group with all other Non-I, S and R variations	Can only be grouped with other I variations
Assessment report	Utilise the Variations AR	Utilise the initials AR and SO+LOQ.
Timetables	Rollback of the clock allowed in exceptional circumstances	Rollback of the clock allowed to facilitate an LoOI.

Other Points to note re Variations Requiring Assessment

- Grouping is not possible between VNRA and VRA
  - For CAP procedures we consider it is best not to submit a linked/consequential VNRA until approval of the VRA.
  - But the application form for VRA has a section for stating if there are linked variations so it is technically possible to submit at the same time
  - In a similar fashion the UPD has a submission comments field- which should include the precise scope but can also include any VRA that are linked.
- Every VRA now requires a commission decision before implementation
  - When the opinion is adopted we will send it to the commission for the commission decision (Article 67).
  - The commission decision may take up to two months if PI changes are involved.
  - MAH's will not be able to implement the variation until they receive the commission decision. (article 68)

Any questions?

Further information

Catherine Griffin, catherine.griffin@ema.europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
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