HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Webinar Q&A -01 November 2023

Changes to the regulatory framework for veterinary medicines

1. Question

The BPG for VRAs talks about common earliest implementation date. After that does the MAH have total discretion on when the change is made, i.e., is there an assigned latest date of implementation?

Answer

With reference to the recently amended BPG for VRAs, "*For quality changes, implementation is when the MAH makes the change in its own quality system. For product information, it is when the company internally approves the revised product information*". Generally, the MAH is expected to propose an implementation timeframe on the application form and subsequently comply with that. The HPRA Guide to implementation of packaging changes to authorised veterinary medicinal products provides additional guidance with respect to the implementation of changes required to the product literature with amendments categorised into three groups according to the perceived risk for public health, animal health, or for the safety of the environment.

At the end of procedure (EoP), the RMS will set and communicate a common earliest possible implementation date (after which implementation can take place). In case of urgent safety issues and other variations requiring urgent assessment, the RMS will set up and communicate a common latest possible implementation date.

The time limit for implementation according to Art. 68 (1) will generally be set by the relevant competent authority, with a 6 month latest date applied by most MSs. The HPRA facilitates a 12 month implementation for the implementation of changes arising from G.I.18 VRAs (updates to QRD v9).

2. Question

In relation to the implementation date following a VRA. If a VRA has a 12 month implementation timeframe does this 12 months start from the EoP or the date of the formal (automated) approval email from the HPRA (which can follow later than the EoP)? It was our understanding that the latter, the approval email, was considered the point at which the MA decision was formally amended.

Answer

Given the short time difference between the Day 30/60/90 EoP and automated approval email (~2 weeks) the applicant may consider the latter as the date of formal amendment of the MA decision.

3. Question
Is volume of sales submissions mandatory? You said that MAH input was low.

Answer
Yes, it is a legal requirement to submit data on volume of sales (VOS) for authorised veterinary medicinal products. The legal basis for this requirement is Article 58 of Regulation 2019/6:

> *11. The marketing authorisation holder shall provide the competent authority, the Commission or the Agency, as applicable, within the time limit set, with all data in its possession relating to the volume of sales of the veterinary medicinal product concerned.*
>
> *12. The marketing authorisation holder shall record in the product database the annual volume of sales for each of its veterinary medicinal products.*

The deadline for submission of 2023 VOS data is February 2024.
While it was not mandatory to submit 2022 volume of sales data, it was an opportunity to use the system, this may be one reason for low input of data for 2022.

4. Question
Does the volume of sales need to be submitted for all pack sizes even if no sales are made? Is this only for antimicrobials? In a previous EMA webinar, we were told it was not necessary to submit volumes of sales when the value was 0.

Answer
Previously the EMA advised that there is no obligation to submit any sales data into UPD when a product is not marketed for a given year, including antimicrobials.
Q&A – UPD – Volume of sales webinar for UPD industry users held on 24 April 2023 question 2.7:
"If there is no Volume of Sales for certain months but a user already entered the respective months in the columns, is it possible to enter a "ZERO" value or alternatively delete such months for products with no sales?

Marketing authorisation holders are not obliged to submit information on packages that were not sold, therefore in these cases, they will either remove the rows corresponding to those packages or will provide the value '0' with all the mandatory information in the CSV file."

That is, when submitting sales data to UPD for a product package the system expects a number, otherwise the validation will fail.
HPRA view: While acknowledging that reporting of sales data (zero) for products that are not marketed may appear as unnecessary, the absence of a value for volume of sales has the potential to be problematic when looking to 'validate' volume of sales data in the system as designed currently as it will not be known if the products with no value for VOS are not marketed or not reported. This may be a problem for antimicrobials in particular where the UPD VOS data will be used by HPRA to generate antimicrobial sales data (required in accordance with Article 57). Where the HPRA is unclear about what has been reported/not reported, this is expected to result in follow-up queries when reviewing/validating the AM sales data. So, based on the system as currently designed, the HPRA preference would be that a value for volume of sales is inputted for all antimicrobial products, both marketed and not marketed.

5. Question
If the product is not marketed for a given year, should the zero sales still be uploaded on UPD?

Answer
Following confirmation from the EMA, there is currently no obligation to submit any volume of sales data into UPD when a product is not marketed for a given year.
However, see HPRA comment above.

6. Question
In a webinar from EMA, there was no requirement to add volume of sales for non-marketed products. This has now changed. It adds additional burden on MAH. Can NCA/ UPD system facilitate, if no value is added, then it is zero. It will save time for all parties.

Answer
Following confirmation from the EMA, there is currently no obligation to submit any volume of sales data into UPD when a product is not marketed for a given year.
However, see HPRA comment above.

7. Question
Will NCA/HPRA extract antimicrobial sales data from the combined submitted (including non-antimicrobial data) data to the UPD by the MAH or will there be separate request to MAHs to submit only antimicrobial sales data to the UPD?

Answer
The antimicrobial volume of sales data submitted by MAHs into UPD will be made available to NCAs automatically. Assuming that these data are complete, a separate request to MAHs for antimicrobial volume of sales data should not be required. However, if the HPRA has concerns about the completeness/quality of the sales data extracted from UPD, then separate requests to MAHs to provide antimicrobial sales data may be required.

8. Question
What is the current turnaround time for email queries related to questions about Volume of Sales uploaded to UPD?

Answer
While there is no set turnaround time, we endeavour to respond to questions as soon as possible. Response times depend on the complexity of the query received and any required corrective actions.

9. Question
With regards to the switch from LM to LR and VPO to POM (plus the additional wording now needed in the package leaflet) - will there be published guidance on this for MAHs? How should MAHs handle these changes if they have already submitted/had approved the G.I.18 QRDv9 variation? Can the changes be made at the next suitable opportunity/update to labelling?

Answer
MAHs are reminded that following the implementation of Regulation (EU) 2019/6, information on the method of sale/supply in Ireland is now only required in the package leaflet (not on the labelling). The correct abbreviations and text to be included is presented in the 'Joint

HPRA/VMD guide to acceptable texts for joint labelling for veterinary medicinal products for use in Ireland and the UK'. During the G.I.18 VRA procedure, applicants will be advised of the method of sale and supply to appear on the package leaflet and this should be implemented by the MAH, together with other national-specific information, when generating the mock-ups. For those MAs that have already undergone a G.I.18 VRA, the updates can be made at the time of next regulatory activity where updates to the product information are proposed.

10. Question

With various requirements to change labelling, some driven by Regulation 2019/06 and some by National Legislation, and some of which are as yet undefined, how can we avoid multiple packaging changes with associated cost and write-offs between now and 2027?

Answer

The HPRA is cognisant of the challenges to MAHs arising from the various changes to product labelling arising from revised National and EU legislation particularly when these changes impact across a wide range of products or indeed the MAH's entire product portfolio. The HPRA has agreed a 12 month implementation for the implementation of labelling changes arising from G.I.18 VRAs. The HPRA will continue to be pragmatic regarding the implementation of other labelling changes and wherever possible, will facilitate combining the implementation of labelling changes arsing from different requirements.

11. Question

In the adverse events section of a generic product SPC, if frequency is listed as "Undetermined" and it came when generic SPC is updated from Reference product to new QRD. Who will be revising undetermined frequency to definite VEDDRA term, is it Generic SPC MAH or Reference SPC MAH. And when (timelines) this should be changed from undetermined to a definite VEDDRA term?

Answer

The frequency descriptors and VeDDRA terms are unrelated. It is expected that the SPC of the generic product is consistent with that of the reference product in terms of the use of the 'Undetermined' category, unless the adverse events are formulation as opposed to active substance related. The use of the 'Undetermined' frequency descriptor is acceptable where insufficient information/data is available to use another frequency descriptor.
However, where data/information becomes available (for either the reference product or the generic product) to revise the frequency descriptor from 'Undetermined' to another category, the SPC should be updated. If the change is first made to the reference product SPC, a C.3 VNRA can be submitted to update the SPC of the generic product (where appropriate).

12. Question

Will there be a fee associated with the VRA submission necessary for mock-up review?

Answer

Yes, the normal VRA-R fee applies to the G.I.15.z for review of mock-ups.

13. Question
Regarding the new process for mock-up review of new MAs with a G.I.15z variation. Does the MAH have to wait until end of procedure to submit mock-ups? Isn't a VRA going to be a longer process for approval of mock-ups than the previous 20 day assessment timeline?

Answer
Mock-up review has always been conducted following the end of the procedure, so there is no change to the timing of when mock-ups can be reviewed. The timelines will not be adversely affected by the new process, as once the VRA procedure has started, the MAH will receive the list of questions at day 20 of that procedure. The revised process will be more streamlined and facilitate a more efficient review of the mock-ups for both the HPRA and the MAH.

14. Question
We expect differences between pioneer texts and ours. If we proceed with submitting new QRD texts before the pioneer and there are differences, will we be expected to submit variations at a later stage to align with the pioneer text?

Answer
The scenario described is not expected to arise very often given that the same approach to assessment of G.I.18 VRAs are expected for both reference and generic products. Although the SPCs for generics are expected to be consistent with the SPCs for reference products, that does not mean that they have to be identical. The decision whether any updates are needed to the SPC of a generic following completion of a G.I.18 VRA for the reference product will depend upon the significance of the differences but would not be expected to be a common occurrence. The HPRA would strongly recommend that MAHs of generic products do not delay submission of G.I.18 VRAs. In the unlikely event that a subsequent amendment to the SPC of a generic is considered necessary following completion of a G.I.18 VRA for the reference product, a C.3 VNRA can be submitted (for which the HPRA does not charge a fee).

15. Question
For legacy products in which there is only a general statement relating to adverse reactions associated with active substances of a given VMP, but no clinical data to support adding such ARs to this section for the product, what does the HPRA suggest MAHs do in this situation?

Answer
The fact that there is existing information relating to the active substance included under the adverse events section indicates that this (or similar) information should be retained when updating the product information.
In line with the EMA's Q&A document on describing adverse events in the PI, an attempt should be made to use VeDDRA terms that most closely reflects the existing information on adverse events. Where there is no/insufficient data available to categorise the frequency of occurrence of the adverse event(s), the 'Undetermined' frequency descriptor category may be used.

16. Question
With reference to Article 107(3) will the EMA be conducting a similar exercise for centralised products?

Answer
This is a matter for the EMA. The HPRA expects that the EMA will take whatever steps it considers necessary to ensure that centrally authorised medicines comply with the requirements of Regulation 2019/6.

17. Question
The national designations of route of supply (e.g. POM(E), LR etc) will not be part of VMP labelling, but will instead be contained in the packaging leaflet?

Answer
That is correct. Information on the method of sale/supply in Ireland is only to be included in the package leaflet. Please refer to the Joint HPRA/VMD Guide to Acceptable Texts for Joint Labelling for Veterinary Medicinal Products for use in Ireland and the UK for further information on the abbreviations and text to be used.

18. Question
What is HPRA position in respect of SPC 3.11 and OCABR in terms of Nat/DCP and CAP? For a product where this is applicable in some territories (but not in IE), how should this be presented/edited by the MAH or indeed the HPRA (e.g. left blank, include "not applicable", leave it in place as per common English PI? (Being conscious that we are all invested in reducing the administrative burden associated with PI deviating across territories).

Answer
Section 3.11 should be left blank unless the information included in this section is relevant for all Member States. For certain products, some Member States may have special restrictions/conditions for use that need to be captured in section 3.11. In these cases, the required information can be included during the national phase of the procedure.

19. Question
For dormant/non-marketed MAs, is it necessary to submit G.I.18 variations for approval before January 2027 or could it be possible to provide a commitment to HPRA to only submit the necessary variation in advance of the product being (re)launched? This could ensure only critical variations are prepared, submitted and assessed prior to the deadline.

Answer
It is accepted that for dormant/non-marketed MAs, submission of G.I.18 variations is not as urgent as for marketed products and it is considered reasonable that MAHs would prioritise submission of G.I.18 variations for marketed products. However, while acknowledging that Article 152 (2) of Regulation 2019/6 specifically refers to '*Veterinary medicinal products placed on the market*', the G.I.18 variation, in addition to the updates to the labels, results in updates to the SPC bringing it in line with Regulation 2019/6. The SPCs for all products, marketed and non-marketed, are published on the UPD and NCA websites. Therefore, there is an expectation that all authorised veterinary medicinal products will be updated by a G.I.18 and brought in line with Regulation 2019/6 within 5 years after application of the Regulation (that is, by end of January 2027).