International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH/12/056
FINAL

PUBLIC CONSULTATION AT STEP 4 OF THE VICH PROCEDURE
OVERVIEW OF COMMENTS RECEIVED

VICH draft Guideline: 56. Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods

VICH EWG: METABOLISM AND RESIDUE KINETICS EWG – SUBGROUP ON HONEY

Name & Country of individual, organisation, or VICH delegation that commented

Comment n°	Name - Country
1	David VanderDussen (EU, Director of NOD Europe Ltd.)
2	USA (provided by Julia Oriani, member of VICH Metabolism and Residue Kinetics EWG - Subgroup on Honey)
3	Marc Legrand (Canada)
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Discussion of comments

GENERAL COMMENTS – OVERVIEW		
Comment N°	**Comment received**	**Outcome of consideration**
3	This study is quite impressive and well framed. The document is well written and the glossary terms clearly explain beekeeping practices in our region or province. We have provided some observations and suggestions using page numbering from the original document.	No action required.

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

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Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
90-96	1	Comment: With formic acid as the Active Substance (a.s.) the levels can drop simply by the dissipation of the formic acid out of the honey while in the hive, due to the volatile nature of formic acid, with no further dilution due to honey or further breakdown of the molecule. Proposed change (if any):	The following change is proposed (additional text is presented underlined): Residue concentrations might also be influenced <u>by dissipation of volatile compounds</u>, by thermal degradation (as temperature inside the hive reaches 32-36 ºC), acidic hydrolysis (honey pH ranges 3.4 – 6.1) or other chemical reactions with honey matrix components.
100-105 and 150-157	1	Comment: I do not understand the need for residue studies for biopesticide products (e.g.: a.s. oxalic acid, formic acid, thymol, menthol) to be conducted in one region but in multiple locations because the risks are very small to start with and the expense of conducting GLP studies for a minor use minor	This is a general guidance document which provides study design recommendations for residue studies in honey for establishing MRLs or justifying withdrawal periods. As stated in 2.3.6., although residue studies

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		species could be keeping effective formulations of such products out of the marketplace. Additionally, as noted previously in the document, honey production rates are not predictable: In a study we conducted in 2016 only 2 of the three locations setup for the study had a honey flow due to drought. I think that there should be at least one GLP study, and perhaps supporting documentation from other studies. See also the comments with recommendations on how to generate the honey samples to be tested. Proposed change (if any):	should generally be conducted in 4 sites, if the studies are intended to support an application for a national license, then 2-3 sites may be considered sufficient. Further reduction of data especially in establishing MRLs does not seem proper. GLP compliance is a requirement for all safety studies conducted in the VICH regions and ensures reliability and quality of the tests.
109-110	1	Comment: The "once a year" statement no longer applies in much of Europe and the rest of the world because resistance has developed to the initially highly effective synthetic chemicals. Recently EMA dropped the efficacy threshold for varroacides from 95% to 80%, due to this reality. IPM appears to be the way of the future. For example, varroa level my ramp up unexpectedly any time of year when brood is being raised; when treatment is required during honey flow, MAQS Formic Acid 68.2g Bee Hive Strip received marketing authorization for such use six year ago. Proposed change (if any):	The sentence is 'Treatments are generally applied once per year after honey harvesting and should be completed before honey flow commences.' and refers to any kind of honeybee treatment against any disease. Section 2.3.6.3. deals with treatments during honey flow.
131	1	Comment: Honey bee colonies are rarely uniform in population. It is an artificial procedure to make the adult population so, which can unbalance the age-designated housekeeping practices of a given colony. Proposed change: Honey bee colonies included in the study should be of adequate strength to gather a significant surplus of honey to be stored in the honey super during a typical expected honey flow of the region during the treatment period.	Experimental colonies are usually set up of uniform strength to reduce data variation. However, <u>the proposed change could be accepted.</u>
136-137	1	Comment: This statement is not practical or possible for Active Substances that are naturally occurring in honey, or if the colonies/hives being used are from beekeepers following organic treatment practices. For example, formic acid is naturally occurring in honey and is core to successful organic treatment regimens; levels return to naturally occurring levels for the location shortly	This is a general principle (a basic requirement). Any deviation should be adequately justified.

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		after treatment ends. This stipulation should be removed for products based on a.s. that are naturally occurring in honey.	
158 and 177-182	1	Comment: A[1]: No supplemental feed should be given during a residue study. If feeding is required then the colony should be removed from the study. B: Please review the full CODEX definition of honey. What is in the brood chamber of a hive is not considered to be honey, it is feed for the colony. This is captured on Line 185. Therefore, honey samples relevant to residue studies can only be taken from honey supers or from a zone of the hive separated from the brood rearing section. C: In theory, residue studies should be conducted during honey flows, even if the products being tested are not going to be applied during honey flows (lines 177 to 182), because that is when the bees are up working in the honey supers.	A: Supplemental feed may need to be given to honeybees to prevent starvation. Following the study design recommended, the time between feeding of honeybees and honey collection may be too long to influence honey production. *E.g.* treatment may be applied in October, feed may be needed in December and honey harvest may begin in June. Supplemental feeding should be reported and decision should be taken on a case by case basis. The following change is proposed (additional text is presented underlined and deletions in ~~strikethrough characters~~): Line 157: In addition, data on the plants in the area in which honeybees forage during the study ~~as well as data on any supplemental feed given to the honeybees~~ should be reported. If supplemental feeding is needed to prevent starvation of a colony, it should be justified that this does not influence honey production. Otherwise the colony should be removed from the study. B: No action required. C: Lines 177-182 refer to 'treatments during honey flow'. The EWG is not in agreement with the statement 'residue studies should be conducted during honey flows, even if the products being tested are not going to be applied during honey flows'.
163	1	Comment: I consider this to be excessive for biopesticides, for the reasons given above. Pooled samples from 6 to 10 colonies on a site per modality reflects beekeeping practices and will provide the data necessary to determine health risks. Please see recommendations on honey sample generation.	The study design recommended in this GL is regarded to better capture health risks, while following the good beekeeping practices. For establishing MRLs 24

[1] A, B, C: Letters added to facilitate responses.

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			colonies are needed (and 24 honey samples are analysed).
165-166	1	Comment: At least two sample time points would be best, three would be better: ideally end of treatment (Day 0) and one and/or two weeks post treatment.	The study design recommended in this GL involves a single sampling timepoint per colony, the first honey harvest, which is regarded as the worst case in terms of residues. See also response to comment above.
165 – 170 and 185 – 189 and 280 - 286	1	Comment: Individual colony response to honey flows is highly variable, as are honey flows themselves. At a first sampling point (Day 0) some colonies may not have surplus honey 75% capped from which to take a sample. Additionally. technician decision making on where to collect the sample can possibly skew results. To overcome this and to get a true representation of what is going on, please consider the following procedure: The honey super frames in the super closest to the brood chamber are numbered from one to nine, starting at one side and going to the other. If there are more frames it does not matter. If there are three time points, then 1/3 of the frames from the colonies in each modality should be removed from the super and completely extracted for each time point, regardless of the amount of capping, so there is no technician discretion. At the first time point frames numbered 1, 4 and 7 and taken from the hives in each modality, extracted, and replaced back in the same hives. For the second round, frames numbered 2, 5 and 8 are extracted and replaced, for the third round frames numbered 3, 6 and 9 are extracted to generate a pooled sample per modality per time point. This will provide efficient, economical, unbiased data on residue levels over the harvest time for the location, it will overcome individual colony honey gathering variation and reflect how beekeepers gather honey for processing. Also, circumstances may arise where "first honey harvest" is not the worst case, in terms of residues, especially with lipophilic products. It would be best to monitor residues for a couple of weeks post the treatment period.	It seems that the recommended in this GL study design has not been fully understood. The one sampling timepoint per colony is at the time when honey is mature to be harvested. At least 75% of the honeycells in a frame should be filled and capped. Section 2.3.6.2 (lines 171-176) refers to lipophilic substances introducing one wax sampling per site in such cases.
	2	Comment: Honey in arid regions (California) is often extracted when combs are less than 75% capped over, since the bees may simply not cap them if the flow is not intense. An alternative would be to specify that the honey must be cured to the extent that it cannot be shaken from the combs.	The following change is proposed in line 169 (additional text is presented underlined): '<u>Alternative criteria to determine when to harvest honey should be justified by the sponsor.</u>'

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118-119	2	Comment: The guidance states, "It is anticipated that in most cases the residue to monitor would be the parent drug. I would reword this to say 'Testing must be for both the parent drug, as well as for any degradation products of health concern.'	After the referenced sentence, the text continues 'If data indicate transformation or degradation of parent drug, an alternative residue or combination of residues may need to be monitored'. [Lines 121-123] No revision required.
109-110 and 179-182	2	Comment: The document does not make it clear that the trials should be set up so that the treatment is applied such that the honey supers are placed immediately after the end of the treatment period specified on the product label. Only by this way would the specified 'zero withdrawal period' be relevant."	Section 2.3.1. explains that, in general, treatments "are applied once per year after honey harvesting and should be completed before honey flow commences." A super box with frames should be added at the start of honey flow. [Lines 133-134] Section 2.3.6.3. refers to treatment during honey flow. In such cases honey supers are in position (hence the reference to 'existing honey' in line 181). No revision required.
Page 2, Section 2.1: Last paragraph and glossary section:	3	The definition of *honey harvested* is clear. However, it is not practical for the Eastern Canadian context because at season's end—and even during the season—honey supers are removed without regard to their content in order to separate the honey or prepare hives for autumn. Their removal is based more on the date than on the amount of honey they contain.	The content of honeycombs that contain less than 75% filled and capped honeycells is regarded as not ripe and mature honey. See the Codex definition of honey.
Page 3, Section 2.2: Lines 104-105	3	This section says GLP studies should be conducted. If so, they should be limited to companies that can support them.	See response to comment above.
Page 3, Section 2.3.1:	3	The second sentence does not apply, since many beekeeping treatments take place in spring (at least in Eastern Canada) and spring treatments are often repeated every seven days. The sentence could easily be removed as it adds nothing to the content.	The text is 'Treatments are generally applied once per year after honey harvesting and should be completed before honey flow commences.' This has been regarded as the best beekeeping practice. However, there is room

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Lines 109-110			for deviations. The term treatment refers to the whole course of treatment (including recommended repetitions, if applicable).
Page 3, Section 2.3.3:	3	Though the list of variables is fairly consistent, could we not add honey moisture content to the list? Certain products such as formic acid, etc. are affected by this.	The following change is proposed (additional text is presented underlined): Variables to be tested include pH, <u>moisture content</u>, temperature, time and exposure to (UV)-light.
Page 3, Section 2.3.4:	3	It would be better to limit hive descriptions to the 10-frame Langstroth model (the one most used in the Americas) and the Dadant model (used more in Europe, though the Langstroth is also popular there). The mother hives of both models are about the same size but differ in terms of honey supers. Limiting the mother hive to these two models should help ensure airborne drug products yield comparable results. It would also go a long way toward narrowing the already huge variations linked to climate, region, type of culture, harvest status, etc. Study apiaries should have a specific number of hives, ideally between 24 and 30, with specified geolocations. One or two hives should be weighed to record daily weight gain or loss, and there should be daily weather checks for temperature, sunlight, and humidity (electronic chips exist for this). Give a more precise definition of the start of honeyflow period. A satellite image could be added to the apiary region's description, since bees can easily cover a range of 1.5 km. Hive layout and tracking methods should be discussed so that bees are not displaced from hive to hive. There should also be methods or systems to assess bee mortality. To avoid drifting, all hives in an apiary should receive the same treatment at the same time.	The Langstroth and the Dadant models are by far the most popular hive types, however since this is a VICH GL it does not seem proper to limit the hive types that can be used in residue studies. Number of colonies to be treated and information [on climate and plants in the area (in which honeybees forage)] to be recorded are kept at the minimum required to generate meaningful data. 'All hives in an apiary should receive the same treatment at the same time': Agreed. In case this is not clear in the draft, the following revision is proposed: Addition of a sentence in line 143: <u>All colonies per site should receive the same treatment at the same day.</u>
Page 4, Section 2.3. 6:	3	Define *agro-ecological area* and *region*. As noted above, a satellite image could be added to the apiary region's description.	The term agro-ecological area refers to combinations of soil, landform and climatic characteristics. However, such definitions do not seem necessary.

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			See response to comment above for minimum requirements.
Page 4, Section 2.3.6.1:	3	Here again, the description of harvest applies only to producers in Western Canada (100 to 200 kg of honey/year) rather than those in Eastern Canada or Europe (30 to 50 kg/year).	See response to comment above.
Page 4, Section 2.3.6.2:	3	Plastic frames, polystyrene hives, and materials like polypropylene, polyethylene or polyvinyl have been replacing wood for many years. How do these materials react with lipophilic or hydrophilic substances?	We do not have data on this. It is not expected that there will be an impact on veterinary drug residue concentrations in honey.
Page 5, Section 2.3.7.1:	3	Wax should be managed more closely, as capping wax homogenates are hard to obtain. Should a melted wax sample also be provided?	For clarity, in line 194 the following sentence (text underlined) maybe added: 'For wax samples, the combs should be homogenized after honey extraction. Sample processing (all activities after sampling and up to analysis) should take into account the stability properties of the residues.' (This sentence is already in line 189-190 for honey samples.)
Page 5, Section 2.3.7.2:	3	Explain exactly how to manage pre-dosage honey samples (which is precisely the goal). For example, take two 500 g samples of honey homogenate from the study hives, put them in glass jars filled to the top, keep one frozen at -20ºC and the other in a dark place at room temperature, etc."	For stability in matrix and the other performance characteristics of the method validation, reference is made to VICH GL 49.