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

VICH/19/048
Final
30 September 2019

Concept Paper to elaborate VICH guidelines on in vitro dissolution testing and biowaivers for in vivo blood BE determinations

1. Introduction

Consistent with the physiological diversity of veterinary species, the diverse product formulations, and the range of administration methods for veterinary pharmaceuticals, there are numerous complex issues unique to the assessment of product bioequivalence (BE) of veterinary pharmaceuticals. While blood level BE studies represent a critical component of this topic, there exists another important issue to be addressed: that of biowaivers. The first success toward achieving international harmonization on the evaluation of product BE occurred in 2015 with the VICH Steering Committee (SC) adoption of Guideline (GL) 52. However, at that time, the BE Expert Working Group (EWG) recognized this accomplishment to be only a first step in an overall effort.

Unlike blood level BE studies (the subject of VICH GL52), the remaining questions are, in many senses, more difficult both from a scientific and regulatory perspective. Because of the multidimensional nature of product BE assessments and the uncertainties associated with the granting of biowaivers, there is a need to implement a tiered approach to the biowaiver issue. Given these scientific and legal challenges, biowaivers need to be addressed from the perspective of : 1) the critical questions and issues to be addressed (i.e., factors influencing the information needed to support biowaivers); 2) development of a GL covering the design and analysis of in vitro dissolution studies to reflect in vivo product performance[1] (one of the pivotal pieces of information contained within most biowaiver applications); and 3) development of a GL covering the considerations and criteria to be incorporated into the granting of biowaivers. It is from this perspective that this Concept Paper is written.

2. Problem Statement and Impact on Public Health, Animal Health, and Animal Welfare:

An assertion of product in vivo BE implies that the active pharmaceutical ingredient(s) (APIs) contained within a test and a reference formulation are equivalent with respect to the rate and extent at which it reaches its site of action. Formulations determined to be BE are considered indistinguishable in terms of their respective safety and effectiveness. When evaluating product BE for APIs that are systemically absorbed, the assessment is relatively straightforward, being based on the use of comparative blood level studies whose designs are backed by principles developed and refined over many years. However, there are some products for which it may not be feasible to assess product comparability based on comparative blood level data. This is particularly true when the drug reaches its site of action prior to or in the absence of systemic absorption. The question is then how best to evaluate product BE under these circumstances.

Furthermore, there are cases when alternatives to in vivo studies can provide the necessary level of assurance for conferring a determination of product BE. In these situations, implementing a requirement for in vivo BE trials can lead to such negative consequences as unwarranted delays in product approval, increased regulatory burden, additional developmental costs, and the unnecessary use of animals. It can impose hurdles that are a disincentive for product development.

Currently, there exist critical international inconsistencies on the acceptability of biowaivers. For example, Japan will only accept biowaivers when the two formulations are identical intravenous (IV)

[1] We will not be discussing in vitro dissolution as it relates to CMC manufacturing specifications.

solutions. In contrast, the European Union (EU), US Food and Drug Administration (FDA), Canada, Australia and New Zealand will consider situations beyond that of IV solutions, such as that of oral dosage forms manufactured in multiple strengths. For these products, an in vivo blood level BE trial is required on only one dosage strength while biowaivers can be granted based on comparative in vitro dissolution data and formulation similarity of the additional tablet strengths within a product line. Another example of where the US and EU allow for a biowaiver-based determination of product BE are those products containing an API that is fully soluble within the range of conditions encountered in the target animal gastrointestinal (GI) tract.

The biowaiver concept is important to generic drug sponsors, allowing them to avoid the need to conduct in vivo test procedures when reliable alternative test procedures exist. From an innovator company, biowaivers can reduce the number and type of bridging studies required to connect data from a range of formulations that may be used during product development.

Up to now, VICH has not addressed the issue of biowaivers, leading to the current situation where:

- Different studies are needed for product approval across the various regions
- Non-VICH regions and countries, wanting to align to VICH would be inclined not to accept biowaivers.

As a result, global companies must conduct a range of different investigations to address these differences in rules, leading to the risk of efforts to "bridge" being rejected because it is not considered a VICH BE standard. Accordingly, the availability of a VICH Biowaiver GL is greatly needed. Nevertheless, we must establish an appropriate and effective framework to support the development of such a GL. This framework can be generated using the following proposed sequential approach:

1. Identifying the Critical Questions: At the very start of this initiative, we need to convene a team of international experts, the BE Expert Working Group (BE EWG), who will summarize existing gaps such as a list of the terminologies (and their definitions) to be used during GL development and identify the existing regulatory hurdles that can impede international harmonization efforts. Note that this step is not intended to generate answers to these questions but rather to make sure that the critical points of discussion are clearly delineated. Example of issues that may be on this list include:
    - Do we need to develop an internationally accepted definition of the term "biowaiver"?
    - How will we define the term "solubility"?
    - How should solubility be assessed? For example:
        - Should solubility be described across conditions reflecting the entire GI tract of the species in question?
        - Should solubility be described only with respect to its behaviour within aqueous media (where the only variables are pH and buffer system used) or can bio-relevant surfactants such as bile salts be included?
        - Do we need to develop a set of VICH recipes for the media to be used when evaluating drug solubility?
    - Is there a need to distinguish between the term "biowaivers" versus "*in vitro* BE" studies? For example, within the US (e.g., see Ref 1), there is an opportunity to use alternatives to *in vivo* clinical endpoint BE studies to support the determination of product BE for certain types of non-systemically absorbed formulations. However, much *in vitro* information (that extends beyond simply dissolution) is needed to support such an in vitro BE assessment. With that in mind, does the VICH wish to limit use of the term "biowaiver" to specific types of situations rather than extend discussions to these more state-of-the-art areas? Where does the concept of *in vivo*/*in vitro* correlation fall within these considerations? How do we want to define a biowaiver (type of formulation, type of data needed)? What validation information would be required to support the various types of comparisons?
    - Within human medicine, we often see the terms Q1, Q2 and Q3 applied to biowaiver requests. When we define product "sameness" using the concepts of Q1, Q2 and Q3 (same components in the same amounts and with the same physicochemical characteristics), what kinds of deviations from "identical" might be considered acceptable to the VICH EWG before

triggering the need for additional studies? How would the magnitude of allowable differences be evaluated for each product (e.g., defining what constitutes equivalent excipients)? Or is such information currently beyond the scope of the VICH?

- What training is needed before proceeding with the development of a dissolution and a biowaiver GL (e.g., biopharmaceutics principles, interspecies differences in formulation considerations and what constitutes formulation critical quality attributes (CQA's), the science of in vitro dissolution testing)? Note that CVM recently published an educational article on in vitro dissolution considerations that provide the scientific underpinnings upon which in vitro dissolution testing is based (see Ref 2).
- What are the appropriate comparators for between tablet strengths biowaivers (when there has been an acceptable *in vivo* BE study on one of the strengths)? There are arguments for comparing across strengths (relative to the lot used in the in vivo BE trial) or across test and reference formulations but within a given strength. The scientific basis for either type of comparison will need to be considered and justified.
- What criteria will be used to confirm the comparability of product in vitro dissolution profiles? This discussion also needs to recognize that there are situations when use of the F2 metric is not appropriate. For more information, please see Ref 3.
- When conducting *in vitro* dissolution tests, what is the allowable between-product differences in tablet potency? Can we implement what is already agreed upon in VICH GL52?
- How do we ascertain if the in vitro dissolution test conditions are appropriately discriminating (i.e., can differentiate between inequivalent products) versus overly discriminating (where the *in vitro* profiles suggest differences that in fact are not borne out *in vivo*)?
- Within the US, we refer to dissolution apparatuses and their corresponding conditions of use in terms of existing USP specifications. Across the other jurisdictions, what are the differences between specifications delineated within the USP versus that contained within the standard-setting documents of other VICH member states?

2. Development of a VICH *In Vitro* Dissolution GL: Dissolution testing is an in vitro laboratory performance test that assesses how efficiently a drug is released from its dosage form. To capture comments on the spectrum of considerations and its utility for developing transformational solutions that benefit patients, a regulators' article was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org) (Ref 4). Given the complexity of biowaiver challenges, an agreement on how to conduct and analyse comparative in vitro dissolution data is an essential first step before embarking on efforts to develop a VICH Biowaiver GL. For example, are there basic principles that can be placed within a dissolution guidance (e.g., validation procedure, procedural justification consideration, number of units to test, methods for comparing profiles) that can be developed irrespective of species for which the dosage form is intended (to be followed by specific considerations within the individual biowaiver GLs)? Separating development of a dissolution vs. a biowaiver GL will simplify this project. The proposed VICH In Vitro Dissolution GL will serve as the foundation for developing, analysing, and utilizing dissolution testing for product comparisons. Once we have agreement on how to conduct and analyse in vitro dissolution data, we can focus on the final set of issues impacting international harmonization on the granting of biowaivers. Prior to its initiation, the Steering Committee will define and agree upon the scope of this GL.
3. Biowaivers: Since there are numerous forms that a "biowaiver" may take, there needs to be consensus on the breadth of the dosage forms and questions to be covered. For example, the level of challenges associated with the granting of biowaivers may differ as a function of oral dosage form (e.g., solid oral formulation, liquid suspensions and solutions, chewable formulations, medicated feeds) and the target animal species for which the dosage form is intended. Another important point for discussion is whether the VICH wishes to address the question of evaluating bioequivalence if the product reaches its site of action prior to or in the absence of systemic absorption.? Given the potential complexity of the many issues that can arise across the various kinds of biowaiver requests, we may wish to consider the simplest and most straightforward situations, with the goal of producing multiple GLs to cover a range of biowaiver scenarios. Prior to initiation of this step, the Steering Committee will agree upon GLs to be developed, the sequence within which each of these GLs will be completed, and the scope of these GLs.

3. Anticipated Benefit:

The benefits that will be obtained through the development of a harmonized VICH BE Guideline are in keeping with the stated VICH objectives, which in turn, are consistent with those of the ICH:

- *Establish and implement harmonized regulatory requirements for veterinary medicinal products in the VICH Regions, which meet high quality, safety and efficacy standards and minimize the use of test animals and costs of product development.*
- *Meeting educational needs, insuring that the key points are defined for training. Such training is needed to ensure that all jurisdictions have an appreciation of the state of the art science and generate quality data.*

Through an alignment on the technical requirements for *in vitro* dissolution testing and biowaivers, sponsors can achieve a positive outcome in more countries with fewer animals and lower cost. By ensuring that studies are done efficiently, we also reduce the risk of failure and the need for repeat BE studies.

- *Provide a basis for wider international harmonization of registration requirements.*

The proposed guideline will provide a framework upon which this international harmonization can be established. Furthermore, consistent with the need to "Provide a basis for wider international harmonization of registration requirements", these GLs will allow for global harmonization.

- *By means of a constructive dialogue between regulatory authorities and industry, it will provide technical guidance enabling response to significant emerging global issues.*

Through the development of a unified set of BE GLs, the proposed initiative will positively impact the issue of human food safety, generic drug approvals, and the import/export of food.

- *Animal Welfare:*

With a decision to allow for such alternative approaches as defined within the biowaiver process, fewer animals will be tested, the number of supporting studies will decrease, and we, as a global community will be actively supporting an increase in animal welfare.

4. Recommendations:

VICH should re-establish the Bioequivalence EWG to elaborate harmonized GLs on in vitro dissolution and for the granting of biowaivers in lieu of *in vivo* blood BE determinations, as appropriate. To maximize the likelihood of success, this endeavour should be undertaken in three steps, with the aim to develop a VICH In Vitro Dissolution GL and one or more VICH Biowaiver GLs. If possible, the same BE EWG should be responsible for all three components of this proposed initiative.

5. Timetable and Milestones: TBD

6. Impact Assessment:

Industry:

a. Clarity and global consistency of requirements
b. Reduction in number of studies needed for global marketing
c. Increased acceptance of bridging of changed formulations
    a. in original development of innovator products
    b. in further development of reference or generic product
d. Global consistency in reviewing BE studies

Regulators:

a. Increase in clarity of requirement (less uncertainty expressed by Industry)
b. Decrease in submission of failed studies
c. Global consistency in reviewing BE studies

References

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