Bioequivalence Expert Working Group

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Introduction

The VICH Bioequivalence Expert Working Group (BioEqEWG) completed a blood level bioequivalence (BE) guideline in 2016. However, not considered in that guideline was the assessment of product BE for solid oral drug products that are manufactured in multiple strengths. These additional strengths are intended to address the large range in body weights across potential veterinary patients. In so doing, these multiple strengths allow for the same mg/kg dose range and same dose-exposure relationship, irrespective of animal size.
Currently, there is not an international agreement as to whether an *in vivo* blood level BE study is needed for each of these tablet or capsule strengths or if an *in vivo* blood level BE study for one strength plus comparative *in vitro* dissolution data for the additional strengths (i.e., a between strength biowaiver) can be an internationally accepted approach for such products. Therefore, the BioEqEWG is currently developing a guideline that addresses this challenge and the data that are needed to support between-strength biowaivers.

Guidelines adopted

The *in vivo* blood level BE guideline was adopted in 2016.

Guidelines under development

The between-strength biowaiver guideline currently under development has identified several new challenges. Notable challenges include the conditions for *in vitro* dissolution testing (e.g., how many conditions (i.e., buffered media) need to be included to support the biowaiver), what are the acceptable *in vitro* dissolution conditions for the biowaivers, which surfactants are acceptable for poorly soluble drugs (and what are the concentration limits that should be placed on these surfactants), the permissible between-strength variance in composition and manufacturing method for strengths included in the biowaiver, and what statistical tests are needed to support between-strength sameness.

New topics

We have defined the pivotal points to be addressed in this guideline and have an initial draft that is undergoing revision. However, an important issue identified by our EWG during this initiative is that member states want this guideline, which includes a description of the *in vitro* dissolution studies needed to support *in vivo* biowaivers, to be distinct from guidelines covering the use of *in vitro* dissolution in support of the development of quality control (QC) specifications.

Key scientific issues resolved

The pivotal point that has been resolved is that all member states agree with a need to establish internationally accepted criteria for the granting of between-strength biowaivers per target species and the conditions that automatically lead to a denial of such biowaivers, even if the *in vitro* dissolution profiles appear to be comparable (e.g., when there are between-strength differences in formulation or manufacturing conditions). We have also agreed upon the existing points needing further consideration as described in the section 'Guidelines under development'.

Key benefits of the harmonized guidelines

To consumers, patients, users: The availability of a between-strength biowaiver guideline provides an opportunity for increased accessibility to high-quality generic formulations and to support between-strength biowaivers for new animal drug products that have undergone a formulation change.

To authorities: Harmonization of the requirements for between-strength biowaivers will encourage international dialogue on the handling of specific drug products, eliminate inconsistent approval requirements, and minimize the occurrence of conflicting regulatory decisions.

To industry: This guideline will encourage the international marketing of new and generic formulations and reduce the need for redundant tests.

To animal welfare: Firstly, through application of the biowaiver guideline, there will be fewer animals needed to support the approval of drug products marketed in multiple strengths (i.e., only one successful *in vivo* BE study will be needed in most situations). Furthermore, by encouraging between-strength biowaivers of *in vivo* BE studies, sponsors will be encouraged to develop generic versions of approved products and innovators will be empowered to modify formulations to meet evolving therapeutic needs.

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