Background
Currently available non-animal methods to evaluate biologics have not been widely implemented in the US. Likewise, consistency approaches are familiar to US industry and regulators but are not widely used. These concepts are closely related but infrequently addressed together in US regulatory policy. Resistance to voluntary consistency measures may contribute to the difficulty in implementing non-animal batch tests for manufacturers and regulators alike. Evidence suggests that direct requirements for compliance with consistency measures may help firms successfully implement non-animal methods.

Objectives
Our organisation routinely communicates with industry and regulators to understand and help remove barriers that limit use of available non-animal test methods that have been validated for regulatory use. While promoting the use of validated non-animal veterinary vaccine potency assays, our interactions with US industry and regulators identify cases in which firms adopt voluntary consistency-type measures in some instances but not in others.

Using our experience with veterinary leptospirosis vaccines as an example, we:

- demonstrate our “bridging the gap” approach for alternatives to target animal batch safety testing (TABST) and leptospirosis vaccine batch potency testing, and
- show that firms’ interest in implementing each of these alternative approaches, and ability to do so, is increased when regulatory guidance explicitly requires consistency measures as a condition of their use.

Methods
Our bridging approach can be viewed as an information collection and dissemination process that is customised to the needs of each biologic for which a non-animal replacement, reduction, or refinement method has been validated for regulatory use in place of an in vivo precedent (Fig. 1). In its simplest form, this approach confirms:

- the conditions under which regulators accept data from an alternative approach, and
- whether manufacturers of biologics have adopted the alternative approach.

Methods (continued)

The bridging process for firms marketing veterinary leptospirosis vaccines in the US takes a similar form, as in the example below (Fig. 1).

Discussion
The bridging approach is helpful for identifying and removing barriers to the implementation of available non-animal methods.

Firms’ adoption of non-animal potency test methods for products licensed in the US is nevertheless voluntary, and firms must satisfy parameters for their use that are not easily met without consistency-like conformity to “the strict application of GMP rules and guidelines, process validation and in process and final product tests”. In the case of leptospirosis vaccines, the possibility of exemption from an in vivo TABST standard requirement has motivated firms to voluntarily modify their production outlines. For the same leptospirosis vaccines, firms’ self-reported inability to qualify for the use of non-animal potency tests may be resolveable through consistency approaches, but such approaches are not requirements of SAM use.

In the absence of a mandate to do so, firms only adopt consistency measures when regulatory guidance clearly indicates that such measures must be included in revised outlines of production in order to qualify for the use of non-animal methods.

Recommendations
Opportunities to facilitate implementation of available non-animal test methods include:

- improving clarity in regulatory guidance,
- providing incentives to adopt consistency measures, particularly where such measures support the implementation of existing validated alternatives,
- ensuring comprehensive communication with regulated firms, beyond guidance documents and review of regulatory submissions, and
- tracking implementation of alternative methods (which is not currently done by USDA for TABST or leptospirosis vaccine batch potency testing exemptions).

Many of these steps were recommended at the 2010 EURL ECVAM/EPAA workshop on the consistency approach and its potential to reduce the number of animal tests used in the quality control of human and veterinary vaccines. The need for these recommendations must be integrated into US regulatory policy.

References and acronyms

Full reference list available at piscltd.org.uk/consistency-congress or via the QR code at right.