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Putting logic into biologics: The North American regulatory process

By Joseph Harvey

Veterinary biological products, including vaccines, are regulated independently of veterinary pharmaceuticals in Canada and the US. This is in contrast to regulation of drugs and biologics for human use, which are regulated by a single agency in each country. Donna Mattson, a project manager for veterinary biologics regulatory affairs at the Triveritas contract research organization, spoke to deputy editor Joseph Harvey about the North American regulatory situation for biologics.

Joseph Harvey: Why are veterinary biologics and pharmaceutical products regulated independently of each other in Canada and the US, and who regulates them?

Donna Mattson: Each country has its own regulatory agencies and separate legislation, regulations and guidance governing veterinary drugs and veterinary biologics. The result being that the requirements for licensing of veterinary drugs and biologics have arisen independently and are therefore quite dissimilar.

Veterinary drugs are regulated by the Food and Drug Administration – Center for Veterinary Medicine (FDA – CVM) in the USA and by the Veterinary Drug Directorate (VDD) at Health Canada.

People who are unfamiliar in the licensing of veterinary biologics in North America often believe that the biologics centers at the FDA (Center for Biologics Evaluation and Research, CBER) and Health Canada (Biologics and Genetic Therapies Directorate, BGTD), are responsible for their evaluation, but this is not the case. Veterinary biologics are regulated in the US by the United States Department of Agriculture (USDA)'s Animal and Plant Health Inspection Service (APHIS)'s Center for Veterinary Biologics (CVB).

The regulator in Canada is the Canadian Center for Veterinary Biologics (CCVB) within the Canadian Food Inspection Agency (CFIA). The agencies regulating veterinary biologics have historically fallen under the oversight of the Minister/Secretary of Agriculture. This is currently true in the US, where the head of the USDA is the Secretary of Agriculture.

In Canada, the CFIA previously reported to the Minister of Agriculture, however, a reorganization took place in 2013 to more closely align the three agencies responsible for food safety in that country. CFIA now reports to the Minister of Health, along with Health Canada and the Public Health Agency of Canada.

JH: Can you highlight some of the differences between licensing of biologics and drugs in the two North American countries?

DM: Dossier format and content requirements are notably different for veterinary biologics and drugs, due to the different legislation and regulations that apply. In the US veterinary drugs are legislated by the Federal Food, Drug and Cosmetic Act and the regulations are published in the Code of Federal Regulations Title 21 (21 CFR), and the US Pharmacopeia, whereas biologics are legislated by the Virus-Serum-Toxin Act, and the regulations are published in 9 CFR.

In Canada, the legislation is the Food and Drugs act, with the associated Food and Drug Regulations. For veterinary biologics, the key documents are the Health of Animals Act, and the Health of Animals Regulations.

The submission fees for a New Animal Drug Application (NADA) to FDA are approximately $400,000, with an additional $200,000 in annual fees; there are no fees associated with USDA-licensing of veterinary biologics. The fees in Canada are less well-defined, however, drug licensing fees are much higher than the cost-recovery fees incurred for a CFIA-licensed vaccine or other biological product (about $6,000).

FDA and Health Canada accept electronic submissions for NADA or investigational animal drug files, whereas the biologics agencies, USDA and CFIA, at this time still require hard-copy submissions for certain sections of the dossier.

The Common Technical Document (CTD) specifications are used for drug submissions, whereas USDA

and CFIA have specific dossier format and content requirements that are defined in USDA Veterinary Services Memoranda and CFIA guidelines.

Compliance with defined quality standards for manufacturing, testing and study conduct (cGMP, GLP, VICH GCP) is obligatory for Veterinary biological products, including vaccines, are regulated independently of veterinary pharmaceuticals in Canada and the US. This is in contrast to regulation of drugs and biologics for human use, which are regulated by a single agency in each country. Donna Mattson, a project manager for veterinary biologics regulatory affairs at the Triveritas contract research organization, spoke to deputy editor Joseph Harvey about the North American regulatory situation for biologics.

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Previous to her position at Bioniche, Ms Mattson spent five years at Novartis Animal Health Canada and Novartis Animal Vaccines UK.

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Compliance with defined quality standards for manufacturing, testing and study conduct (cGMP, GLP, VICH GCP) is obligatory for veterinary drugs, whereas this is optional for veterinary biologics in Canada and the US.

The focus of the safety evaluation can be quite different, with toxicity of repeat doses and overdoses important for drugs, whereas a large field safety study, combined with safety testing of each batch (serial) prior to release, is more appropriate for products prepared from micro-organisms, and with an immunological mechanism of action.

The process of 'serial release' by the biologics agencies (USDA and CFIA) is unique, there is nothing similar required for drugs in North America. The agencies require submission of samples from each serial, along with the manufacturer's test results, and they conduct confirmatory testing on a random selection of the submitted samples, prior to releasing the serial for sale. They also conduct confirmatory testing of Master Seed and pre-licensing serials.

There are also differences in the pharmacovigilance obligations for the license holder in terms of reporting adverse events and submitting annual summary reports.

JH: How different are the requirements for licensing a veterinary biological in Canada versus the US?

DM: The requirements in the two countries are actually quite similar. CFIA interprets the Health of Animals Act and regulations in much the same way that the USDA interprets the Virus-Serum-Toxin Act and Code of Federal Regulations Title 9 (9 CFR). It is quite common for firms to pursue licensing of products in Canada and the US concurrently.

JH: Can you comment on dossier submission and evaluations for biologics?

DM: Licensing of veterinary biologics with CFIA and USDA is accomplished by 'phased submission', which has the benefit of consultation and agreement at each phase.

The initial submission includes the Master Seed test report and details of planned manufacturing and testing of the product. In addition, the efficacy study protocol and others (as required), are provided for review prior to proceeding with additional development work. The agency then provides written permission to submit the Master Seed to the agency for testing; and if everything is okay, they will provide written permission before the Working Seed can be transferred into the licensed manufacturing facility.

The second submission will consist of the efficacy study report and other supporting data (as applicable), stability data and inactivation kinetics/validation. The potency test report, label text and field safety study protocol will also be submitted for review at this time.

The final submission consists of the field safety study report, results of testing for the three pre-licensing serials, the final label text, and a residue clearance report, if a 'novel' adjuvant is used, or if a reduced withdrawal period is requested. Phased submission has the real benefit of allowing a constant dialogue between the applicant and the regulatory reviewer, during development of the product.

JH: In the UK it is possible to obtain a provisional or limited marketing authorization. Is there an equivalent (derogation?) situation in Canada and the US?

DM: CFIA and USDA each have a mechanism for issuing a license with 'conditions', for purposes defined in 9 CFR 102.6, including "to meet an emergency condition, limited market, local situation or other special circumstance including production solely for intrastate use under a State-operated program". The expedited procedure requires demonstrated purity and safety, and a reasonable expectation of efficacy.

The terminology used by USDA is a 'conditional license', whereas Canada issues a 'Permit to Release Veterinary Biologics'. This type of license is issued for a finite period of time, often one year. This conditional-type license may be renewed, providing that significant progress has been made toward meeting the requirements of the full license.

It is important to remember that this section of 9 CFR specifically states 'issue a US Veterinary Biological Product License'. To fully interpret the implications of this statement it is necessary to be aware that only products manufactured in the US qualify for a 'product license'. Products manufactured outside the US, including in Canada, qualify for a 'US Veterinary Biological Product Permit for Distribution and Sale'. So veterinary biologics manufactured outside the US do not qualify for a conditional license.

JH: Given the differences you have described between regulation of veterinary biologics and drugs in the North American countries, is it common for regulatory affairs personnel to 'specialize' in one area or the other?

DM: The independent regulation of veterinary drugs and veterinary biologics in North America can be a trap for the unwary. The requirements for biologics (9 CFR) have very little in common with those for drugs (21 CFR). Thus within the field of veterinary regulatory affairs, specialization in either veterinary biologics or veterinary pharmaceuticals is often seen. Specific USDA/CFIA experience is essential to effectively navigate the idiosyncrasies of the unique regulatory requirements for veterinary biologics in North America.