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RESIDUES OF VETERINARY MEDICINAL PRODUCTS IN FOOD –

Regulation and testing outside of the European Union

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A previous white paper[1] described the requirements that the European Union (EU) place upon Member States and trading partners for the control of Veterinary Medicinal Products (VMPs) in food. This paper covers the regulation of VMP residues in other regions of the World.

Harmonisation - The Codex Alimentarius Commission

To facilitate the fair trade of food, and to ensure a consistent and evidence-based approach to consumer protection across the globe, the Codex Alimentarius Commission ("Codex") was established in 1963. Codex is a joint agency of the FAO (Food and Agriculture Office of the United Nations) and the WHO (World Health Organisation). It is responsible for producing and maintaining the Codex Alimentarius: a compendium of standards, guidelines and codes of practice relating to food safety.

Codex has 187 member governments, plus the European Community as a member organisation. It is organised into approximately twenty Technical Committees. One of these is the Codex Committee for Residues of Veterinary Drugs in Food (CCRVDF)

CCRVDF was established in 1985, with a remit to recommend Maximum Residue Limits (MRLs), sampling schemes, develop codes of practice, and to assess the suitability of laboratory test methods for VMP residues in food.

MRLs are set in national law. The imposition of national MRLs should not be used as a barrier to trade; they must be set on the basis of scientific risk assessment. If a food complies with Codex Alimentarius standards then this is a starting point for resolution of any World Trade Organisation disputes in cases where an importing country has refused to accept a food on the grounds of safety.

Despite this, there are occasional cases of dispute. Codex MRLs[3] are only advisory: it is the responsibility of individual governments to set their own MRLs. Usually they follow Codex recommendations, but sometimes they do not. Many governments have their own risk assessment bodies, for example the Food and Drug Administration (FDA) in the US or European Medicines Agency (EMA). Different risk assessors can sometimes reach different conclusions from the same data. For example, Codex advisory MRLs[4] are legally accepted into EU legislation unless the European Commission objects to them on the grounds of science. There is disagreement between the US and the EU as to whether the EU blanket ban on growth promoters is truly an objection on the grounds of science. Codex have concluded that any residues of 17β-oestradiol, testosterone or progesterone are safe if these VMPs are used as recommended and have advised MRLs for melengestrol acetate, trenbolone, zeranol and ractopamine. All are growth promoters.

Codex advisory MRLs are set following an independent risk assessment by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), or by agreeing the adoption of a risk assessment from any other reputable organisation. To date, Codex have assessed 76 VMPs. Instead of setting MRLs, Codex may give a Risk Management Recommendation; effectively, advice that the VMP should be prohibited. The following VMPs fall into this category:

carbadox	furazolidone	nitrofural (nitrofurazone)
chloramphenicol	ipronidazole	olanquindox
chlorpromazine	malachite green	ronidazole
dimetridazole	metronidazole	stilbenes

[2]UN Resolution 39/248 (1985) :

"When formulating national policies and plans with regard to food, governments should take into account the need of all consumers for food security and should support and, as far as possible, adopt standards from the Codex Alimentarius or, in their absence, other generally accepted international food standards"

[3]"In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of carbadox or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of carbadox in food. This can be accomplished by not using carbadox in food producing animals."

Authorisation, distribution and control of Veterinary Medicinal Products

The legal framework for the authorisation, distribution and control of VMPs varies from country to country, but certain common principles apply which are described in the Codex guidelines[5]. VMPs should be specifically authorised for each animal species. Withdrawal periods should be specified. Farmers (including fish farmers and beekeepers) should be required to keep records of VMP administration to their animals, and food from those animals should be traceable back to those records. There should be a mechanism for post-authorisation surveillance; both in reporting adverse reactions, and in monitoring the residue levels in food.

The largest regulatory variation between different countries is in how tightly the distribution and sale of VMPs is controlled. This can vary from them being on general sale, with farmers able to buy VMPs over-the-counter and administer to their own animals, to being prescription-only but self-administered, or to being only administered under the direct supervision of a veterinarian. This variation underpins the public perception that VMPs are used much more liberally in some countries than others.

Table 1 illustrates the differences in controls between three large meat-producing countries.

Table 1: Summary of VMP Controls in Three Meat-Exporting Countries

	USA[6]	Brazil[7]	China[8]
Authorisation	Approval is granted by the Food and Drug Administration (FDA). This is at a National, rather than Federal, basis. The FDA evaluates and publishes an approved method ("standard method") for testing of residues. There is a legal procedure for emergency and ad-hoc ("off-label") use. Some medicines are specifically prohibited; chloramphenicol, nitrofurans, nitroimidazoles, diethylstilbestrol and some sulphonamides.	Approvals are granted by the Secretariat of Animal and Plant Protection (SDA). MRLs are adopted, by default, from Codex and enacted into National legislation. There is little legislation or guidance on off-label use of VMPs A succession of legal acts over the past 10 years have prohibited the use of most VMPs that are prohibited within the EU, such as crystal violet, hormones for growth promotion, and some zootechnical feed additives.	Approval is granted by the Ministry of Agriculture (MoA). This is at a National, rather than Regional, basis. Historically, individual approvals have been governed by individual pieces of legislation, including detail such as default withdrawal periods and target species. Legislation is the definitive point of reference rather than the medicines' label. The MoA publish a compendium of conditions of use. Although legislation can be difficult to navigate, authorisations and conditions of use are largely in line with their EU equivalents.
Distribution	VMPs may be licensed as either prescription-only or over-the-counter. Distribution is governed at a Federal, rather than National, basis. Licenced veterinarians can generally sell prescription VMPs on to farmers, for them to self-administer. A farmer can re-purchase unlimited times within 12 months on a single prescription. The exception is VMPs where the FDA consider that the administration instructions are too complex for a layman to follow; these may only be administered by a veterinarian. Over-the-counter VMPs are sold direct to farmers by licenced distributors, such as agricultural merchants. The range of over-the-counter VMPs available to farmers is relatively wide, including a number of antibiotics which are prescription-only in the EU and some VMPs which are banned in the EU.	Approximately 150 of the 800 approved VMPs are prescription-only, but the majority are available over-the-counter. All VMPs must be supplied through a licensed wholesaler or pharmacy, and each licenced distributor must employ a responsible veterinarian and is inspected at least annually. Responsibility for licensing and inspecting the distributors is often delegated to one of the 27 regional, rather than National, governments.	Although most original authorisations did not control VMPs through prescriptions, new legislation in 2014 introduced a list of VMPs which became prescription-only. VMPs can only be distributed through licensed wholesalers/retailers, which are subject to annual inspection by the Ministry of Agriculture. These inspections have periodically uncovered the sale of counterfeit or black market VMPs. To demonstrate enhanced confidence in the regulatory oversight of exported food, some VMP distributors and farms are ringfenced within the Export-Oriented Scheme. These operators are additionally inspected by the Entry-Exit Inspection and Quarantine Bureau (CIQ), and many have a CIQ official permanently stationed on site to oversee the sale or use of VMPs.
Traceability	Although no specific legal requirement to keep medicine administration records, farmers can be prosecuted under general legislation if they do not keep them.	Meat and poultry farms are required to keep medicine records, but this requirement does not extend to fish farms.	Farmers are required to keep medicine records of any treatments that have been administered.

Post-authorisation surveillance for residues

A comprehensive compliance-testing programme is no substitute for an effective control system at primary production. This principle is embedded in the Codex guidelines for residues control.

> [5]"The continuous application of good practice and regular control contribute more to food safety than end product testing"

A certain amount of surveillance testing is required, however, in order to verify the effectiveness of the authorisation, distribution and administration controls. The Codex guidelines lay down a minimum number of samples to be tested in a national scheme; some countries, notably the EU, require a far larger number of samples to be tested. The common principle to all schemes is that sampling design must be risk-based.

The key difference between Codex sampling plans and EU-prescribed sampling is that EU sample numbers are proportional to production volumes. Codex states that, once a statistically-significant number of samples are collected, further sampling gives no increase in confidence, irrespective of the production volumes. The size of Codex sampling plans are capped. This can have a huge impact for large industries (e.g. 300 samples vs 10,000 samples per year). Codex sampling guidelines also stress the importance of sampling throughout the whole food chain, from primary production through to distribution and retail, unlike EU sampling plans which relate only to primary production.

USA

The US Department of Agriculture (USDA) Food Safety Inspection Service operate a national sampling plan for residues in meat. The residues/species to be included are risk-based, with some tests being rotated year-on-year, and the sample numbers generally following Codex recommendations (i.e. surveys of 300 samples are typical). Surveys typically include arsenic as a mandatory test, because arsenical compounds have been authorised for use in the US.

These are supplemented by EU-style (volume-dependent) sampling, only from those abattoirs which are specifically licensed to export to the EU.

For non-meat animal products (particularly milk and fish), the Food and Drug Administration (FDA) operate national sampling plans. This includes a large industry-test scheme for milk, where dairy companies are required to submit their own test results to the FDA.

Brazil

A split production system is operated, with production authorised for EU export subject to an EU-scale sampling scheme. This has been supported by industry-wide surveillance schemes for different commodity types, such as the Brazilian Health Regulatory Agency "PAMvet" scheme for processed milk[9].

China

There are two parallel surveillance plans, using two parallel networks of laboratories. The Ministry of Agriculture operates a sampling scheme dictated by National legislation, which sits between Codex guidelines and EU requirements in terms of its scale. Within the Export-Oriented Scheme, the Entry-Exit Inspection and Quarantine Bureau (CIQ) network operates an EU-scale sampling scheme. CIQ laboratories also operate a comprehensive programme of pre-export testing for VMP residues; effectively, positive-release testing for banned antibiotics such as nitrofurans and chloramphenicol.

Laboratory test methods – performance requirements

In the first years after its formation the CCRVDF fulfilled its remit to advise on appropriate laboratory test methods by supporting inter-laboratory validation studies and then publishing these as validated (recommended) methods. This follows the traditional US legal approach of only accepting standard methods (e.g. inter-laboratory validated by the AOAC[10]) for regulatory compliance testing. More recently, the emphasis has moved to in-house (single laboratory) validation, and the Codex guidelines now include comprehensive detail on how laboratories should validate their own in-house methods, or verify methods that are transferred from another laboratory. These were revised in 2014 to include the validation of multi-residue methods.

The method performance characteristics described in the Codex guidelines echo the IUPAC guidelines[11] for single-laboratory validation, with added detail on confirmation of identity. They differ slightly to the mandatory method performance characteristics[12] applicable in EU Member States. Codex places an emphasis upon limit of detection and limit of quantification rather than "decision limit" and "detection capability", and has criteria for confirmation of identity which are marginally more flexible than the EU "identification points" tables.

Regulatory oversight and inspection of laboratories

Most importing countries require that trading partners operate – as a minimum – a residue testing scheme that is equivalent to the importer's own domestic scheme. It is increasingly common for the regulatory authority in the importing country to audit the laboratories in the exporting country, to assure that this is in place. For many years, the USDA and the EC Food and Veterinary Office have operated comprehensive audit programmes and licensing schemes for all countries that want to export animal-origin food to the US or the European Union respectively.

More recently, countries such as China and the Russian Federation have instigated their own reciprocal audit programmes for their trading partners. Many of the audit criteria are similar, but most authorities have their own specific laboratory performance requirements: for example, the USDA like to see a system of routine laboratory quality control samples that are "blind" to the analyst, and demand that arsenic residue testing is included, whilst the Russian Federation require laboratory detection limits for tetracycline residues that are tenfold lower than for most other countries. Regulatory laboratories that support export to multiple trading partners need to ensure that their Quality Management Systems, method validation protocols, analyte suites, and detection limits comply with the requirements of all countries to which they export.

Reciprocal agreements and regional harmonisation

There are clear advantages, in terms of free trade, to reciprocal recognition of control systems of VMPs without the need for audit, inspection or end-product testing. A number of trading partners and regions are working towards this. For example, the Southern African Development Community members (Angola, Botswana, DR Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia, Zimbabwe) have harmonised procedures[13] for the authorisation and distribution of VMPs. The EU-Australia 2008 Partnership Framework (to be superseded by the 2017 Framework Agreement) reduces the demand for testing at port of entry. Southern American countries (primarily Argentina, Brazil, Paraguay and Uruguay) work to harmonise their national VMP controls through Technical Committees of MERCOSUR, the South American Common Market.

Conclusions

Regulatory control of Veterinary Medicinal Products and compliance limits for residues in food are defined in individual national law. Residue limits and schemes to monitor the effectiveness of VMP controls both must be based on risk assessment. Different risk assessors can draw different conclusions from the same data. Attempts at global harmonisation, notably through the Codex Alimentarius Commission, have been largely successful. Some inconsistencies and disagreements remain; these have not proven insurmountable barriers to trade. Differences in national rules can be difficult to navigate, but any laboratory conducting VMP residue testing to support export certification must be aware of the rules in each export market, and may be audited by the importer's regulatory authority.

About the author

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1 Residues of Veterinary Medicines in Food – Regulation and Testing in the European Union

2 UN General Assembly Resolution 39/248 of 16 April 1985

3 http://www.fao.org/fao-who-codexalimentarius/standards/veterinary-drugs-mrls/en accessed 17 October 2017

4 Regulation 470/2009 of the European Parliament and of the Council 0f 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin

5 CAC/GL 71-2009: Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programme Associated with the Use of Veterinary Drugs in Food Producing Animals, Revision 2014, Codex Alimentarius, FAO/WHO

6 Final Report of an audit carried out in The United States from 18 to 29 October 2010 in order to evaluate the control of residues and contaminants in live animals and animal products including controls of Veterinary Medicinal Products, European Commission Health and Consumers Directorate-General Directorate F, DG(SANCO) 2010-8444-MR FINAL.

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12 Commission Decision 2002/657/EC of 12 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results

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