

Australian comments to the proposed setting of US import tolerances

RE: Docket Number 01N-0284

**Federal Register Notice of 10 August 2001
(66 FR 42167)**

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Australia, through the Department of Agriculture, Forestry and Fisheries Australia (AFFA) welcomes the opportunity to provide comment on the plan to propose a regulation for establishing import tolerances.

We would like to provide comments to the questions raised by the United States Food and Drug Administration (FDA) in the Federal Register Notice of 10 August 2001 (66 FR 42167). Although the FDA has indicated that it is seeking comment on all aspects of import tolerances it has specifically asked for comment on the following issues:

1: There are different approaches that can be taken to the setting of safe import tolerances.

The FDA has outlined three scenarios that would be compatible with its legislation

- look at toxicity and residue data and build a conservative safety factor
- also review conditions of use such as good agricultural practices, route of administration, and dose, which may result in different safety factors
- additionally consider manufacturing information such as required for domestic applications which would result in a different safety factor

Australia considers that establishing an import tolerance requires a technical assessment that differs from registration of a product as the product itself is not sold in the USA. The responsibility for determining whether the product is safe (environment, target animal and user), effective for its intended use, and the manufacture, processing and packaging are adequate to preserve its identity, strength, quality and purity lies with the country requesting the import tolerance. In establishing an import tolerance, it is the human food safety aspect that needs to be verified by the FDA. Therefore, Australia proposes that the FDA restrict the evaluation to determining the safe level of residues in the imported commodity and, in the first instance, whether or not the proposed tolerance represents a safe level. To achieve this Australia suggests that the FDA should request information on the use pattern (dose, slaughter withholding period, good agricultural practice etc), toxicology (to set an Acceptable Daily Intake), metabolism, analytical methodology and residues at the withholding period (WHP). The amount of information requested would depend on whether or not the drug is registered in the USA.

Cases that need to be considered are:

- the drug is not registered in the US or is registered but not on a food-producing animal species. The data required would include a full toxicology package, farm animal metabolism, residues trials and analytical method; and.
- the drug is currently registered in the US on another food-producing animal species. The data required would include a residue decline trial and depending on whether the FDA considers the application to be for a minor-use/minor species, farm animal metabolism and analytical method for the species of interest. A supporting letter from the owner of the toxicology data used by the FDA to set the ADI (this takes care of any data ownership issues) may be

required depending on FDA policy in this area. Alternatively toxicological data may be required to be submitted. It may be that the FDA permits the extrapolation of the major species data to minor species and the additional metabolism study would not be required.

In all systems for tolerance setting, the standard for protecting the consumer (human safety) is the ADI, established after reviewing appropriate toxicological data.

It is our understanding that the approach taken by the FDA in setting residue tolerances is to first set the ADI (units mg drug/kg bodyweight/day). In establishing tolerances, the FDA determines the maximum residue that can be present in a tissue. In the absence of information to the contrary, the FDA assumes that all residues of the drug are at least as toxic as the parent compound. The safe concentration of residue in a tissue is then calculated for a 60 kg person using the following food consumption figures: 300 g muscle, or 50 g fat, or 100 g liver, or 50 g kidney. If the drug is involved in milk or egg production the relevant consumption figures are 1.5 L milk or 100 g eggs¹.

A marker residue is chosen for monitoring purposes (often the parent compound) and the ratio of the marker to the total residues present in a tissue is estimated using the results of studies with radiolabelled drug (metabolism and/or residue decline studies with radiolabelled drug). The tolerance is the safe concentration × the ratio of marker to total residue.

The WHP is the time at which residues of the marker in each of the commodities is below the relevant tolerance and is calculated from a residue decline trial using a statistical approach. The resulting WHP often does not correlate with the WHP that might be assigned according to Good Animal Husbandry²; moreover, the dietary exposure of the populace is generally grossly overstated.

An example reported on the FDA Center for Veterinary Medicine (CVM) web-site serves to illustrate the FDA CVM process and will be contrasted with that used by Australia.

Ivermectin (IVOMEC® Injection for Cattle, NADA 128-409).

¹ If the drug is used on lactating dairy cows as well as other meat-producing species, a part of the ADI (usually ½) is reserved for milk, if the use includes both laying hens and other animals a part of the ADI (usually 1/5th) is reserved for eggs.

² *Good Animal Husbandry (GAH)* may be defined as the nationally authorised safe uses of a veterinary drug or pesticide under actual conditions necessary for effective disease/pest control. It encompasses a range of levels of drug/pesticide applications up to the highest authorised use, applied in a manner which leaves a residue which is the smallest amount practicable. Authorised safe uses are determined at the national level and include nationally registered or recommended uses, which take into account public and occupational health and environmental safety considerations.

Good Practice in the Use of Veterinary Drugs (GPVD) is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions (Procedural Manual of the Codex Alimentarius Commission, 12th edition, 2001).

The ADI for ivermectin was established by the FDA as 1 µg/kg bw/day based on a No Observable Effect Level (NOEL) of 0.5 mg/kg bw/day in a 90-day dog study and using a safety factor of 500.

a. Acceptable Daily Intake (ADI)

$$\text{ADI} = \frac{\text{NOEL}}{\text{safety factor}} = \frac{0.5 \text{ mg/kg/day}}{500} = 0.001 \text{ mg/kg/day} = 1 \text{ } \mu\text{g/kg/day}$$

b. Safe Concentration (SC) [of total residues]

$$(\text{SC}) = \frac{\text{Acceptable Daily Intake} \times \text{Human Weight}}{\text{Food Factor}}$$

Where:

Human weight = 60 kg

Food Factor³:

muscle = 500 g

fat = 125 g

liver = 250g

kidney = 167 g

$$\text{SC (muscle)} = \frac{1 \text{ } \mu\text{g/kg/day} \times 60 \text{ kg}}{500 \text{ g/day}} = 0.12 \text{ } \mu\text{g/g} = 0.12 \text{ ppm}$$

$$\text{SC (fat)} = \frac{1 \text{ } \mu\text{g/kg/day} \times 60 \text{ kg}}{125 \text{ g/day}} = 0.48 \text{ } \mu\text{g/g} = 0.48 \text{ ppm}$$

$$\text{SC (kidney)} = \frac{1 \text{ } \mu\text{g/kg/day} \times 60 \text{ kg}}{167 \text{ g/day}} = 0.36 \text{ } \mu\text{g/g} = 0.36 \text{ ppm}$$

$$\text{SC (liver)} = \frac{1 \text{ } \mu\text{g/kg/day} \times 60 \text{ kg}}{250 \text{ g/day}} = 0.24 \text{ } \mu\text{g/g} = 0.24 \text{ ppm}$$

Data included in a previous NADA showed that ivermectin H₂B_{1a} represents approximately 42% of the total residue in liver at the WHP of 35 days. This would give a marker tolerance of 240 × 0.42 = 101 ppb. The tolerance for ivermectin (H₂B_{1a}) was set at 100 ppb in liver for the USA. Similarly, a tolerance was also established for muscle at 10 ppb⁴.

The extremely conservative nature of the exposure estimates is illustrated by the monitoring results for ivermectin. In 1999, the FSIS monitoring program tested 2209 cattle liver samples for ivermectin with 16 detections (Limit of Quantitation = 2 ppb) or 0.7% of samples contained detectable residues. No samples exceeded the US tolerance. The average and median residues were <2 ppb; that is 50× less than the US tolerance.

³ Food factors were revised after the NADA for ivermectin was published. The ones listed were used in 1995.

⁴ At 28 days after injection, ivermectin B1b accounts for 67%, 37%, 54% and 15% of the Total Radioactive Residue for muscle, liver, kidney and fat respectively.

Australia contends that an alternative system for tolerance setting used by Australia⁵ for pesticides and veterinary drugs and by Codex (CCPR/JMPR) for pesticides results in tolerances that represent safe levels for the consumer. The difference between the FDA and Australian methodology lies in the setting of tolerances and WHPs. In Australia, the ADI is established in a similar way as for veterinary drugs by the FDA. Metabolism studies utilising radio-labelled drug (hot studies) are used to define the marker residue for compliance/monitoring purposes and for the estimation of dietary exposure. Residue decline trials using unlabelled drug (cold studies) are used to estimate tolerances for the marker residue with the withholding period based on GAP⁶. There is no interpolation of residues between sampling intervals, i.e. the WHP must be one of the slaughter times after last treatment in the residue decline trial. The tolerance is set using measured marker residue levels in tissues and must be reconciled with the ADI. In Australia, a National Estimated Dietary Intake (NEDI) calculation is performed for chronic (long-term) exposure and a National Estimated Short-Term Intake (NESTI) calculation for acute (short-term) exposure estimates.

Australia and Codex (CCPR/JMPR) recognise that utilising Maximum Residue Limits (tolerances) in calculations results in gross overestimation of dietary exposure. A simple, though still conservative, refinement is to utilise the supervised trial median residue (STMR) in exposure estimates. In the case of crops this is just the median residue value for a series of trials conducted according to the maximum allowed rate and harvested at the withholding period. For animal studies the median individual animal residue from a trial or series of trials conducted with treatment at the proposed rate is used. Probabilistic modelling (not yet used in Australia) utilises information such as monitoring data, percent crop or animals likely to be treated and information on residue decline and has been employed by the US EPA to further refine dietary exposure estimates.

The Australian approach to tolerance setting can be illustrated by the IVOMECE® Injectable case. The Australian WHP for IVOMECE® is 28 days. This is considered compatible with GAP as the animals are not sick at time of slaughter, it is consistent with animal husbandry practices and compatible with any domestic animal movement requirements in/out of local quarantine zones (eg pest control programs). The proviso for considering if the WHP is acceptable, is that the dietary consumption of residues can be demonstrated to be compatible with the protection of human health, i.e. the residues can be reconciled with the ADI. The metabolism study identified ivermectin H₂B_{1a} as the major component of the total radioactive residue while the toxicologists did not raise any concerns regarding any of the minor metabolites. A validated analytical method exists for H₂B_{1a} in tissues. Therefore, H₂B_{1a} was selected as being appropriate as a residue definition for both compliance and dietary intake estimation.

⁵ For dietary intake estimation, Australia follows the principles outlined by the Joint FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals (Geneva, Switzerland 1997). The diet for which the intake is calculated is an average diet derived from dietary survey information for comparison with the ADI (intake every day for a lifetime) and the 97.5th percentile consumption for comparison with the acute RfD (intake during a single day).

⁶ In Australia, GAP is defined as the nationally recommended, authorised or registered use-pattern of chemicals that is necessary for effective and reliable pest control under actual conditions at any stage of production, storage, transport, distribution and processing of food commodities and animal feed.

The residue depletion trial with unlabelled drug (reported in NADA128-409) gave the following results:

Days withdrawal	H ₂ B _{1a} Residue (ppb)	
	Liver	Injection site
21	46±37	NA
28	27±16	1280±2979
35	10±10	576±817
42	3±3	570±1037
49	3±4	231±724
56	NA	NA

NA = not analysed

At 28 days the maximum residue for ivermectin H₂B_{1a} in liver was 0.075 ppm⁷. MRLs in Australia are selected from the following sequence ... 0.01, 0.02, 0.03, 0.05, 0.07, 0.1, 0.2, 0.3, 0.5... A maximum residue of 0.075 ppm in the residue trials would lead to an MRL of 0.1 ppm in liver. Other Australian MRLs for ivermectin in cattle tissue are 0.01 mg/kg for cattle kidney and 0.04 mg/kg for cattle meat [in the fat].

The recommended MRLs and any other information from the residue trials (median residue values) are used to estimate the dietary exposure. If the dietary exposure estimate exceeds the ADI or acute RfD, the WHP is amended and new MRLs are proposed. The procedure is repeated until the proposed MRLs can be reconciled with both the ADI and acute RfD. The National Estimated Dietary Intake (NEDI) is calculated using the mean consumption figures for the Australian population 2 years and older and is shown below using Australian MRLs for cattle commodities. For the purpose of this illustration, only the commodities relevant to the IVOMECA[®] Injection NADA have been included. Normally all commodities for which there are Australian MRLs for ivermectin would be included (milk, sheep, deer, horse and pig commodities).

NEDI calculation for ivermectin

Commodity	ADI = 0.001 mg/kg bw/day		Mean consumption g/kg bw/day*	NEDI, mg/kg bw/day
	MRL mg/kg			
Cattle liver§	0.1		0.0043	0.000004
Cattle kidney¶	0.01		0.0037	0.000000
Cattle meat [in the fat]£	0.04		0.11059	0.000044
Total				0.000005
				0.49 % of the ADI

NOTES:

* mean consumption figures for population 2 years old and above, average weight is 67 kg

£ Cattle meat [in the fat] indicates that the compound is fat soluble and the trimmable fat should be analysed

In Australia it is policy to assume meat contains 10% fat and add this consumption figure to that reported for fat per se = 0.1×1.0839 + 0.0022 = 0.11059 g/kg bw/

§No consumption data are available for cattle liver. The combined consumption figure for liver of cattle, pigs, sheep and goats was used instead

¶No consumption data are available for cattle kidney. The combined consumption figure for kidney of cattle, pigs, sheep and goats was used instead

The use of the median residue from the animals slaughtered at 28 days in the trial instead of the MRL in the NEDI calculation would result in a lower exposure estimate. The mean consumption figures, on a 60 kg bw basis, are 65 g of meat, 7.8

⁷ The data in NADA 128-409 were reported as mean±SD rather than for individual animals. For the purposes of the discussion it is assumed the maximum residue observed in an individual animal in the trial was mean±3×SD.

g of fat, 0.26 g of liver and 0.22 g of kidney and are much lower than those used by the FDA to establish the safe concentration. Similar mean consumption figures would be expected for the US population as the WHO GEMS Food program has identified Australia and the USA as belonging to the same diet cluster.

It is recognised that the ADI corresponds to the amount of a drug that can be consumed daily over a lifetime without appreciable risk and that short term excursions above the ADI are permitted. To ensure that these short term excursions do not pose a risk to human health the concept of acute exposure (one meal or one day) and the acute reference dose (amount of drug that can be safely consumed in a single meal or over the period of a day) have been introduced. In Australia, dietary risk assessment for short-term exposure is carried out using the methodology described in the most recent JMPR Reports⁸.

In these intake calculations the large portion is used, typically 97.5th percentile consumption figure for the target population. The National Estimated Short Term Intake (NESTI) calculations for each commodity are shown below.

NESTI calculations for ivermectin

acute RfD = 0.025 mg/kg bw/day[‡]

Commodity	MRL mg/kg	97.5th percentile consumption g/kg bw/day	NESTI, mg/kg bw/day	%acute RfD [‡]
Cattle liver [§]	0.1	3.11	0.000311	1.2
Cattle kidney [¥]	0.01	3.11	0.000031	0.1
Cattle meat [in the fat] [£]	0.04	0.9297	0.000037	0.1

Notes

* 97.5th percentile consumption figures for population 2 years old and above, average weight is 67 kg

£ Cattle meat [in the fat] indicates that the compound is fat soluble and the trimmable fat should be analysed

In Australia it is policy to assume meat contains 10% fat and add this consumption figure to that reported for fat per se = 0.1×6.967 + 0.233 = 0.9297 g/kg bw/day

§No consumption data are available for cattle liver. The combined consumption figure for edible offal of cattle, pigs and sheep was used instead

¥No consumption data are available for cattle kidney. The combined consumption figure for edible offal of cattle, pigs and sheep

‡the acute reference dose has been assumed to be 0.025 mg/kg bw/day, based on a safe concentration of ivermectin in 500 g of injection site of 3 ppm reported in NADA 128-409

The calculations for short-term intake are calculated for each commodity and are not summed. In this calculation the highest residue in the trials from the animals slaughtered at the WHP of 28 days would normally be used instead of the MRL (tolerance). The use of the highest residue in the calculation would result in a lower acute exposure estimate than illustrated above. The 97.5th percentile consumption figures on a 60 kg bw basis are 418 g of meat, 56 g of fat and 187 g of edible offal of

⁸ The case that is appropriate for meat and eggs is case 1: The concentration of residue in a sample or in a composite sample (raw or processed) reflects that in a meal-sized portion of the commodity (unit weight of the whole portion is <25 g).

$$\text{NESTI} = \text{LP} \times (\text{HR or HR-P}) \div \text{bw}$$

Where LP = large portion reported (eaters at the 97.5th percentile of consumption), in kg of food per day

HR = highest concentration of residue in composite sample of edible portion found in supervised trials from which the MRLs (tolerances) or STMR values were derived, in mg/kg

HR-P = highest concentration of residue in the processed commodity, in mg/kg

bw = body weight (kg)

For milk the relevant case is case 3: Bulking and blending of a processed commodity means that the STMR-P value probably represents the highest concentration of residue

$$\text{NESTI} = \text{LP} \times (\text{STMR-P}) \div \text{bw}$$

Where STMR-P = the supervised trial median residue in the processed commodity, or in the case of animals the median residue in supervised trials from which the MRL was derived.

cattle, pigs and sheep. It is interesting to note that these figures are closer to the FDA Food factors than the mean consumption figures. In summary, Australia proposes that the FDA accept the methodology used by Australia to establish tolerances as suitable for the setting of safe import tolerances.

2: The FDA is concerned about data ownership and asks “only the drug marker residue for the drug substance, not the product formulation or the sponsor of the import tolerance, can be determined by the type of analytical method that is typically used to assay imports. Are there analytical techniques or other approaches that would allow us to determine whether a residue is due to use of the drug product for which the tolerance is approved?”

Australia is unsure as to the intent of the question. Currently, established domestic tolerances apply not only to commodities produced locally and treated with FDA approved products (NADA) containing the active ingredient but also to residues in commodities produced outside the USA.

Is the FDA proposing that the import tolerance will be country specific? Australia would suggest that import tolerances once set by the FDA should apply to all imported produce and not only produce from the country that applied for the import tolerance, i.e. be general and not country specific.

It should be noted that to access the import tolerance set by the USA a country must have registered the compound for use on food producing animals and have established relevant domestic tolerances.

3: The FDA is concerned about whether or not it should inform the public of an application for an import tolerance and if so when, how and the amount of detail.

Australia is aware of the need for transparency in the process for setting standards for food. As such Australia is supportive of disclosure but would request that the level of disclosure is no different from that applied to applications for NADA's and that the applicant be given an opportunity to review and comment on any commercial-in-confidence information in the disclosure document.

4: The FDA is considering amending the regulations at 21 CFR 25.33 to allow the categorical exclusion for import tolerances under the National Environmental Policy Act if there is information that shows that establishing import tolerances does not have a significant effect on the environment.

Australia notes that the FDA is required under National Environmental Policy Act of 1969 (NEPA) to consider the environmental impact of investigating and approving new animal drugs as an integral part of its regulatory process. Under these regulations, sponsors filing investigational exemptions or new animal drug applications must submit an environmental assessment (EA) unless the exemption or application qualifies for a categorical exclusion from the requirement to prepare an EA. Currently, an EA is not required for most minor use applications. “In most cases, an application for use in a minor species will be granted a categorical exclusion from the requirement to provide an EA. The regulations under which a categorical

exclusion for a minor species can be granted are included in 21 CFR 25.33(d)(4), 25.33(c), and 25.33(d)(5). Section 25.33(d)(4) provides a categorical exclusion specifically for drugs intended for minor species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used. FDA believes similar animal management practices generally include dosage, duration of use and concentration of the medication, as well as management style, such as feedlot, pasture or open pens. A categorical exclusion can be applied to a minor species application when the animal drug is already being used under similar animal management practices, and no significant differences from the major use approval are anticipated in the environmental introduction, fate and effects of the drug”.

Australia contends that as the import of treated product does not have an environmental impact with respect to the manufacture and disposal of the new animal drug, it is appropriate to exclude import tolerances under the National Environmental Policy Act.

5: Other aspects

Australia wishes to raise six other issues related to the setting of import tolerances which were not specifically commented on in the Federal Register Notice of 10 August 2001 (66 FR 42167).

5.1 There appears to be some overlap in the legislation of the EPA (FIFRA) and FDA (FFDCA and the ADAA) with respect to the responsibility for registration of certain products. Is there any guidance as to which agency is responsible for import tolerances when the compound is registered for agricultural use by the US EPA but has veterinary use overseas? eg some external parasite treatments.

According to the FDA legislation a drug is defined as:

- *articles recognised in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and*
- *articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and*
- *articles (other than food) intended to affect the structure or any function of the body of man or other animals; and*
- *articles intended for use as a component of any article specified above (food and dietary supplements are generally excluded).*

While a new animal drug means any drug intended for use for animals, including any drug intended for use in animal feed (but not including such animal feed) – the composition of which is generally not recognised as safe and effective or as a result of investigations to determine its safety and effectiveness is recognised as safe and effective but otherwise has not been used for the purpose intended (paraphrased).

The EPA legislation defines a pesticide as “*any substance that will prevent, destroy, repel or mitigate any pest...(FIFRA section 2(a) 40CFR152.3 Definitions) while an “organism is declared to be a pest under circumstances that make it deleterious to*

man or the environment, if it is [among others] (b) any invertebrate animal, including but not limited to, any insect, or other arthropod, nematode ... but excluding any internal parasite of living man or other living animals;" (40CFR152.5 Pests).

Clearly treatments for external parasites can be the responsibility of the EPA and have been evaluated in the past by this agency. Is there any direction the FDA can provide as to who will have responsibility for pesticides that have both crop and direct animal uses?

5.2 What is the impact of minor uses on the data required?

Application of the concept of minor-use can result in less stringent data requirements. The FDA defines a minor use as the use of new animal drugs in minor animal species⁹ or new animal drugs in any animal species for the control of a disease that occurs infrequently or occurs in limited geographical areas. For example sheep are considered a minor species in the USA or the pest/disease is not relevant to the USA and so in the USA would be considered a minor-use.

5.3 What will the process be for making an application for an import tolerance?

5.4 How long will the process take to establish an import tolerance? Is it 180 days for an initial response as specified in 21USC 360b (c)?

5.5 Is it possible to fast-track an application if an application is made in response to a detection in the US port-of-entry import testing program?

5.6 What procedure will be followed when/if the US receives competing, and possibly different, applications from different countries for establishing an import tolerance for the same chemical?

- Will applications be processed on a first come first processed basis?
- Will the US establish a single chemical import tolerance that applies to all product irrespective of its country of origin?
- Will the US develop differing import tolerances for a chemical depending on the country of origin?

⁹ In the case of potential food animals, minor species means animals other than cattle, horses, swine, chickens and turkeys.