New Zealand Food Safety
Ministry for Primary Industries
Manatū Ahu Matua

Data Assessor Workshop – ACVM Team

Friday 18th October 2019, 9.00am - 4.00pm

TSB Tower, 147 Lambton Quay

Level 1 Meeting Rooms (1.02, 1.03, 1.04)

Wellington

AGENDA

8.45am - 9.00am	**Tea and coffee available**
9.00am - 9.10am	**ACVM welcome and housekeeping** (KB)
9.10am – 9.30am	**General** Introduction to ACVM Act (WH) • purpose of ACVM Act • how data assessment fits into registration process • purpose of data assessment reports
9.30am – 9.50am	**Discussion on common questions and issues** (SL & JD) **(**Note: AC/VTA/VM specific questions will be discussed in breakout sessions)
9.50am – 10.15am	**How can DA templates be improved?** (All)
10.15am - 10.45am	**Morning tea**
10.45am – 11.45am	**Animal Transfer and residue assessment** (AB)
11.45am – 12.15pm	**Discussion**
12.15pm - 1.15pm	**Lunch**
1.15pm – 2:15pm	**Split Sessions** **Vet Med** – New chem and manufacturing guidance (JD) **Ag Chem** – Discussion of draft chemistry and manufacturing guidance development (EBR)
2.15pm – 3.00pm	**Vet Med** – Bioequivalence (MM) **Ag Chem** – Questions (All)
3.00pm – 3.20pm	**Afternoon Tea**
3.20pm – 4.00pm	**Joint session - Questions and general discussion** (All)
4.00pm	**End**

New Zealand Food Safety
Haumaru Kai Aotearoa

Agricultural Compound Regulation In New Zealand

Warren Hughes
Principal Adviser ACVM
ACVM Team

Ministry for Primary Industries
Manatū Ahu Matua

Outline

- Regulation of Agricultural Compounds
- Registration Process
- Post-Registration
- Restricted Veterinary Medicines
- Exempt from Registration

Regulation of Agricultural Compounds

The ACVM Act and Regulations

- **The Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997**
- **The ACVM (Exemptions and Prohibited Substances) Regulations 2011**
- **The ACVM (Fees, Charges, and Levies) Regulations 2015**
- Regulates all compounds used in, on, or around animals, plants and their environments
    - Veterinary medicines, agricultural chemicals (crop chemicals), vertebrate toxins (pest control products), animal feeds, fertilisers, etc.

The ACVM Team

- In the Assurance Directorate of the New Zealand Food Safety in MPI
- Responsible for the administration of the ACVM Act
    - Registration of agricultural compounds: veterinary medicines, agricultural chemicals, vertebrate toxins (pest control products)
    - Sets guidelines, guidance and operational policies
    - Independent scientific assessment and review of all technical aspects of product management – manufacturing, importing, sale, and use
- Also responsible for assessment and setting of Maximum Residue Levels (MRLs) under the Food Act 2014

ACVM Act – Purpose

- Manage risks associated with use of agricultural compounds being
    - Risks to animal welfare
    - Risks to public health
    - Risks to agricultural security
    - Risks to trade in primary produce
- Ensure that the use of agricultural compounds does not result in breaches of domestic food residue standard
- Ensure the provision of sufficient consumer information about agricultural compounds

ACVM Act – Scope

- Scope is set by the definition of an agricultural compound:

> Any substance, mixture of substances, or biological compound, used or intended for use in the direct management of plants and animals, or to be applied to the land, place or water on or in which plants and animals are managed

ACVM Act – Scope

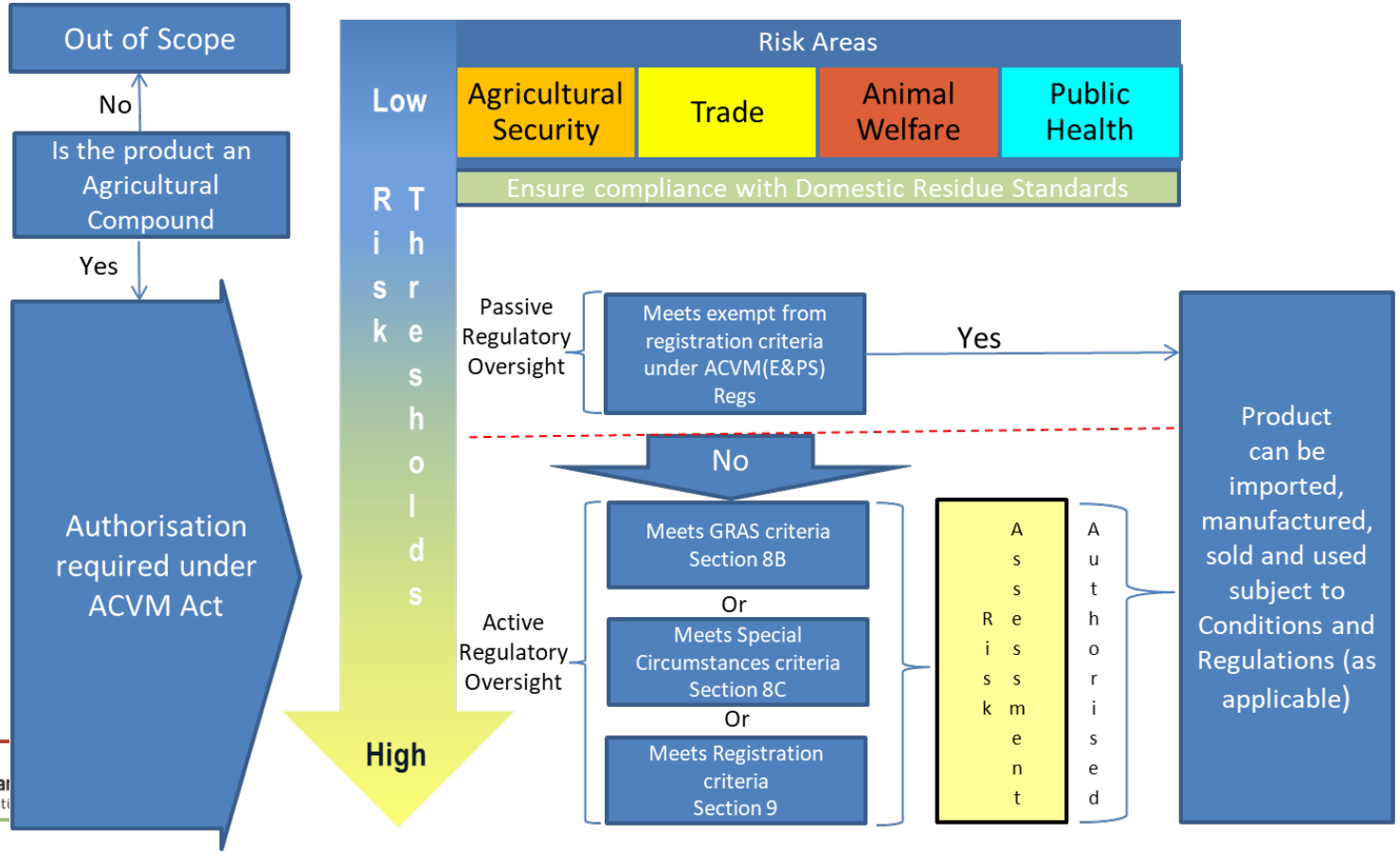
- For the following purposes:
  - Managing or eradicating pests, including vertebrate pests
  - Maintaining, promoting, or regulating plant or animal productivity and performance or reproduction
  - Fulfilling nutritional requirements
  - The manipulation, capture, or immobilisation of animals
  - Diagnosing the condition of animals
  - Preventing or treating conditions of animals
  - Enhancing the effectiveness of an agricultural compound used for the treatment of plants and animals
  - Marking animals

ACVM Act – Authorisation

- Three types
  - Registration (section 21)
  - Provisional Registration (section 27)
  - Exempt from Registration (section 8A)
    - Exempt under Regulations (section 75(1)(a))
    - Listed as Generally Recognised as Safe (section 8B)
    - Approved in special circumstances (section 8C)

- Authorisation only granted if risks can be managed by applying conditions

ACVM Risk Framework



Registration

- Focus is on therapeutic uses and pest control
  - Includes antibiotics, drenches, vaccines, fungicides, herbicides, and insecticides
- Trade Name Products
  - Defined formulation
  - In a discrete package
- Regulatory Timeframes
  - 40 working days for non notified
  - 70 working days for notified applications

Risk Management by Registration

- Subject to compliance with conditions
- Level of risk dictates controls
- All products must
    - be manufactured, labelled, advertised, and sold in accordance with approval
    - have adverse events reported to MPI
- Can also restrict importation, distribution, and use of the product based on risk

Regulatory Tools - Conditions of Registration

Section 23 of the Act allows conditions to be set on:

- Use
- Specifying standards in many areas including:
    - Competence
    - Quality and purity
    - Labelling
    - Advertising
    - Testing methods
- Restrictions on who can manufacture, import, or use

Regulatory Tools - Other

- Recognition of Persons, Classes of Persons and Organisations
    - For specified functions and activities for the purposes of the Act eg recognition of Veterinarians

- Operating Plans
    - Associated with conditions of registration

Confidential Information Protection

- Starts on receipt of application and ends after the specified period below once registration is granted or refused

Type	Protection Period
Innovative TNPs	10 years
Non Innovative TNPs	5 years
New Use or Method of Use	5 years
Reassessment	5 years

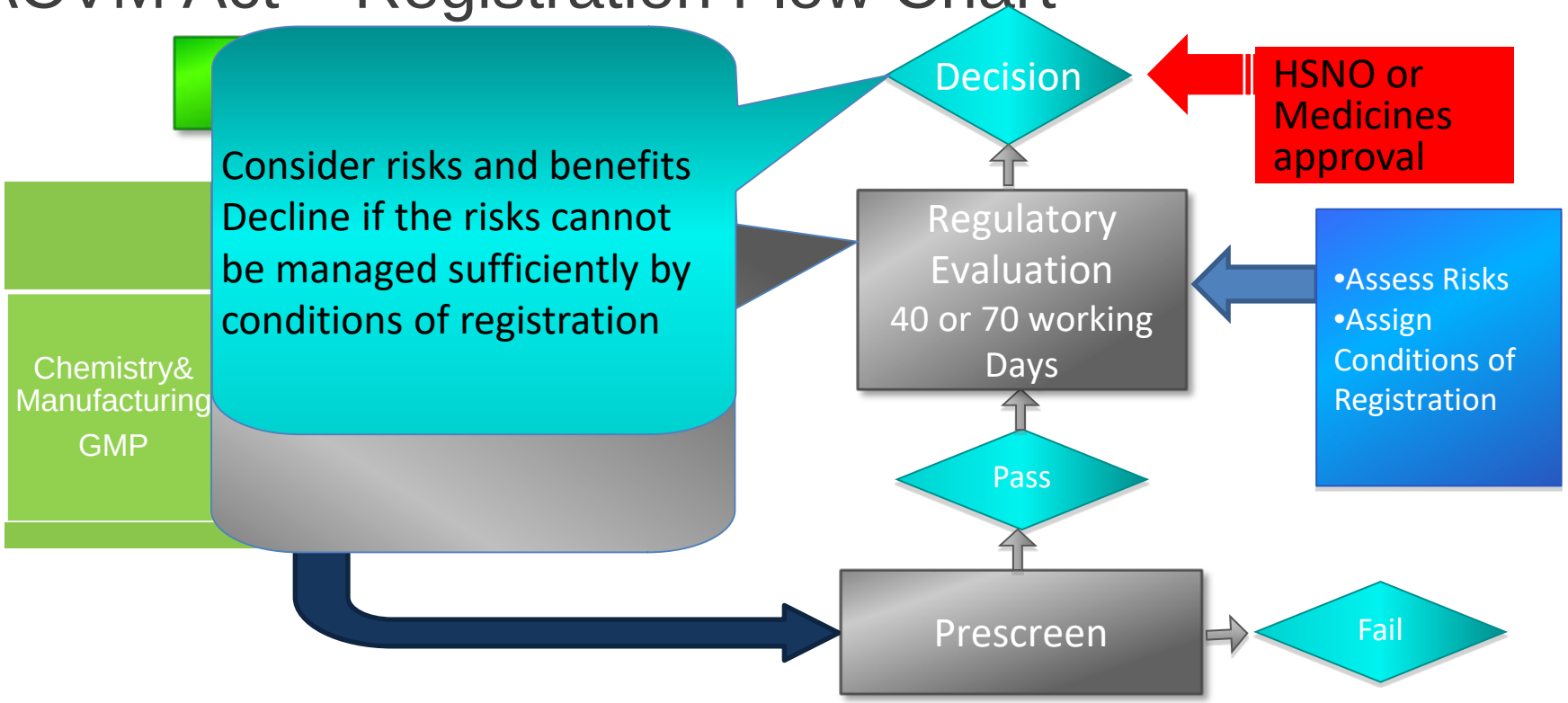
Fees, Charges and Levies

- ACVM (Fees, Charges, and Levies) Regulations
  - Establishes what MPI can charge for and the amount
  - Most applications and compliance activities charged on hourly basis ($135 plus GST)
  - Annual Renewal Levy for Registered Trade Name Product

- Fully cost recovered

Registration Process

ACVM Act – Registration Flow Chart



MPI Regulatory Documents

Sets expectations and requirements

- Guidance (aka information requirements) and forms
- Policies
- Fees

Based on as much as possible on best international practices eg VICH and OECD

Application Package

Applicants need to submit:

- Application form
- Product Data Sheet (PDS)
- Confidential Information Protection Form
- DAS Reports for relevant Guidelines
- GMP Approval Document (for VMs and VTAs)
- Other approvals eg HSNO and Biosecurity (Biosecurity applications can now be made with ACVM applications)
- Draft Label
- Fee
- The data

MPI Application Form

- Explains the purpose of the application
  - Such as Registration or variation to a registered TNP

- Summary of details on the Trade Name Product
  - Such as applicant, type of application and information supplied

MPI Product Data Sheet

- Covers the scope of the application
  - ➢ Such TNP, Formulation, Manufacturer(s), Release and Expiry Specifications, Packaging etc

- Linked to Conditions of Registration
  - ➢ Sets the scene for compliance

MPI DAS Reports

Based on Information Requirements for:

- Product Chemistry
- Efficacy
- Target Animal/Crop Safety
- Residues

➢ Relevancy of trials to Information Requirements and appropriateness of results

Draft Label

Labels must have information on:

- Directions for use (species/crop, conditions to be treated, dose rates, etc)
- Warnings and contraindications
- Regulatory statements required by registration conditions relating to use
- Withholding period information
- Restriction statement if it is an Restricted Veterinary Medicine (RVM)

Post-Registration

Monitoring and Surveillance

MPI has a number of feedback routes:

- MPI Residue Programmes
- Total Diet Study
- GMP Audits
- Sector Analysis Audits
- Adverse Event Reports
- Complaints form public, users, industry sectors and manufacturers

Management Tools

- ACVM Act allows MPI to:
  - Recall Products
  - Suspend registrations
  - Issue prohibition notices
  - Reassessments
- Most offences are ‘knowingly’

Restricted Veterinary Medicines (RVMs)

Restricted Veterinary Medicines (RVMs)

Certain veterinary medicines need restrictions to manage greater risks associated with sale and use

- Risks to Animal Welfare
  - Treats a condition that needs a veterinary diagnosis
  - Needs veterinary monitoring during or after use
  - Needs veterinary administration
  - Needs post-administration monitoring for side effects

➢ Antibiotics, anaesthetics, certain vaccines, controlled substances

RVMs – Veterinarian's Role

Veterinary Authorisation

- A veterinary authorisation is set of instructions from a registered practising veterinarian to authorise use of a RVM. It allows:
  - The veterinarian to administer
  - Purchase and use of a RVM in accordance with the instructions of the authorising veterinarian
    - Hold an RVM in anticipation of later use
- Equivalent to the commonly used term 'veterinary prescription'

RVMs – Veterinarian's Role

Veterinary Authorisation

- To authorise a RVM, the Veterinarian has to ensure:
  - They sufficient information based on their professional judgement
  - There is emergency or follow up care
  - The person (other than the authorising veterinarian) has sufficient expertise and/or experience to administer the RVM
    - Including management of anticipated adverse events

If the Veterinarian can not ensure the above, then they must not issue the authorisation

Exempt from Registration

Risk Management by Exemption

- Low risk and/or non-therapeutic products
    - Includes oral nutritional compounds (animal feeds), topical products used to treat minor injuries, non-medicated poultices, semen extenders
- Product registration not required, but products still subject to regulatory requirements
- Exempt product groups and their regulatory requirements specified in the ACVM (Exemptions & Prohibited Substances) Regulations
- Manufacturers and users are required to ensure exempt products are fit for purpose, and meet the conditions of exemption applied to each group

Thank you!

New Zealand Food Safety
Haumaru Kai Aotearoa

Data Assessment Reports – Common Issues

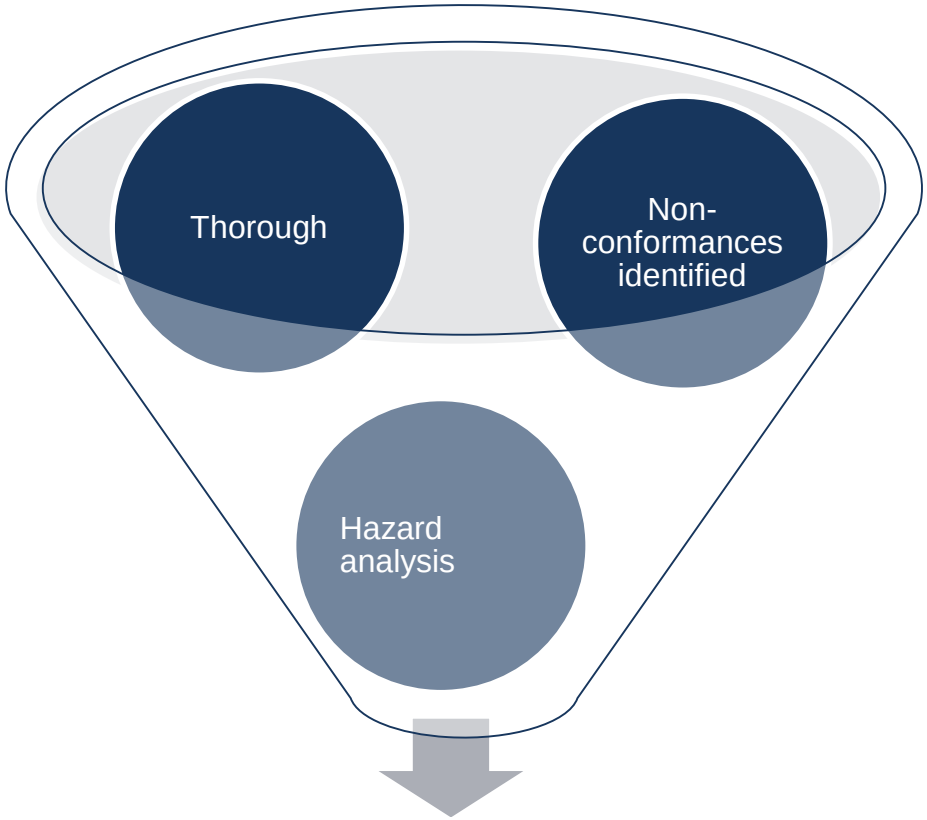
Group Discussion

Ministry for Primary Industries
Manatū Ahu Matua

Data Assessment Reports

- Appropriate data assessment report format
- Plain English
- Attention to detail
- Evaluate data against relevant ACVM expectations
- Are methods appropriate?
- Does data support conclusions?
- Identify deficiencies that impact on reliability or relevance of data

What makes a good Data assessment report?



Data Assessment Report

The purpose of a data assessment report

- A data assessment report is **a hazard identification and hazard analysis document rather than a risk assessment or risk management document.**

- Identify potential hazards relevant to the data being reviewed (C & M, efficacy etc) with reference to the product label and PDS **BEFORE** you start. This makes it easier to identify when data is missing.

- When a DAR is done well, all potential product hazards will be identified and there will be clear statements regarding whether or not the data provided is sufficient to have adequately characterised the nature of each individual hazard.

Hazard vs risk

Data Assessment responsibilities:

Hazard = Any product factor that could lead to or contribute to an unplanned or undesirable event that could result in non-compliance with any of the ACVM Act risk thresholds.

Hazard Analysis = The process of identifying all hazards associated with the product and documenting their unwanted consequences with reference to the ACVM Act risk areas.

ACVM responsibilities:

Risk Assessment = Judging the likelihood of an identified hazard creating a negative consequence

Risk Management = Putting measures in place to reduce the likelihood of a negative consequence to a regulatory acceptable level

Please don’t make risk management suggestions – the applicant can (and often does) consider this resolved and then won’t address the deficiency.

What to do if there is a data gap…

- Point it out – refer to applicant during assessment, otherwise in DAR
- Ensure that you highlight gaps as a deficiency in the non-conformance section as well as in the relevant area of the report.
- The **applicant** must address it, through data or argument, even if it seems obvious.
- NEVER dismiss a non-conformance on behalf of the registrant, even if you think it is small

If the applicant makes an argument instead of providing data, what do I do?

Think about wording that you use when highlighting deficiencies or discussing applicant's arguments – make it clear that it is ACVM's decision, and leave door open for us to request more information:

"This argument will be considered by ACVM during appraisal"

Assessing the data

- Do data sets have sufficient data points for the analysis?
- Make sure outliers are dealt with correctly-justified rather than just dropped out, some variability in a biological system is to be expected.

List all information assessed

- Please list and identify all information used in your assessment and give date or version number where possible.
- If large volumes or irrelevant information is provided, please note that this was included and whether you considered it.
- Include page number in your assessment

If I am not listed in an area, can I still do that data assessment?

- Yes, as long as you have the appropriate qualifications and experience. You should state that you are not listed in this area on the relevant DAR.

How can Data Assessment Templates be Improved?

What works well?
What can be improved?

Some copies of the current templates are printed.
www.mpi.govt.nz/processing/agricultural-compounds-and-vet-medicines/acvm-data-assessors/
If you have any ideas throughout the day, please add them to the board.

How do I know if ACVM will think I have a conflict of interest?

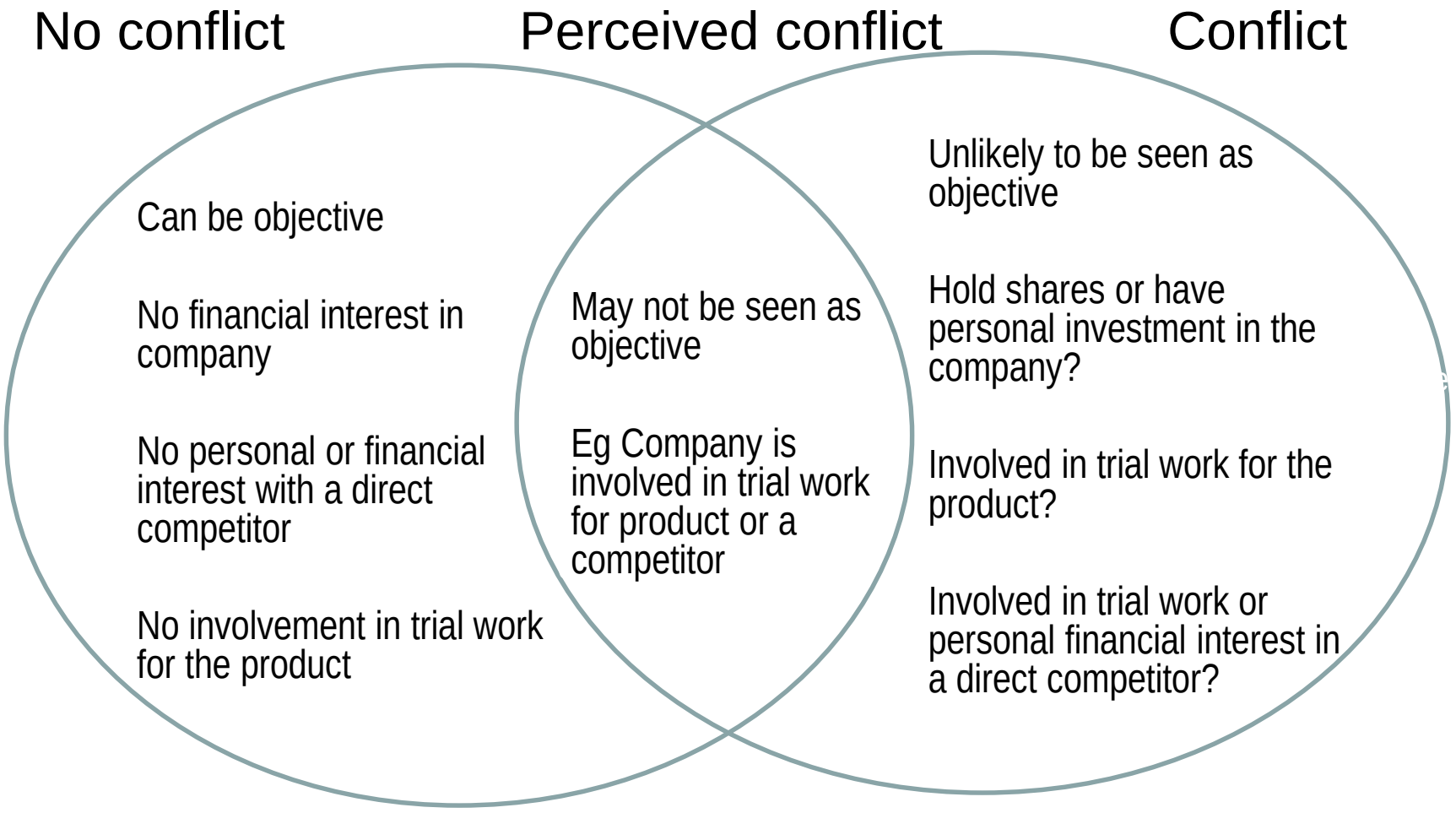
No Conflict

- No personal or financial interest in the company
- No personal or financial interest with a direct competitor
- No involvement in trial work for the product
- Can be objective

Conflict

- Involved in trial work for product
- Hold shares or have personal interest in the company
- Personal or financial interest with a direct competitor

In reality, may be more like this:



New Zealand Food Safety
Haumaru Kai Aotearoa

Agricultural Compound Residues Management

Awilda Baoumgren

Data Assessor’s Workshop

18 October 2019

Ministry for Primary Industries
Manatū Ahu Matua

Agricultural Compound Residues Management

- Animal Transfer Residues Assessment
- Tissue Residues Assessment and WHP determination
- Milk Residues Assessment and WHP determination
- MRL Promulgation

Animal Transfer Residues Assessment

Animal Transfer Residue Assessments

- Assessment completed whenever ag chemical use is likely to result in animal exposure:
  - ➢ grazing pasture, fodder crops, leaf plucking, crop harvest for animal feed production
- Four Steps to an animal transfer assessment:
  1. Evaluation of crop residue and animal data
  2. Calculation of expected animal dietary burden
  3. Use burden calculation and animal feeding studies to determine tissue residues and calculated MRLs
  4. Trade Analysis

Animal Transfer: An example

- A new compound is proposed for use on wheat grain as a fungicide. The compound is novel to New Zealand, but has overseas (US, Canada, EU) and Codex MRLs for both plant and animal commodities. The following data has been provided:
    - Crop residue trials: residue trials to NZ GAP evaluating residues in grain, straw, forage, aspirated grain fraction, and gluten feed meal; plant metabolism studies; rotational crop metabolism
    - Animal Residue trials: animal metabolism studies (goats and hens); feeding studies (lactating dairy cows)

Animal Transfer Assessment: Data Evaluation

- Crop residue assessment completed before the animal transfer assessment is undertaken
    - Establishes that the use patterns used in the trial work is GAP for NZ
    - Evaluates the data to determine STMR and HR for plant commodities
    - **Identifies the key commodities for animal feed and the highest potential risks for transfer residues**

Animal Transfer Assessment: Data Evaluation

Residue Definition	MRL-compliance and dietary intake estimation (plant commodities): Parent Compound only		
Commodity	WHP	STMR (mg/kg)	**Highest Residue (mg/kg)**
Wheat grain	42	0.01	**0.04**
Wheat straw (DW)	42	1.8	**6.9**
Wheat forage	28	1.6	**12.8**
Aspirated grain fraction		0.7	**2.8**
Gluten feed meal		0.03	**0.11**

Animal Transfer Assessment: Data Evaluation

Metabolism Studies

- Goats: dosed with C^{14} labelled compound for 7 consecutive days at 30 mg/kg (2kg feed/animal/day); milk was collected twice daily, and tissues were collected approximately 12 hours after the final dose.
- Hens: dosed with C^{14} labelled compound for 14 consecutive days at 12mg/kg in feed; eggs were collected daily, and tissues were collected approximately 12 hours after the final dose. Yolks and whites were analysed separately.

➢ **Residues are fat soluble; tissues of concern were liver (goat) and skin + fat (hen); parent compound suitable for animal commodity residue definition**

Animal Transfer Assessment: Data Evaluation

Feeding Studies

- Residues evaluated in lactating cattle after feeding at 3.5 mg/kg, 16.4 mg/kg, and 32.5 mg/kg for 28 days. Milk was collected twice daily through the trial period, and animal tissues were collected 22-24 hours after the final dose.
- Milk analysed as whole milk, skimmed milk, and cream to evaluation partitioning
- Hen feeding studies NOT conducted

Animal Transfer Assessment: Dietary Burden

- Dietary burden calculated using OECD guidelines: calculates burden based on STMR and HR plant residues and animal consumption of specified commodities
    - Extrapolated from Australian data set as the closest approximation to NZ, with amendments

❖ MPI project underway to gather New Zealand consumption data in FP animals as per the OECD guidelines – expect this to be completed in 2-3 years with the aim to submit data to OECD

Animal Transfer Assessment: Dietary Burden

Wheat Forage:

STMR = 1.6 mg/kg, HR = 12.8 mg/kg

								OECD FEEDSTUFFS DERIV		
								CATTLE		
								BEEF		
								US	EU	AU
CROP	FEEDSTUFF	Highest residue	STMR or STMR-P	Residue Level	DM (%)	Maximum residue in mg/kg DM	Mean residue in mg/kg DM	CAN		
Sugarcane	tops			HR	25	0.0	0.0	*	*	50
Trefoil	forage			HR	30	0.0	0.0	*	20	100
Trefoil	hay			HR	85	0.0	0.0	15	20	90
Triticale	forage			HR	30	0.0	0.0	*	20	100
Triticale	hay			HR	88	0.0	0.0	15	20	100
Triticale	straw			HR	90	0.0	0.0	10	20	50
Triticale	silage			HR	35	0.0	0.0	*	*	90
Turnip	tops (leaves)			HR	30	0.0	0.0	*	40	80
Vetch	forage			HR	30	0.0	0.0	*	25	90
Vetch	hay			HR	85	0.0	0.0	15	25	90
Vetch	silage			HR	30	0.0	0.0	*	*	90
Wheat	forage	12.8	1.6	HR	25	51.2	6.4	*	20	100
Wheat	hay			HR	88	0.0	0.0	15	20	100

Animal Transfer Assessment: Dietary Burden

ESTIMATED MEAN DIETARY BURDEN													
BEEF CATTLE													MEAN
Commodity	CC	Residue (mg/kg)	Basis	DM (%)	Residue dw (mg/kg)	Diet content (%)				Residue Contribution (ppm)			
						US-CAN	EU	AU	JP	US-CAN	EU	AU	JP
Wheat forage	AF/AS	1.6	STMR/STMR-P	25	6.40		20	100			1.28	6.4	
Wheat asp gr fn	CM	0.7	STMR/	85	0.82	5				0.041176			
Wheat gluten meal	CM	0.03	STMR/	40	0.08	5	15			0.00375	0.0113		
Wheat grain	GC	0.01	STMR/	89	0.01	20	40		25	0.002247	0.0045		0.0028
Total						30	75	100	25	0.047174	1.2957	6.4	0.0028

Animal Transfer Assessment: Dietary Burden

Class	Mean Burden	Maximum Burden
Dairy Cattle	3.84 mg/kg	30.72 mg/kg
Beef Cattle	**6.4 mg/kg**	51.2 mg/kg

- These values assume 100% beef cattle dietary consumption and 60% dairy cattle consumption for wheat forage, well above NZ farm use
- Choice of estimate to use based on expected NZ consumption - generally use high estimate for pasture/crop in cattle and for grain in pig/poultry
    - Mean beef cattle values still high estimate for NZ farm use in this case
- **Correct crop GAP is critical for this – entire estimate hinges on expected crop residues being correct, and estimate dictates MRLs**

Animal Transfer Assessment: Residues

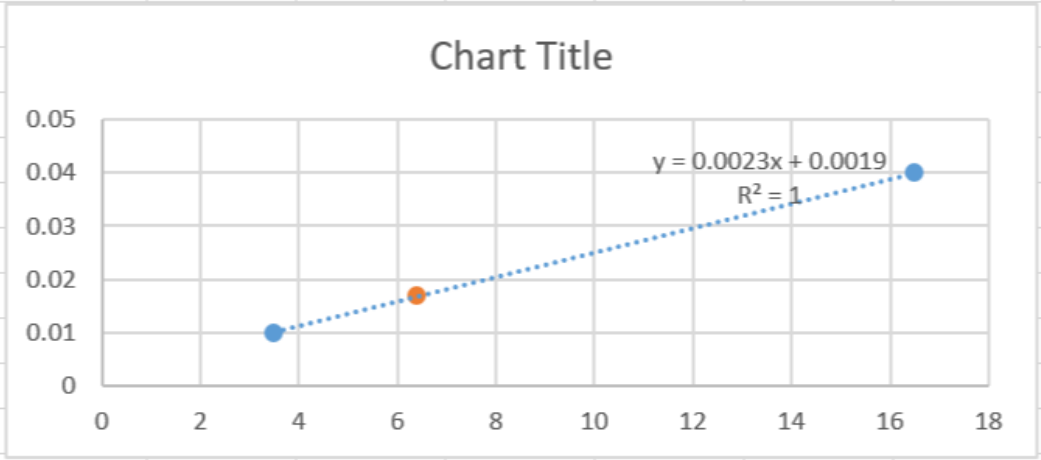
- Dietary burden estimate is 6.4 mg/kg

	3.5 mg/kg	6.4 mg/kg	16.5 mg/kg
Fat	<0.01		0.01
Kidney	<0.01		0.01
Liver	<0.01		0.04
Meat	<0.01		<0.01
Whole Milk	<0.01		<0.01
Skimmed Milk	<0.01		<0.01
Cream	<0.01		0.01

Animal Transfer Assessment: Residues

- Dietary burden estimate is 6.4 mg/kg

Dose	Liver	
3.5	0.01	
16.5	0.04	0.001923077
6.4	0.017	
Intercept	0.001923	
Slope	0.002308	Interpolated residue
Regression	0.017	
		From y=mx+b



Animal Transfer Assessment: Residues

Estimated residues in animal commodities when compound is used according to NZ GAP and WHPs are followed (as proposed):

	3.5 mg/kg	6.4 mg/kg	16.5 mg/kg
Fat	<0.01	**0.01**	0.01
Kidney	<0.01	**0.01**	0.01
Liver	<0.01	**0.02**	0.04
Meat	<0.01	**0.01**	<0.01
Whole Milk	<0.01	**0.01**	<0.01
Skimmed Milk	<0.01		<0.01
Cream	<0.01		0.01

Animal Transfer Assessment: Residues

But what about the hens?

- No feeding studies conducted in hens, but we do have metabolism data to evaluate
- Metabolism data can sometimes be used as an indicator
    - Feeding a minimum daily dose of 16.3 mg/kg, yolk residues remained at <0.02 mg/kg throughout the trial; tissue residues in in muscle and liver were <0.001 mg/kg
    - Poultry dietary burden data limited, but highest estimate is 1.4 mg/kg

➢ Estimated burden << dose used in metabolism study; Limited export risk

Animal Transfer Assessment: Trade Analysis

- First consideration is alignment as much as possible, especially with Codex
    - Codex have mammalian and poultry MRLs for offal at 0.01 mg/kg, but no wheat MRL (only soya bean)
    - EU, Canada, and the US all have wheat MRLs and animal commodity MRLs
    - Liver commonly set at 0.03 mg/kg or higher, other commodities generally 0.01 mg/kg
    - It's possible that the JMPR assessment may not have considered wheat as a commodity, and the impact it would have on animal transfer
- **Best way to support NZ GAP and trade is 0.02 mg/kg in liver, 0.01 mg/kg in all other animal commodities including poultry commodities and eggs**

Orchard Grazing and Leaf Plucking

- Overall animal transfer assessment process similar to standard assessment: evaluation of plant residues, evaluation of animal studies, dietary burden assessment, and trade analysis
- **GAP must be correct –** these analyses even more sensitive to GAP as exposure profile is often more significant
    - longer period of exposure confined to treated orchard/vineyard
    - Inter-row grass grazing and leaf plucking will be happening simultaneously
    - Grazing/plucking is 100% of that animal's diet
- Clean feed intervals/animal WHPs often need to be applied

Tissue Residues Assessment and WHP Determination for Veterinary Medicines

Residue Data Assessment

Overall review of data

- Formulation matches that being registered
- Product use matches worst-case GAP use pattern established in efficacy and safety trials
- Animal numbers and classes representative of field use and statistically sound
- All actives analysed
- MRLs and residue definitions are appropriate for the compound and species
- Trial technical information is reported and appropriate – analytical methods, sample storage, LOD/LOQ, validation

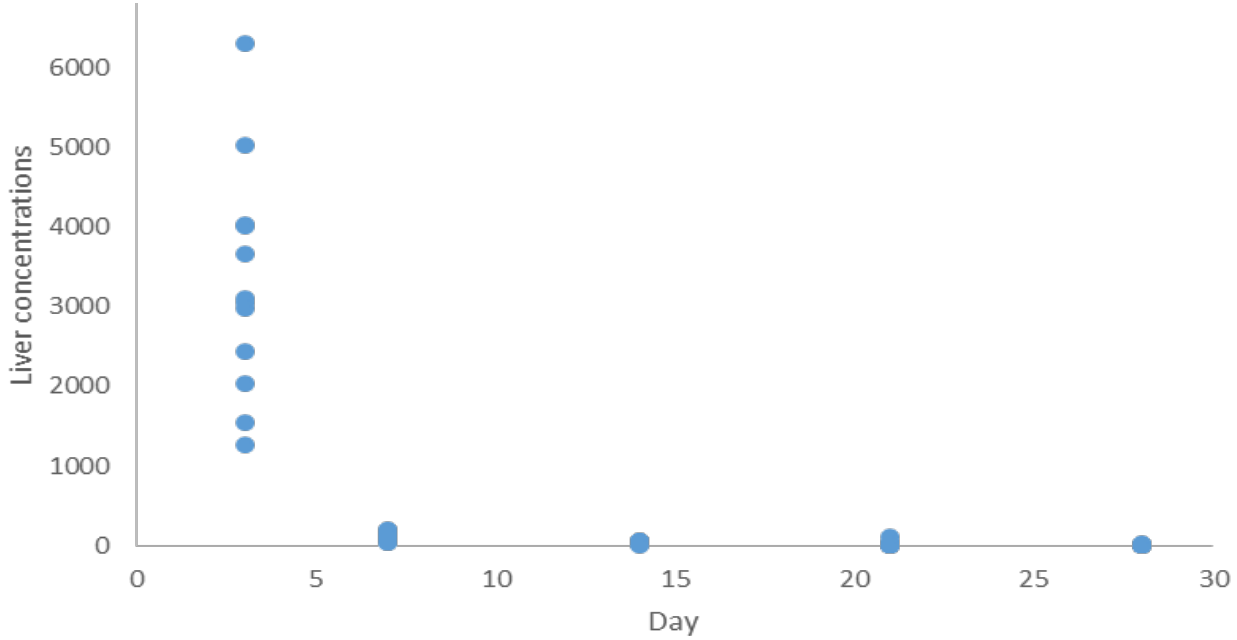
Tissue Residue Data: Corrected Data

Liver Residue Concentrations (ug/kg) - Adjusted

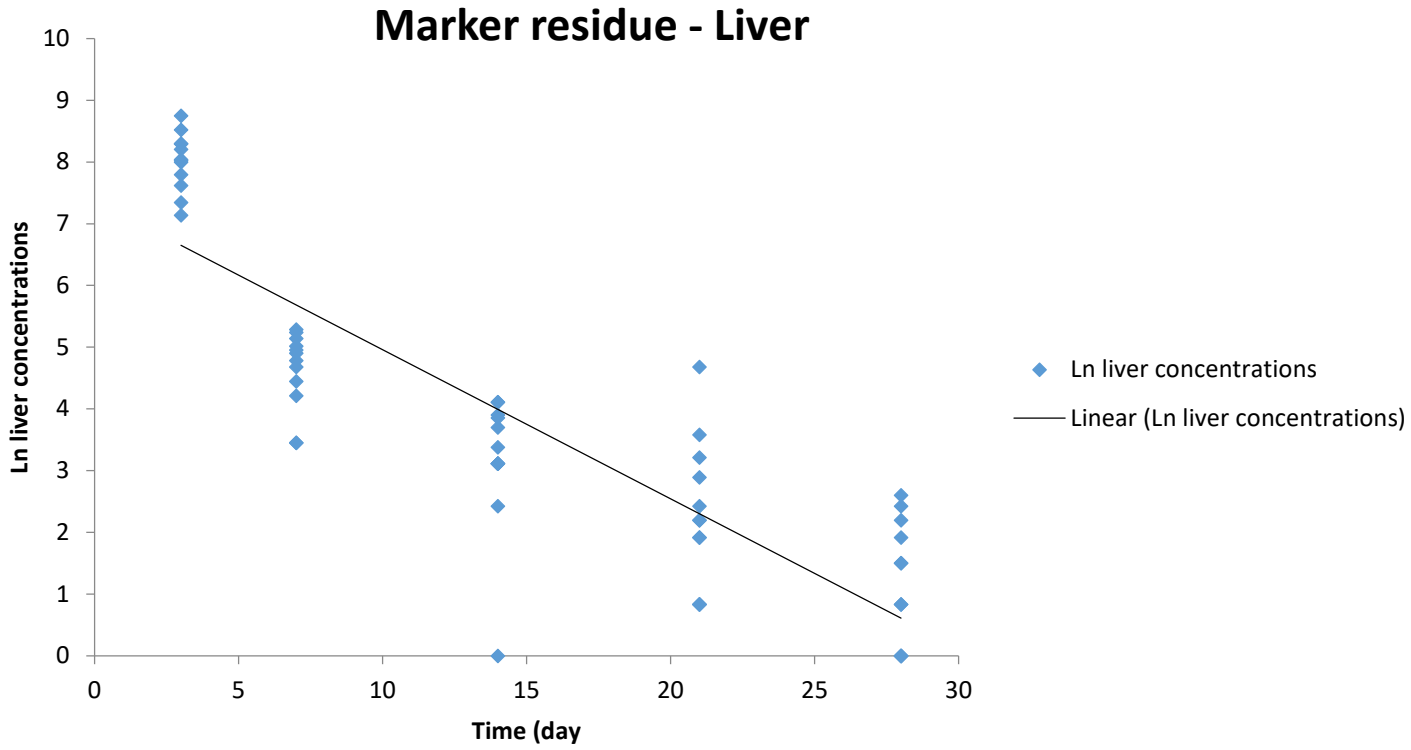
Day	3	7	14	21	28
	2040	85.5	1	36	4.5
	5031	141.8	22.5	9	2.3
	3048	198	60.8	9	11.3
	4031	31.5	60.8	6.8	9
	6301	119.3	47.3	18	1
	2431	108	22.5	6.8	4.5
	3100	171	11.3	108	1
	4010	31.5	22.5	11.3	1
	2983	189	49.5	2.3	2.3
	1256	67.5	22.5	2.3	6.8
	1547	135	40.5	24.8	13.5
	3654	150.8	29.3	2.3	1

values < LOD set at 1/2 LOD = 1ug/kg

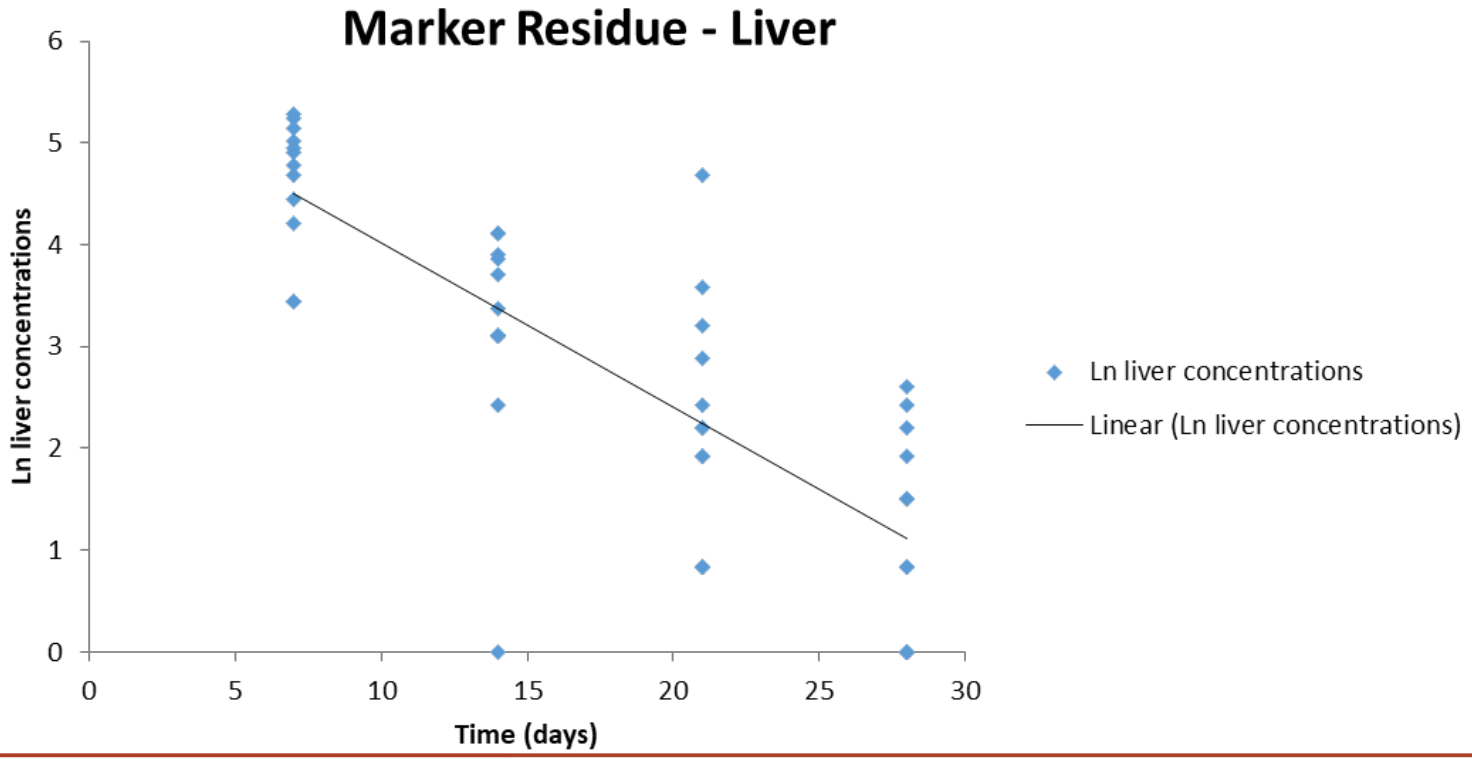
Tissue Residue Data: Corrected Data vs Time



Tissue Residue Data: Linearity vs Time



Tissue Residue Data: Linearity vs Time V2

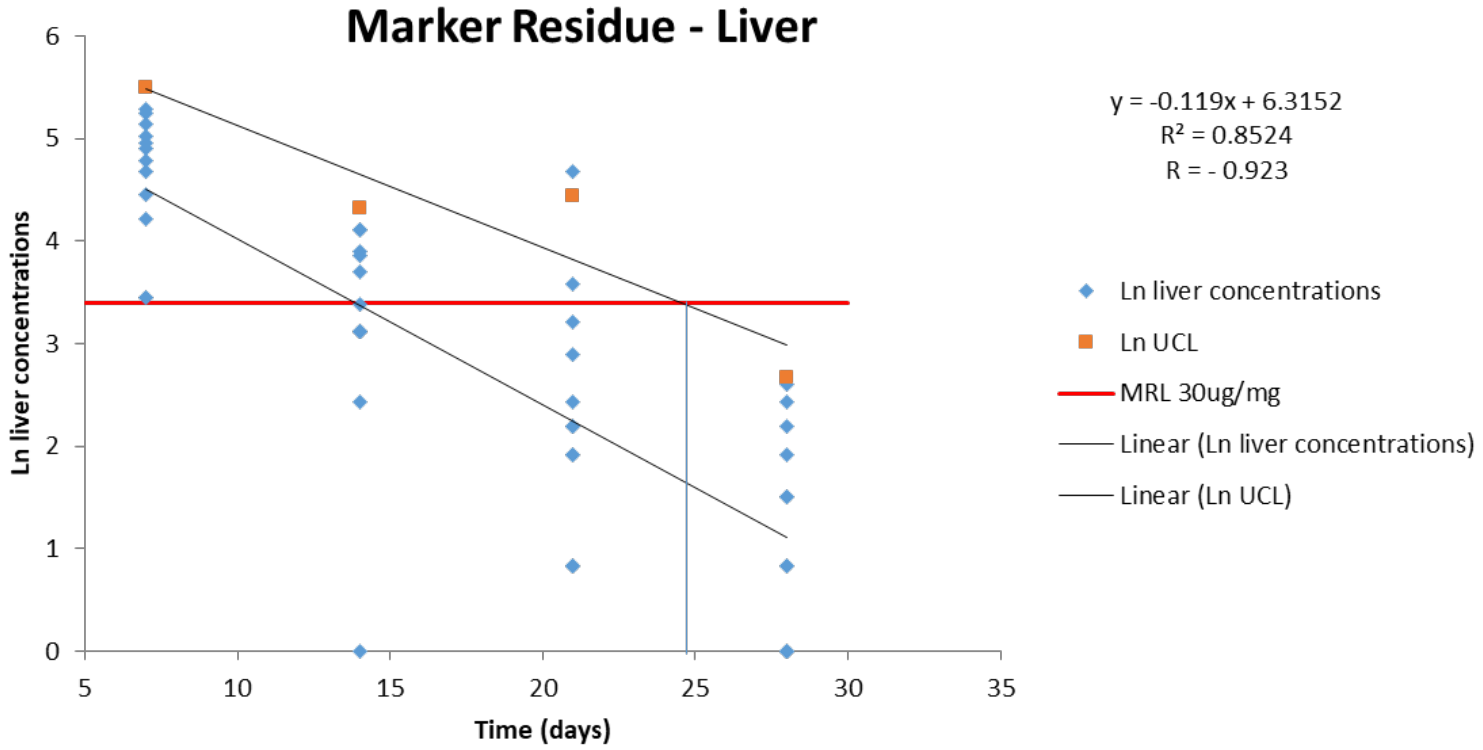


Tissue Residue Data: Analysis and Reduction

Liver Residue Concentrations (ug/kg) - Adjusted

Day	7	14	21	28
	85.5	1	36	4.5
	141.8	22.5	9	2.3
	198	60.8	9	11.3
	31.5	60.8	6.8	9
	119.3	47.3	18	1
	108	22.5	6.8	4.5
	171	11.3	108	1
	31.5	22.5	11.3	1
	189	49.5	2.3	2.3
	67.5	22.5	2.3	6.8
	135	40.5	24.8	13.5
	150.8	29.3	2.3	1
Mean	119.1	32.5	19.7	4.9
SD	56.3	19.1	29.6	4.4
UCL	243.45	74.82	85.11	14.51
Ln UCL	5.49	4.32	4.44	2.67

Tissue Residue Data: WHP calculation



Assigning Meat Withholding Periods

Calculated WHP = 24.5 days *[22.2 days without outliers]*

- ACVM Standard dictates that WHPs beyond 14 days are applied at weekly intervals → **Assigned WHP = 28 days**
    - Built-in conservatism using UCL and weekly interval rule to account for outliers and individual animal variation
    - Room to adjust if there would be benefit in managing risks, managing on-farm production, or if outliers a significant factor → considered case by case
- If SC injectable, data from IM injection required – ISRs must be <10x MRL; if not, included in meat WHP calculations +/- accidental IM injection statement

Milk Residues Assessment and WHP Determination for Veterinary Medicines

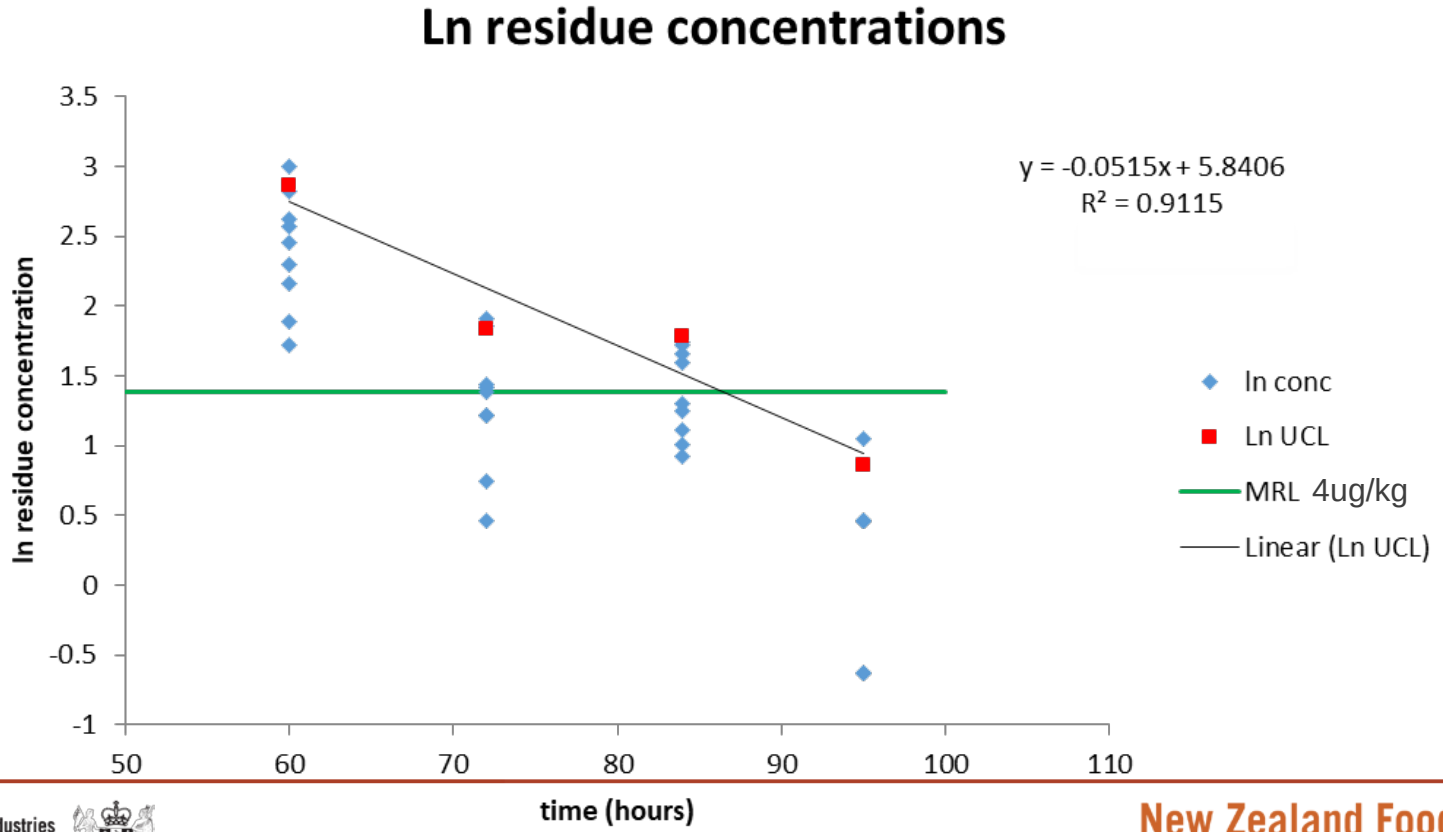
Milk Residues Assessment

- General methodology, requirements, and data analysis the same as for tissue residue data, **except**
    - Time points are usually 12-hourly to match standard twice-daily milking
    - Both residue analysis and milk volume yield must be reported for each cow and time point
    - A weighted mean and weighted SD is calculated for each time point to standardise results
    - Weighted means and SDs are used to calculate UCL as per tissue residue assessment (same linearity considerations apply)

Milk Residues Assessment

cow	60h	72h	84h	95h
10	20.00	3.37	5.58	0.53
91	8.63	3.37	5.68	1.58
124	5.58	4.00	2.74	1.58
125	9.89	4.11	3.47	0.53
153	6.63	6.74	5.26	0.53
155	11.68	4.21	2.53	1.58
157	16.84	6.42	4.95	2.84
165	13.05	2.11	3.68	1.58
208	13.79	1.58	3.05	1.58
weighted mean	11.22	3.99	4.16	1.35
weighted SD	4.50	1.66	1.29	0.74
g (n= 9)	4.143	4.143	4.143	4.143
UCL	17.43	6.29	5.94	2.37
Ln UCL	2.86	1.84	1.78	0.86

Milk Residues Assessment



Assigning Milk Withholding Periods

Calculated WHP = 86.5 hours

- ACVM Standard dictates that WHPs are set at 12-hourly intervals → **Assigned WHP = 96 hours or 8 milkings**
    - Built-in conservatism using UCL and weekly interval rule to account for outliers and individual animal variation
- Registrants can also request WHPs for once-daily milking, **with data**
    - It isn't always a direct correlation due to the milk volume and clearance variables → twice daily for 8 milkings isn't always = to once-daily for 4 milkings

MRL Promulgation

Maximum Residue Levels

- Maximum Residue Levels (MRLs) are set under the Food Act 2014 as a Notice
- Criteria for setting MRLs is established in the Food Regulations 2015
- MRL Notice
    - MRLs for registered agricultural compounds are set in Schedule 1
    - Exemptions from MRLs are set in Schedules 2 and 3
    - Where no MRL exists, default of 0.1mg/kg applies

Maximum Residue Levels

Situations where a new or amended MRL is required:

- New compound, used on any food-producing animal or crop
- Known compound with a new target species or crop
- Change in GAP (e.g. dose/rate, timing)
- A change to the dietary intake profile

- Plants: Treated crops (grains, fruits, vegetables, other edible commodities)
- Animals: Treated with VMs or exposed to ACs (meat, fat, kidney, liver, milk)
- Residues need to be managed for other compounds: former ag compounds, VTAs

MRL Assessment

Three stages to determining a MRL

1. Establish good agricultural practice (GAP) for the compound

2. Determine whether the residues from use according to GAP are likely to cause any human health risks: Dietary exposure risk assessment

3. Trade considerations

MRL Assessment

1. Establish good agricultural practice (GAP) for the compound

- Done during registration/variation assessment
    - Efficacy and safety data to determine dose rates and treatment intervals to achieve desired effect
    - Residue data to find the point where residues are at their lowest but the compound is still achieving effect

MRL Assessment

2. Determine whether the residues from use according to GAP are unlikely to any human health risks: Dietary exposure risk assessment

- National Estimated Daily Intake (NEDI) = uses all authorised uses for the compound and mean food consumption data to estimate exposure
- NEDI value compared to established Health Based Guidance Value (HBGV)
    - Potential Daily Exposure$_{(food)}$ (PDE$_{(food)}$) set by the EPA
    - Internationally established Acceptable Daily Intake (ADI)
    - MPI-determined ADI
- MRL is acceptable if compliance means NEDI is less than or equal to 100% HBGV

MRL Assessment

3. Trade considerations

- International MRLs reviewed to ensure MRLs based on NZ GAP can facilitate trade
    - **Veterinary Medicines:** Codex, Australia, Canada, China, the EU, Japan, and the US
    - **Agricultural Chemicals:** Codex and Australia
    - **Both:** Other regions considered as required
- More significant for animal commodities due to MPI official assurances
- Try to align MRLs where possible while still supporting New Zealand GAP, especially for Codex

New Zealand Food Safety
Haumaru Kai Aotearoa

MRL Assessment Process

MRL promulgation request received

- Usually through ACVM registration or variation applications
- Can also be received as a stand-alone MRL request (e.g. for import MRLs)

GAP determined and residues assessed

- Good Agricultural Practice (GAP) established by efficacy and safety data relevant to NZ use pattern, target crop/species & conditions, and residue data establishing NZ WHP(s)
- MRLs based on NZ GAP at the WHP:
  - **Plants:** food from treated crops
  - **Animals:** meat, fat, liver, kidney, milk, and eggs in treated animals (for Vet Meds, and for Ag Chemicals when treated crops are used as animal feed)

Dietary intake estimate calculated

- The National Estimated Daily Intake (NEDI) is calculated using MRLs from all VM and AC approved uses and NZ mean food consumption data
- NEDI then compared to the established Health Based Guidance Value (HBGV)
- MRLs are acceptable if NEDI from all uses is less than or equal to 100% of the HBGV

Trade risk assessment conducted

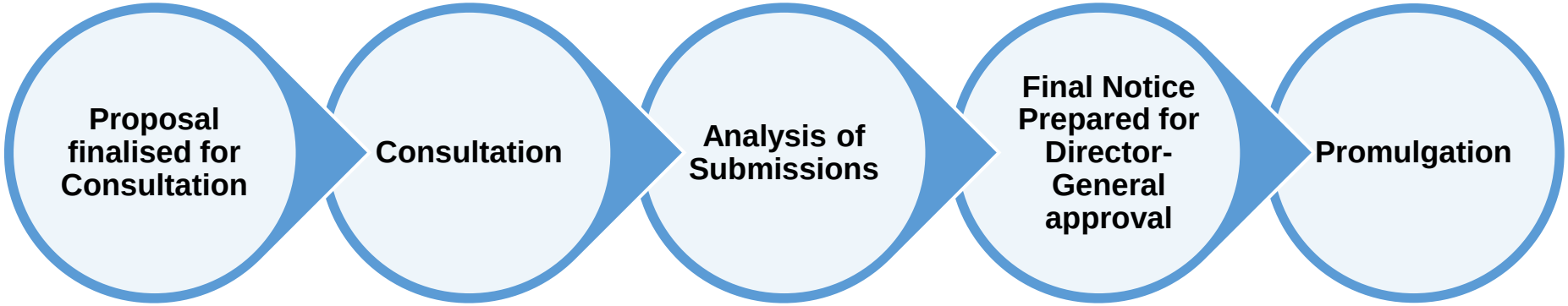
- International MRLs reviewed to ensure MRLs can facilitate trade
- **Ag Chemicals:** Codex and Australia
- **Vet Medicines:** Codex, Australia, Canada, China, the EU, Japan, and the US
- **Both:** Other regions considered as needed
- MRLs are set to align where possible while still supporting NZ GAP, especially with Codex

Proposed MRLs reviewed, all risks managed → **Final MRLs proposed in the next round**

Proposed MRLs reviewed, trade or dietary intake risks remain → **Reassess GAP and adjust as needed**

Proposed MRLs reviewed, risks remain and GAP adjustment not possible → **No MRLs Set, product or new use cannot be approved**

MRL Notice Amendment Process



- Director review before release
- Minister for Food Safety notified of consultation

- Domestic Consultation via website
- International Consultation via WTO notification
- 60 Working Days

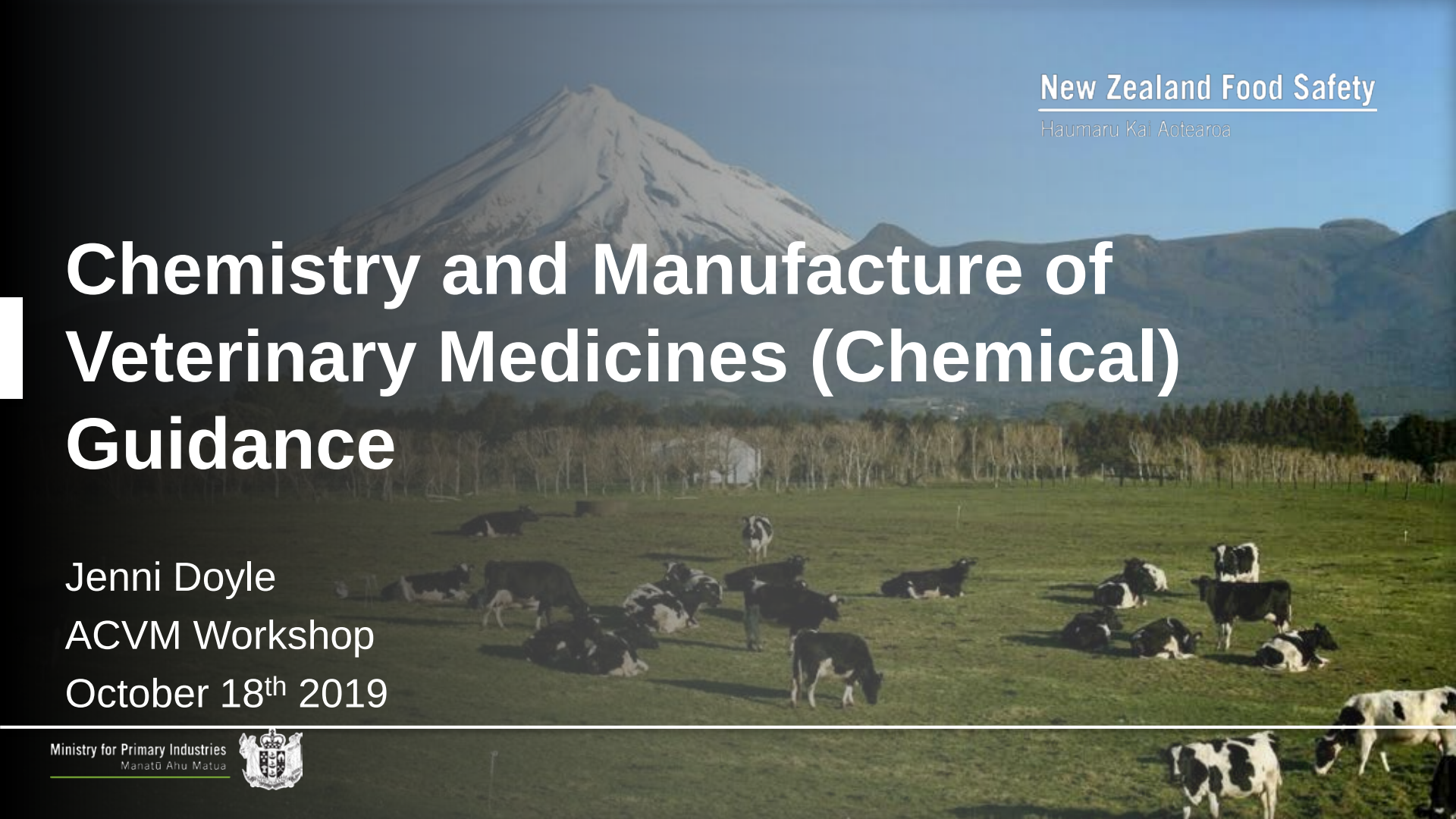
- Reviewed with further consultation as needed
- International submissions involve MPI Market Access

- Submission responses drafted and reviewed
- Finalisation of amended Notice, summary of submissions, and recommendation to approve drafted for D-G

- MRLs come into force at date on Notice
- Minister notified of promulgation
- Revised Notice tabled in Parliament and Gazetted
- Information collection and data review starts for the next MRL round

Usually 4-6 months

Thank you!



New Zealand Food Safety
Haumaru Kai Aotearoa

Chemistry and Manufacture of Veterinary Medicines (Chemical) Guidance

Jenni Doyle

ACVM Workshop

October 18th 2019

Ministry for Primary Industries
Manatū Ahu Matua

Chemistry and Manufacture of Veterinary Medicines (Chemical) Guidance

- Key changes in the revised Guidance
- Standard vs. Guidance
- Impact of changes on Data Assessment

Key Changes in the Revised Guidance

Key Changes in the Revised Guidance

- **The new Guidance document is a complete overhaul compared to the current Standard – changes in all sections including appendices**
    - More detailed guidance and updates on expectations relating to:
        - Active and excipient ingredient management
        - Manufacturing information including process validation
        - Product packaging
        - Stability studies, including in-use stability

Key Changes in the Revised Guidance

- **The new Guidance document is a complete overhaul compared to the current Standard – changes in all sections including appendices**
    - New guidance on expectations relating to variations and self-assessable changes
    - New Appendices for product types, release and expiry specifications, a checklist for new product submissions
    - New Appendix for guidance on recognised evidence of GMP certification (TBC)

Key Changes in the Revised Guidance

- **The shift from a Standard to a guidance document also means more flexibility in terms of meeting requirements**
    - Previously, Standards set the mandatory requirements, and guidelines advised how to meet the standard
    - Going forward, the only information requirement will be the ***ACVM Requirement: Registration Information Requirements*** → describing product identity, performing risk analysis, and product documentation
        - All other documents are guidelines on how to meet that requirement, making all content best practice expectations rather than mandatory information requirements

Current Chemistry and Manufacturing Standard vs. The New Guidance Document

Current Standard vs. New Guidance

Standard	Guidance
1 Introduction	**1 Purpose; 2 Background; 3 Definitions and Abbreviations; 4 Information Needed; 5 Additional Guidelines**

- 'Definitions and Abbreviations' updated and significantly expanded to include 36 new definitions
- 'Information Needed' added to provide general advice on deviations, technical discussions, and consultants
- Reference list revised to 'Additional Guidelines' and updated to include all applicable VICH guidelines and other overseas guidance

Current Standard vs. New Guidance

Standard	Guidance
	6 Registration of a new Trade Name Product
2 Formulation and Ingredient Requirements	**6.1 Product type, formulation type, and description** **6.2 Formulation of the Product** **6.3 Active ingredients** **6.4 Excipient Ingredients**

- Four distinct sections created to provide more detail on product and formulation presentation, active ingredient requirements, and excipient ingredient requirements

Current Standard vs. New Guidance

6.1 Product type, formulation type and description

- Provision of pharmaceutical development information for the product to help characterise the formulation and manufacturing controls → the "why" of the product details

6.2 Formulation of the product

- One distinct and fixed formulation per TNP (deviations considered case by case)
- Stability related overages (section 6.2.2) and manufacturing related overages (section 6.5.4) and their associated risks managed separately

Current Standard vs. New Guidance

6.3 Active Ingredients

- Introduction of JP as an MPI-recognised pharmacopoeia, provision for use of third-country pharmacopoeial monographs with additional information
- Introduction of the functional active ingredient category, to manage ingredients that are not therapeutic actives but are not excipients

6.4 Excipient Ingredients

- Introduction of the critical excipient category, to manage those excipients that are true excipients but have a direct impact on the product's risk profile
    - Example: penetrants for pour-on products

Current Standard vs. New Guidance

Standard	Guidance
	6.5 Formulated Product Manufacturing
3.1 Manufacture of the trade name product	6.5.1 Manufacturer identity and GMP
3.2 Manufacturing process	6.5.2 Manufacturing Information
3.3 Identification and management of critical manufacturing control points	6.5.3 Manufacturing process
3.4 Quality control	6.5.4 Manufacturing related overages
	6.5.5 In-process quality control testing
	6.5.6 Manufacturing process validation

Current Standard vs. New Guidance

6.5.1 Manufacturer identity and GMP

- Introduction of guidance on GMP approvals and evidence of GMP
- Clarification around repacker/relabeller and release for market entities, and the activities they are approved to undertake

6.5.2 Manufacturing information

- Manufacturing batch formulas and final product formulations will now be separate information, to assess their individually unique risks
    - The batch formula table will be incorporated in the upcoming revised PDS

Current Standard vs. New Guidance

6.5.3 Manufacturing process

- More detail around what is expected for the recording and approval of manufacturing processes

6.5.4 Manufacturing related overages

- As per notes on the stability related overages, the two types will be managed separately going forward

6.5.5 In process quality control testing

- More detail about what qualifies as in-process quality control testing, and what information to provide

Current Standard vs. New Guidance

6.5.6 Manufacturing process validation

- Detailed guidance on process validation, and how to present it
  - What should be validated
  - When only a validation protocol is acceptable, and what it should contain
  - What should be included in a validation report
  - Sterilisation process validation

Current Standard vs. New Guidance

Standard	Guidance
4 Specifications	**6.6 Finished product specification** **6.7 Formulated product batch analyses** **6.8 Product packaging**

- More consistent application of the term “specification” to refer to the full set of testing parameters and results
- Introduction of an expectation for providing specification rationales, and what should be included in that rationale discussion
- More detail around packaging information expectations

Current Standard vs. New Guidance

6.6 Finished product specifications

- Expectations around specification parameter/value rationales (6.6.1), more detail around what is expected in formulated product release (6.6.2) and expiry (6.6.3) specifications, and method validation, and expectations around specifications for functional AIs (6.6.4)

6.7 Formulated product batch analyses

- Specified expectations for formulated product batch analysis and reporting

6.8 Product packaging

- More detailed expectations for product packaging information, including packaging materials and closure systems

Current Standard vs. New Guidance

Standard	Guidance
5 Stability testing of the finished product	**6.9 Shelf life stability** **6.10 In-use stability**

- More detailed guidance around how to propose and support a shelf life, including batch selection and trial expectations
- Introduction of the concepts of shelf life extrapolation and establishing an interim shelf life
- Expectation of a commitment to an ongoing stability programme
- Detailed information regarding the expectations around in-use stability trial work, including in-feed and in-water products

Guidance Section 7: Variations

Guidance
7.1 Changes to approved formulation details
7.2 Changes to approved active ingredient manufacturers
7.3 Changes to approved active ingredients and functional active ingredients
7.4 Changes to approved excipient ingredients
7.5 Changes to approved formulated product manufacturers
7.6 Changes to the manufacturing process and quality control
7.7 Changes to the finished product specifications or test methods
7.8 Changes to product packaging
7.9 Changes to formulated product shelf life and storage conditions

Guidance Section 7: Variation Guidance

- **Detailed guidance on Variation Applications**
  - ➢ Covers C1-C3 “standard” variation types
    - C10 (Reassessment) and C12 (conditions change) are case by case and not strictly related to chemistry and manufacturing so not covered
  - ➢ When a change requires notification, administrative change, technical variation, or a new registration
  - ➢ What documents, information, and data are required for each type of variation
  - ➢ Where in the guidance more information can be found, or other guidance (e.g. VICH) that may be referenced, where applicable

Guidance Section 7: Self-Assessable Changes

- **Introduction of self-assessable changes**
  - Case-by-case guidance of when self-assessable changes can apply, and how to manage them
  - Overall, they are actioned based on the registrant's risk assessment and the product information is updated at the next variation or registration renewal
  - Allowable changes in certain circumstances: removal of a manufacturer, removal of a testing site, tightening of specification parameters and batch sizes within the approved range, some other changes to pharmacopoeial standards and specifications, adding pack sizes within an approved range, and shortening of a shelf life

Appendices

Standard	Guidance
Appendix: Declaration for stability exemptions	Appendix 1: Product Types
Annex 1: Definition of formulation types	Appendix 2: Formulation Types
Annex 2: Veterinary medicine ingredient specifications for cited chemicals	Appendix 3: Expected release and expiry specifications by product and formulation type
Annex 3: Shelf life exemptions for veterinary medicines	Appendix 4: Checklist for new product submissions
Annex 4: Recommended chemical and physical parameters for stability studies based on dosage form	Appendix 5: Evidence of GMP certification recognised [working title]

Appendices

- **Appendix 1: Product types**
  - Provides the MPI definitions for the different product types as requested in the PDS
  - Includes the newly agreed definitions for antibiotic, antifungal, antimicrobial, antiprotozoal, antiseptic, and antiviral
- **Appendix 2: Formulation Types**
  - Updated and expanded from Annex 1 in the current Standard
- **Appendix 3: Expected release and expiry specifications by product and formulation type**
  - Updated from Annex 4 in the Standard, and expanded to include more detailed release and expiry information

Appendices

- **Appendix 4: Checklist for new product submissions**
  - Provides a one-page summary of the different sections for quick reference when compiling submissions

- **Appendix 5: Evidence of GMP certification recognised [working title]**
  - When finished, this Appendix will provide more detailed guidance regarding international GMP certificates, submission expectations, and other GMP-related information

Appendices

NOT carried over from the Standard to the new Guidance:

- Appendix: Declaration for stability exemptions
  - This would be managed through a deviation request and is redundant
- Annex 3: Shelf life exemptions for veterinary medicines
  - This would also be managed through a deviation request, so standardised exemptions no longer considered necessary or appropriate

Impact of the Changes on Chemistry and Manufacturing Data Assessments

Expectations of Data Assessment

Overall

- Greater focus on the “why” – make sure that all information is provided with rationales and justifications where needed
- The shift from Standard to guidance allows for more flexibility but it means Data Assessment then becomes more important to application assessments
  - Make sure you are evaluating what is presented and whether or not it meets the guidance, and identifying what doesn’t align with guidance or is absent
  - If information deviates from the guidance or something is missing, don’t justify the deviation/absence for the registrant

Expectations of Data Assessment

Describing and Characterising the Product: Sections 6.1 and 6.2

- Pharmaceutical development information is sufficient to allow assessment of the formulation and manufacturing controls
- The formulation is thoroughly characterised, and:
  - The product has one distinct and fixed formulation, or has justified their deviation
  - All ingredients are identified appropriately and their role in the formulation has been described
  - Stability related overages have been identified and justified

Expectations of Data Assessment

Ingredients Management: Sections 6.3 and 6.4

- Monographs are from a MPI-recognised pharmacopoeia, or sufficient detail provided for third-country pharmacopoeia or MS (including copies of monographs)
- Sufficient information provided for therapeutic active ingredients, functional active ingredients, critical excipients, and standard excipients according to their requirements and risk profile – case-by-case depending on the product, registrant needs to make their function and risk clear
- Sufficient and appropriate information provided on manufacturers including intermediate manufacturers

Expectations of Data Assessment

Formulated Product Manufacturers and Process: Section 6.5

- Manufacturers have the appropriate approval(s), and are performing functions allowed for in their approval – note sites solely approved for repacking/relabelling must not breach primary packaging
- The batch formula and manufacturing process information includes:
    - all critical points, including in-process quality control tests, with adequate detail an supporting information, and
    - Identification and justification for manufacturing overages
- Process validation information (and/or validation protocol) is complete and sufficiently detailed to allow assessment

Expectations of Data Assessment

Specifications and Packaging: Sections 6.6, 6.7, and 6.8

- Finished product specifications (release and expiry) meet expectations for that product and formulation type, and parameters and acceptable values/ranges are described and justified
- Formulated product batch analyses are of an appropriate size and at least representative of production scale manufacture, and submitted with sufficient information to evaluate them
- Product packaging information is complete and adequately detailed to allow the risks associated with the materials and closure systems relative to the formulated product to be evaluated

Expectations of Data Assessment

Unbroached Stability and In-Use Stability: Sections 6.9 and 6.10

- The stability data provided meets expectations in terms of testing and batch size/number, and can sufficiently support the proposed shelf life
- In-use stability data, information, or deviation discussion is provided for all multi-use containers **– not just sterile products!**
- In-feed stability data characterises mixing and transport in an appropriate representative feed or feeds, over an appropriate period of time
- In-water stability adequately characterises mixing, and appropriate label instructions are present (solution vs. suspension)

Expectations of Data Assessment

Section 7: Variations

- Data assessment likely to be limited to significant formulation changes, significant changes to manufacturing, or captured as part of other variations to the product
- Key factor for data assessment is to ensure that the information provided adequately characterises the change to the risk profile compared to what was originally evaluated and approved for the product
    - may need to consider efficacy, safety, and residue risk profiles too
- When in doubt, refer back to Section 7 and/or what would be required if this was a new product as a starting point

Thank you!

Ministry for Primary Industries
Manatū Ahu Matua

Equivalence of Veterinary Medicines

October 2019

www.mpi.govt.nz

Why generate equivalence data?

- Support efficacy of generic registrations.
- Support variation registrations
  - Cross reference data held by ACVM for nominated reference product.

Methods to establish equivalence

1. Chemical equivalence
2. Pharmaceutical equivalence
3. Biological equivalence

Important definitions

Therapeutic equivalence:

- two TNPs are pharmaceutically equivalent; and
- after administration of the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined by appropriate *in vivo* bioequivalence or *in vitro* studies

Important definitions

Biological equivalence:

- two veterinary medicine TNPs are bioequivalent when the rate and extent of absorption of the same molar dose of the active ingredient(s) or therapeutic moiety as determined by comparison of measured parameters (e.g. active concentration in blood or pharmacological effect) is demonstrated to be similar (within predefined acceptable limits), when administered under similar experimental conditions

Important definitions

Pharmaceutical equivalence:

- two TNPs contain the same active ingredient(s) manufactured to meet the same or comparable compendial standards; and
- same dosage form; and
- administered via the same route; and
- and are identical in active concentration or strength

Important definitions

Similar Products:

- trade name products that contain the same API(s) at the same concentration, and
- have the same formulation type; and
- are administered in the same dosage form and dose rate to the same target animal for the same clinical indications.

The non-active ingredients in the test formulation are likely to have similar properties and be present in similar proportions as the reference product

Important definitions

Closely Similar Products:

– **Similar** trade name products that:

- contain the same or equivalent non-active ingredients at the same or equivalent concentrations or,
- *if* non-active ingredients are not the same or equivalent, differences are minor and will not affect product quality or biological activity,
- *and* the product specifications and physicochemical properties are the same or equivalent or, if different, will not adversely affect product quality or biological activity

Methods to establish equivalence - 2

PHARMACEUTICAL EQUIVALENCE

- Most relevant when the bioavailability of the API is minimally dependant on the dosage form
- *Or* moderately formulation-dependant dosage forms when there is an *in vitro: in vivo* correlation.

- Must identify differences between products where possible (formulation, manufacturing, specifications, PC properties) and provide data/argument to confirm any differences observed will be clinically insignificant.

Reference Product

- ‘Similar’ product registered by MPI
- Innovator registration
  - First generic registration if innovator not available
  - BUT IN ALL CASES SHOULD have history of safe and effective field use in NZ.
  - Use in published clinical trials with confirmed efficacy for clinical indications sought is a good basis for use.

PE – When it may apply

1. Reformulated generics
2. Simple aqueous solution (when administered)
   - IV, IM, SC, oral, dermal, ophthalmic or aural route
3. Aqueous IV solution
4. Solution – IM or SC injection or Systemically acting topical
5. Aqueous oral solution (at administration)
6. Medicated premix containing a soluble API
   - Acts as aqueous solution *in vivo*

PE – When it may apply

6. Simple topical solution intended for local therapeutic effects
   - ophthalmic, otic, nasal, dermal

8. Inhalant volatile anaesthetic

9. Solution that does not contain pharmacological API's
   - Lubricants

10. Oral dosage form not intended to be systemically absorbed
    - Radio-opaque media

11. Identical Products
    - Identical APIs, excipients, manufacturing processes and PC properties

PE – When it may apply

12. Solid or Semi-solid oral immediate release dosage form with systemic action
    - Criteria *based upon* human BCS
    - API has high solubility and permeability (in Target animal) – Class I
    - (Maybe API has high solubility and low permeability) – Class III
    - Products are very rapidly dissolving (>85% in 15 minutes)
    - Excipients that may affect bioavailability are qualitatively and quantitively the same.

PE – BCS

- Solubility – A work in progress

The amount of API equivalent to twice the highest dose for the maximum anticipated bodyweight for the target species should be soluble in a specified volume of an aqueous solution. This “specified” volume should be justified by reference to the physiology and gastric fluid volume for the (sub)-species. Testing across species relevant pH range (including at pKa).

May consider Dose number

$$Do = \frac{M_o/V_o}{C_s}$$

Do reflects the relationship between drug aqueous solubility (C_s), dose (M_0) and volume (V_0) within which the drug must dissolve.

Estimate the Do as a function of animal species, dose to be administered, and the in vivo conditions within which the drug must dissolve. If the Do < 1, we can anticipate that the drug will be fully solubilized in vivo.

PE – When it may apply

- Permeability/absorption

An active substance is considered to have complete absorption when the extent of absorption has been determined to be ≥ 85 % in comparison to an intravenous reference dose. Complete absorption is generally related to high permeability.

Generally use data from the public domain.

- *In vitro* dissolution

See EMA/CVMP GLs

No surfactants in media

Very rapidly dissolving if 85% dissolved in 15 minutes

- Excipients

Should be the same or similar. Look for excipients that may affect bioavailability.

PE – When it may apply

13. Solid oral dosage forms with multiple strengths where BE has been shown for one (usually the highest) dose strength.
    - The products are manufactured using the same processes.
    - The composition of all formulations are qualitatively identical.
    - The ratio between concentrations of active ingredient(s) and excipients among the different strengths is identical (proportional formulations).

If not proportional composition may consider if:

- the amount of API(s) is less than 5 % of the tablet core weight/capsule content and,
  - the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed; or
  - the amount of a filler is changed to account for the change in amount of API. The amounts of other core excipients or capsule content should be the same for the concerned strengths.

Information requirements

1. Justify choice of nominated similar/closely similar reference product
   - documentation that active ingredient(s) plus strength/concentration, dosage form, administration route, and label clams for the test and reference product are the same

2. Where possible provide a side-by-side comparison of the test and reference product formulations, both quantitative and qualitative, if this information is available for the reference product;

3. Provide comparative physicochemical testing of a minimum of two batches of the test product and the NZ reference product using the proposed release specifications and test methods developed for the test product;

Information requirements

4. comparative impurity profiles for a minimum of two batches of test active ingredient, test product, and reference product using a methodology with adequate specificity;

5. active ingredient aqueous solubility;

6. additional testing for solutions could include comparative pH, viscosity, specific gravity determinations, or any test that may be relevant to compare the test and reference product;

Information requirements

7. Soluble powders and medicated premixes
   - FDA GFI # 171 (currently withdrawn and being rewritten)

8. Immediate release solid and semi-solid oral dosage forms
   - EMA /CVMP /016/2000-Rev 3 Appendix 1

     MUST PROVIDE
     pH-solubility profile for the API
     Data pertaining to absorption/permeability of the API
     In vitro dissolution data for test and reference product
     Excipients should be similar Esp for consideration of BCS - Class III APIs

Information requirements

9. scientific discussion should include the rate limiting steps in absorption of the active ingredient(s) for drugs with systemic action, or for the active ingredient achieving access to the site of effect if applicable;

10. provide relevant scientific argument to justify the case for equivalence based on pharmaceutical equivalence without in vivo studies and consider the clinical consequences of therapeutic inequivalence.

Methods to establish equivalence

BIOLOGICAL EQUIVALENCE

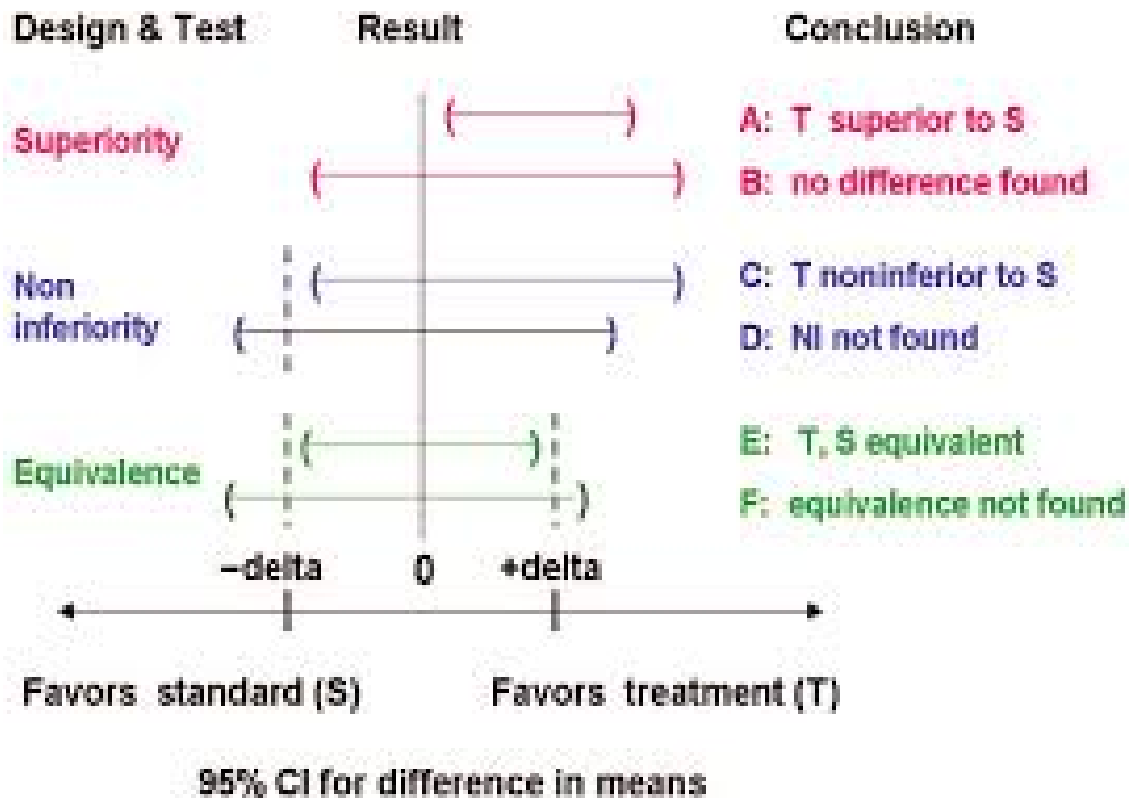
- SIMILIAR products where differences in formulation, manufacturing process, specifications and physicochemical properties mean that we can't be confident that bioavailability and/or efficacy of the API will be the same.
- Require *in vivo* data to support equivalence.

Bioequivalence Studies – When and Why?

- **Generic registrations**
- register multiple TNPs containing the same new API using different dosage forms
- bridging studies between different formulations in product development
- to support new or variation application for a veterinary medicine that has an alternative dosage form or active strength or route of administration;
- to support approval of a change in formulation or manufacturing processes that may impact API bioavailability.

Bioequivalence studies

- Study design
  - Superiority
  - Equivalence
  - Non-inferiority



Bioequivalence studies

- Safety
  - BE studies only address safety of the API.
- Residues
  - May need to address separately
- Palatability
  - May need to address separately for oral dosage forms

Bioequivalence studies - Hierarchy

- blood level study
- pharmacological end-point study
- clinical end-point study

Blood level BE Studies

- Study should reference ACVM GL which references VICH GLs
- Who conducted the study?
- What is the standard the study is designed, conducted and reported too?
- Has the study been audited, and by whom?

Blood level BE Studies

- Test product
  - Final formulation (or representative of)
  - From commercial scale batch if possible
  - Pilot scale minimally
    - Use this batch to specify the critical quality attributes of the product e.g. dissolution, pH
- Reference product
  - Justifed selection in the protocol
  - NZ registered product that contains the same API as test product
  - Should be innovator registration for which data is held

Blood level BE Studies

- Non-NZ Reference product
  - Registrant must provide sufficient evidence to demonstrate that the reference product is qualitatively and quantitatively the same as the ACVM registered nominated reference product

Blood level BE Studies - design

Crossover vs Parallel

2 x 2 cross off most common study design

Eliminates between subject variability in PKs

Washout 5x terminal elimination half life (API ± metabolite)

Single vs Multiple dose

Blood level BE Studies - design

- Dose
  - Generally use the highest approved label dose rate, round up where relevant.
  - Can use higher than approved dose (up to 3x) if needed to achieve measurable dose levels if linear PKs (and safe)
  - Cross over studies
    - Should use same total dose in each animal in each period
    - Adjustments where large weight changes occur over periods need to be considered on case-by case basis
  - Tablets
    - Must not grind or shave to achieve equal dose, dose as per intended use.
    - May divide if this is allowed *and* have content uniformity data
  - Study report should include dose administered to each animal in each period

Blood level BE Studies - design

- Dose Route
  - Use same route and site of administration for the test and reference products.
  - If intended for more than one route, test BE using each route
- Test Animals
  - Clinically healthy and homogenous groups
  - Represent intended population
  - Randomised and equal numbers per group
  - BE for each major target species

Blood level BE Studies - design

- Prandial State
  - Consistent with welfare
- Excluding data
  - Must decide before analysis of blood samples (to avoid bias)
    - Should be addressed in protocol
    - Must provide valid justification
      - E.g. vomited after dosing

Blood level BE Studies - design

- Sample Size
  - Calculated based on estimated treatment differences and variances – example provided in supplement to GL52
  - Base on parameter with greatest variability (e.g. C_{max})
  - Guide: internationally acceptable *minimum* of 12 animals per treatment
    - 6 per group for 2 x 2 cross over study (N=12)
    - 12 per group for parallel study (N=24)
  - Justified in protocol

Blood level BE Studies - design

- Sampling Schedule
  - Based on known PKs/pilot studies
  - Include frequent sampling around T_{max} to estimate C_{max}
    - Don't take first sample corresponding to C_{max}
  - Duration of sampling extend till $AUC_{0\text{-last}}$ is ≥80% $AUC_{0\text{-}\infty}$ to estimate extent of exposure
  - Min 3 samples in terminal log-linear phase to reliably estimate k_e and hence $AUC_{0\text{-}\infty}$

Blood level BE Studies - design

- What to measure
  - *Generally* the parent compound (free + protein bound)
  - Pro-Drug – Measure active metabolite
    - When pro-drug has negligible systemic concentrations
    - Provide justification
  - Enantiomers
    - Rare instances may need enantiomer specific assay

Blood level BE Studies - design

- Analytical test method + validation
  - Should be conducted in GLP compliant laboratory
  - Quality control (QC) samples obtained during in-phase runs
    - Precision
    - Accuracy
- PK Parameters
  - Single dose studies
    - $C_{max,}$ $T_{max,}$ $AUC_{0\text{-}last,}$ $AUC_{0\text{-}\infty}$
  - Multiple dose studies
    - $C_{max,}$ $T_{max,}$ $AUC_{0\text{-}last,}$ $AUC_{0\text{-}\infty,}$ $AUC_{\tau,}$ $C_{\tau\ ss,}$ $C_{max\ ss,}$ $T_{max\ ss,}$
  - Non-compartmental models should be used to determine PK parameters

Blood level BE Studies - design

- Statistical Analysis
  - Use 90% CI approach
    - $C_{max,}$ $AUC_{0\text{-}last,}$ $AUC_{0\text{-}\infty}$
  - ANOVA
    - Model using ANOVA (by convention)
    - 2 x 2 crossover
      - effects include sequence, animal within sequence, period, treatment
    - Parallel
      - Treatment is the effect tested the ANOVA model
  - Use residual error from model to calculate CIs

Blood level BE Studies - design

- Ln - Transformation
  - VICH recommends Ln transformation
    - Raw data often skewed – don't meet assumptions of model
    - PK models multiplicative
    - Stabilize variance
    - BE comparisons usually expressed as ratios (rather than mean differences)
    - Our guidance allow analysis using untransformed data if normally distributed
- Acceptance criteria
  - Point estimate and 90% CI within the bounds of 0.80-1.25 (transformed) for AUC and C_{max}

Blood level BE Studies – The Report

- All individual concentration data and pharmacokinetic parameters by product – reported conc > LOQ
- Justification for any withdrawal of data or test subjects.
- Method used to derive the pharmacokinetic parameters from the raw data must be described. Include summary statistics
  - e.g. geometric and arithmetic mean, median, standard deviation, coefficient of variation, minimum and maximum.
  - data in a format that enable the calculation of pharmacokinetic parameters and the statistical analysis to be repeated by us. Electronic submission

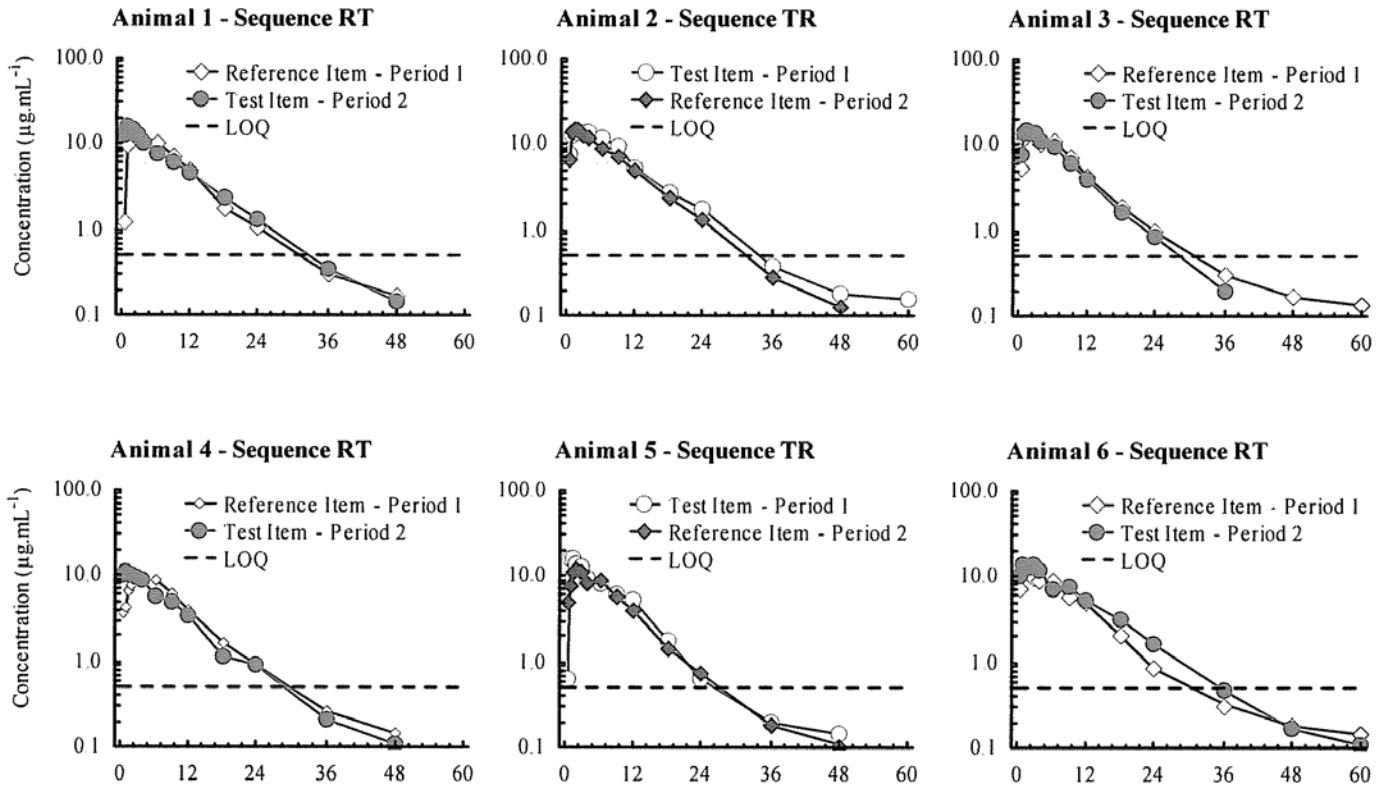
- Present individual plasma concentration/time curves in linear/linear and log/linear scale.

Blood level BE Studies – The Report

- The parameters to be analysed are AUC, Cmax and Cmin (if applicable).
- For AUC, Cmax (and Cmin if relevant), present both the point estimate and 90% confidence intervals.
- Present ANOVA or other applicable statistical model used to calculate estimates of the error variance and the least square means used to calculate 90% confidence intervals.
- Statistical software should be validated (see GL 52 supplement)

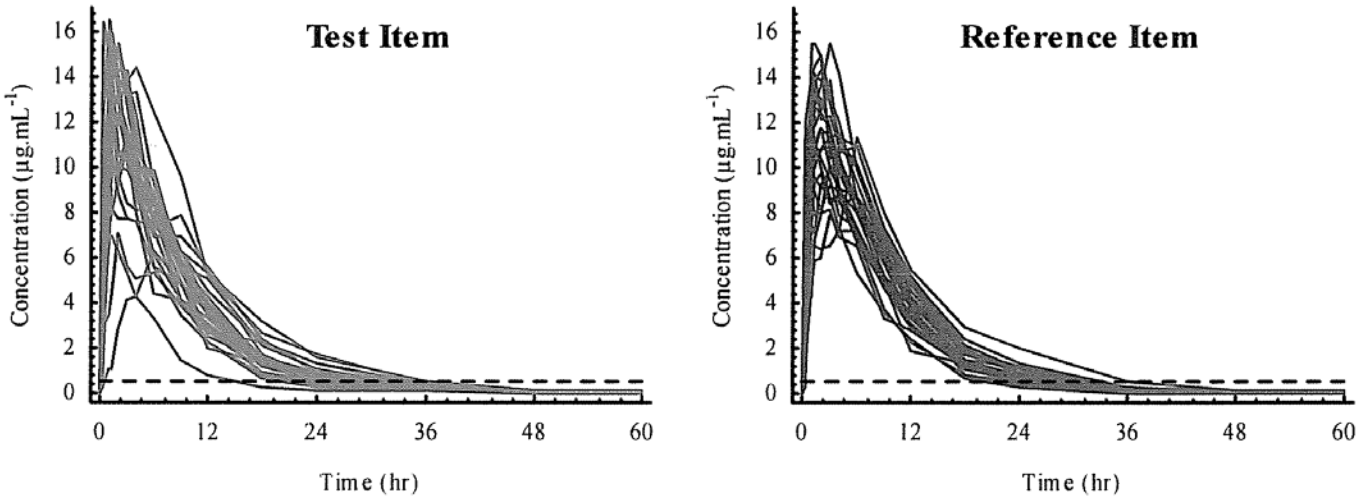
Blood level BE Studies – Data and Analysis Example

Fig. 1c: Phenylbutazone Concentrations in Individual Animals – Test and Reference Item (Anim. 1 – 12) – log scale

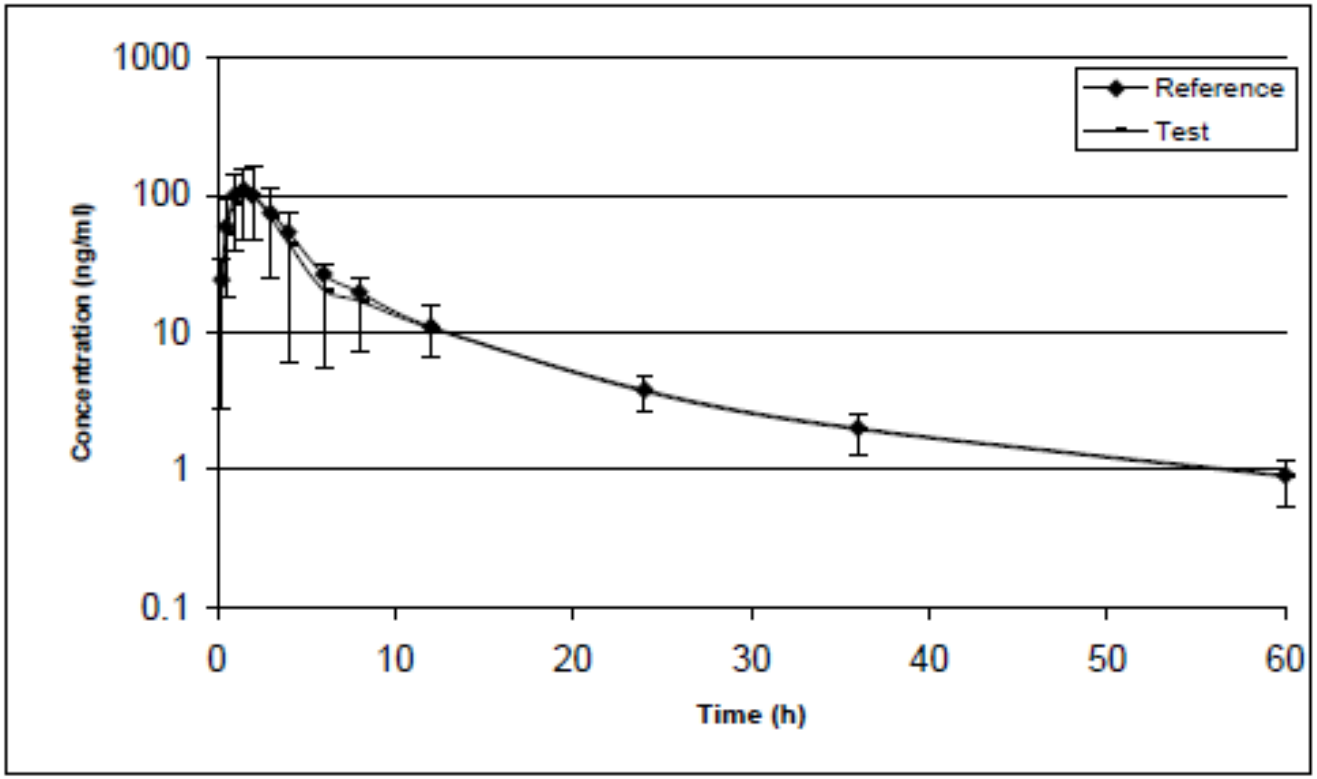


Blood level BE Studies – Data and Analysis Example

Fig. 2a: Phenylbutazone Concentrations in Equine Plasma – Overlay Plot – Test and Reference Item



Blood level BE Studies – Data and Analysis Example



Graph 1: Comparison of mean ± SD benazeprilat concentrations between test and reference items

Blood level BE Studies – Data and Analysis Example

- PK parameters often calculated using software
  - Must describe methods used in software i.e. assumptions made.
  - Generally use non-compartmental methods
  - Below example used EquivTest2 software
  - (Software needs to be validated)

7.4.1 AUC_t

Individual areas under the curves from time zero to the last sampling (AUC_t) exceeding the limit of quantification (LOQ) were calculated with the linear trapezoidal method using the *trapArea* function. C_{last} (last c_i > LOQ) was calculated from the ln-concentration time curve.

Blood level BE Studies – Data and Analysis Example

Table 5b: Pharmacokinetic Parameters – Reference Item

Animal	Period	Sequence	C_{max} ($\mu g.mL^{-1}$)	T_{max} (hr)	k_{el} (hr)	$t_{1/2el}$ (hr)	AUC_t ($\mu g.hr.mL^{-1}$)	AUC_i ($\mu g.hr.mL^{-1}$)	residual area (%)	AUMC ($\mu g.hr^2.mL^{-1}$)	MRT (hr)
1	1	RT	13.591	1.5	0.125	5.6	133.07	141.48	5.95	1 278.1	9.0
3	1	RT	14.150	2.0	0.124	5.6	137.65	145.35	5.30	1 251.0	8.6
4	1	RT	10.037	3.0	0.129	5.4	108.33	115.46	6.17	1 095.7	9.5
6	1	RT	12.184	1.0	0.148	4.7	122.82	128.36	4.32	1 114.6	8.7
9	1	RT	14.319	1.0	0.131	5.3	146.69	154.67	5.16	1 345.8	8.7
12	1	RT	12.977	2.0	0.102	6.8	125.14	137.77	9.17	1 400.7	10.2
24	2	TR	12.196	1.0	0.178	3.9	87.06	91.30	4.65	584.1	6.4
n			24	24	24	24	24	24	24	24	24
Arithmetic mean			12.017	2.1	0.134	5.3	114.12	121.21	5.68	1 060.3	8.6
SD			2.168	1.2	0.020	0.8	21.29	23.72	2.28	320.7	1.3
CV (%)			18.040	58.2	14.6	14.9	18.7	19.6	40.1	30.2	14.6
Median			11.943	1.8	0.131	5.3	116.02	119.56	5.35	970.6	8.6
Geometric mean			11.823	1.8	0.132	5.2	112.13	118.92	5.33	1 015.8	8.5
Harmonic mean			11.622	1.6	0.131	5.2	110.08	116.59	5.02	973.0	8.5
Minimum			7.776	1.0	0.097	3.9	73.85	78.42	2.90	551.7	6.4
Maximum			15.441	6.0	0.178	7.2	146.69	155.91	13.60	1 940.5	12.7
Exp (mean±SD, LN-data)			9.806	1.1	0.114	4.5	92.35	97.20	3.72	752.8	7.4
			14.254	3.0	0.153	6.1	136.15	145.50	7.62	1 370.8	9.8
90 % Confidence interval			11.259	1.6	0.127	5.0	106.67	112.91	4.88	948.1	8.2
			12.776	2.5	0.140	5.6	121.57	129.51	6.48	1 172.5	9.1

Blood level BE Studies – Data and Analysis Example

Analysis of variance table:

	df	SS	MS	F	P-Value
Inter-Subjects					
Carry-over	1	0.0154	0.0154	0.1402	0.7116
Residuals	22	2.4252	0.1102	3.4092	0.0028
Intra-Subjects					
Drug	1	0.0606	0.0606	1.8756	0.1846
Period	1	8.097E–05	8.097E-05	0.0025	0.9605
Residuals	22	0.7113	0.0323		
Total	47	3.2128			

Blood level BE Studies – Data and Analysis Example

The formula for the confidence interval is

$$CI = \left(\overline{X}_{IVP} - \overline{X}_{RVP}\right) \pm t_{n_{Seq1}+n_{Seq2}-2;0.05} SD \sqrt{\frac{1}{2}\left(\frac{1}{n_{Seq1}} + \frac{1}{n_{Seq2}}\right)}$$

The first part of this is just the difference between the two means

$\left(\overline{X}_{IVP} - \overline{X}_{RVP}\right)$

The second part involves the t-statistic that was defined in the previous cell and then the SE of the difference.

$$SE_{DIFF} = SD \sqrt{\frac{1}{2}\left(\frac{1}{n_{Seq1}} + \frac{1}{n_{Seq2}}\right)}$$

Blood level BE Studies – Data and Analysis Example

SPECIFICATIONS

Date:	Monday, October 27, 2014 at 22:45:43
Data Set:	AUC_t
Analysis:	Means - Crossover Design [Multi Vars/Subject]
	Period1: Period1 Period2: Period2 Sequence: Sequence 1:RT
Equivalence Parameter:	Difference of Means [Log Scale]
90.00% CI: **Antilogged 90.00% CI:**	[–0.1602, 0.0180] [0.8519, 1.0182]
Equivalence Bound(s)	**[Lower]:** –0.2231 **[Upper]:** 0.2231
Alpha Value(s)	**[Lower]:** 0.0500 **[Upper]:** 0.0500

Note(s): This crossover analysis assumes that there are no carry over effects.
The results are presented for data transformed according to the natural logarithm (ln).

Information requirements

Questions?