# Submitting Data to JECFA

**24th CCRVDF side event**

**22 April 2018, Chicago**
**Dr. Silke Thielen on behalf of HealthforAnimals**

www.animalhealthmatters.com
www.healthforanimals.org

# HealthforAnimals

- Global representative body of companies and associations
- Veterinary medicines, vaccines, other products
- Research & Development, manufacturing, commercialisation

**85+% global animal health sector**

## Main global companies

Boehringer Ingelheim
zoetis
MERCK Animal Health
BAYER
Virbac
Elanco
vetoquinol ACHIEVE MORE TOGETHER
Phibro ANIMAL HEALTH CORPORATION
ceva

## 29 Regional associations

**NORTH AMERICA**
Canada
Mexico
United States

**EUROPE and AFRICA**
Europe
Belgium
Denmark
France
Germany
Ireland
Italy
Netherlands
Portugal
Spain
Sweden
Switzerland
United Kingdom
South Africa

**CENTRAL/SOUTH AMERICA**
Argentina
Brazil
Chile
Paraguay

**ASIA/PACIFIC**
India
Australia
Indonesia
Japan
Korea
New Zealand
South-East Asia
Thailand

**250+ SMEs represented**

# Purpose of the presentation

Health for Animals
global animal medicines association

The goal is to facilitate and increase the understanding of the Codex Alimentarius MRL process, by explaining the overall requirements, investments and other considerations related to submitting a compound to JECFA for assessment.

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# Candidate Selection – From Research to Market

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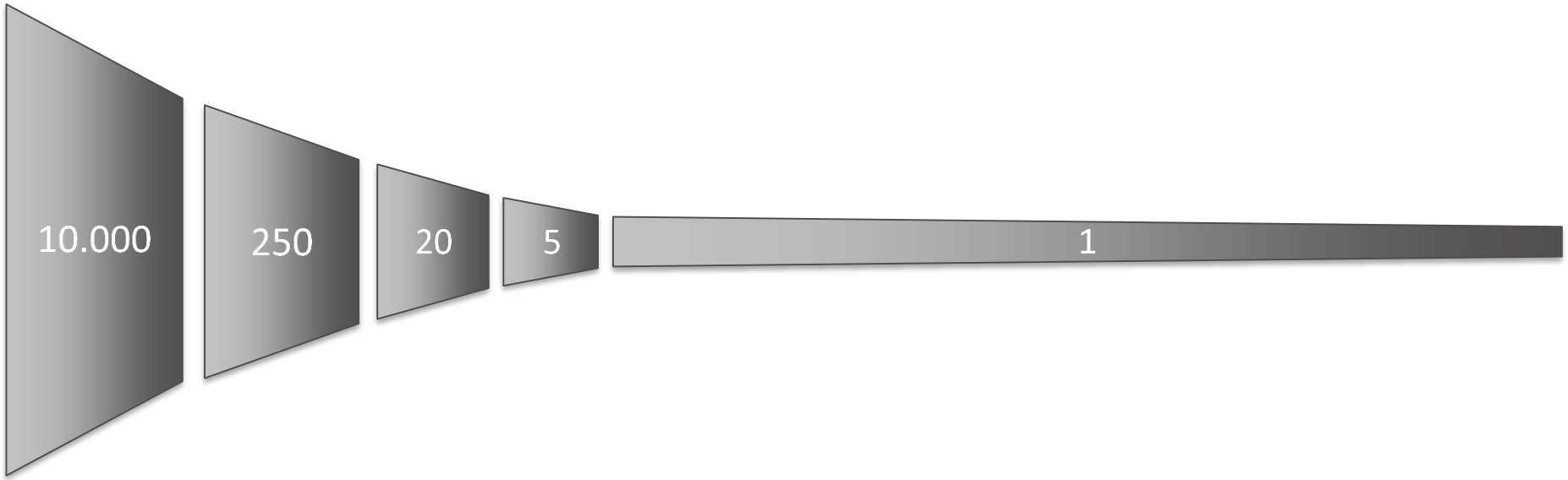



2 years

8 years

**50-100 Mio. USD**

# Veterinary Drug Development

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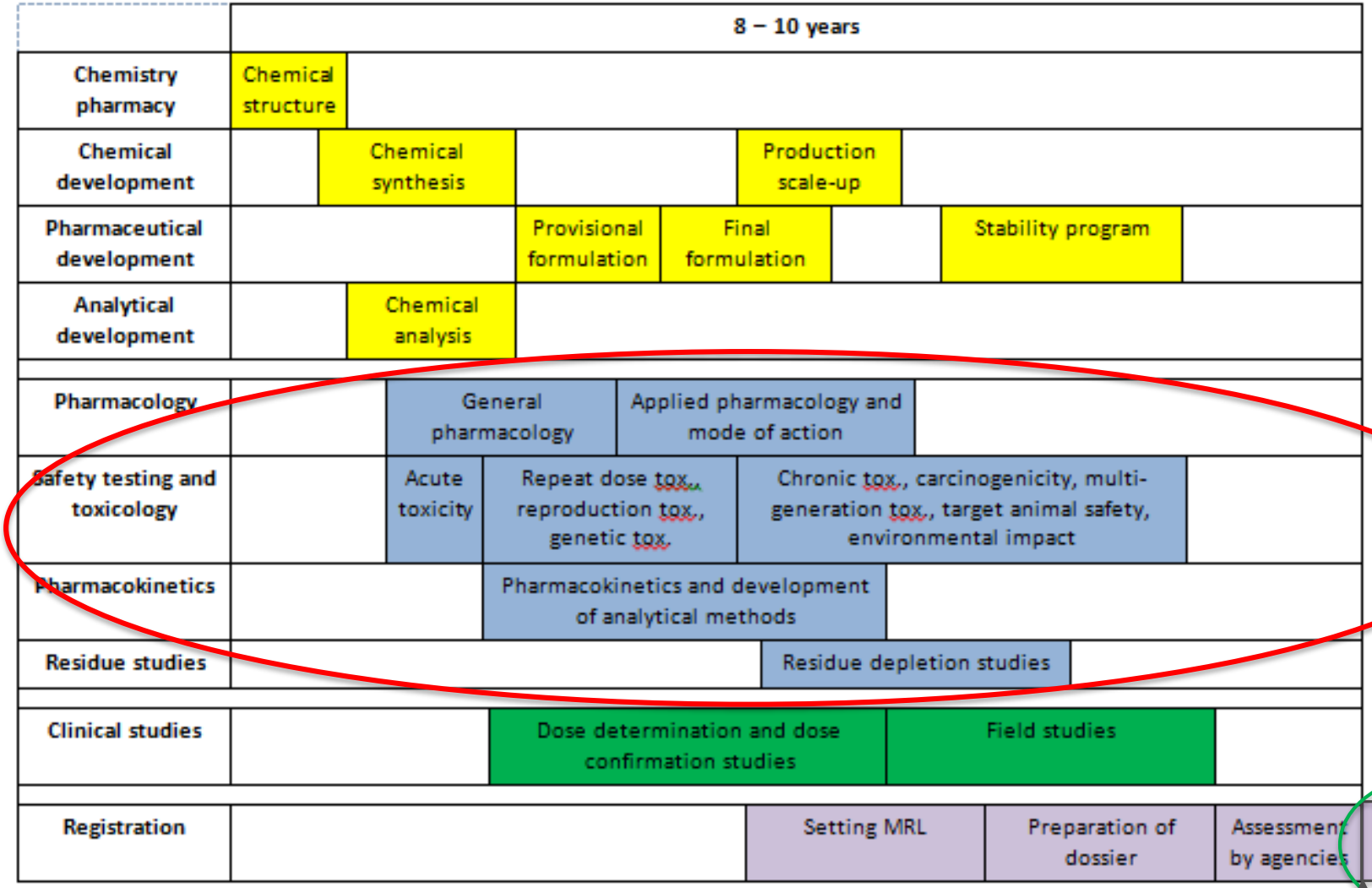


# Regulatory Processes

- Product license approval is based on three pillars, namely **safety, efficacy, chemistry, manufacturing & controls (CMC)**
- Principle is globally accepted although specific data requirements may vary between countries / regions
- Regulatory processes are well established and are generally followed by national competent authorities
- Codex/ JECFA safety data requirement are (generally) consistent with regulatory requirements
- Codex /JECFA procedures are unique
  - Product Priority List
  - JECFA meeting schedule can be uncertain
  - Limited interaction with Expert Panel
  - Multi-step approval process

# MRLs and Trade

- Imported foodstuffs must comply with local residue requirements
- Food with residues without MRLs/tolerance levels in importing countries considered not fit for human consumption cannot be imported if residues are detected

**Goal:**

Harmonized, global MRLs

OR

MRLs set in major countries

OR

Codex MRL

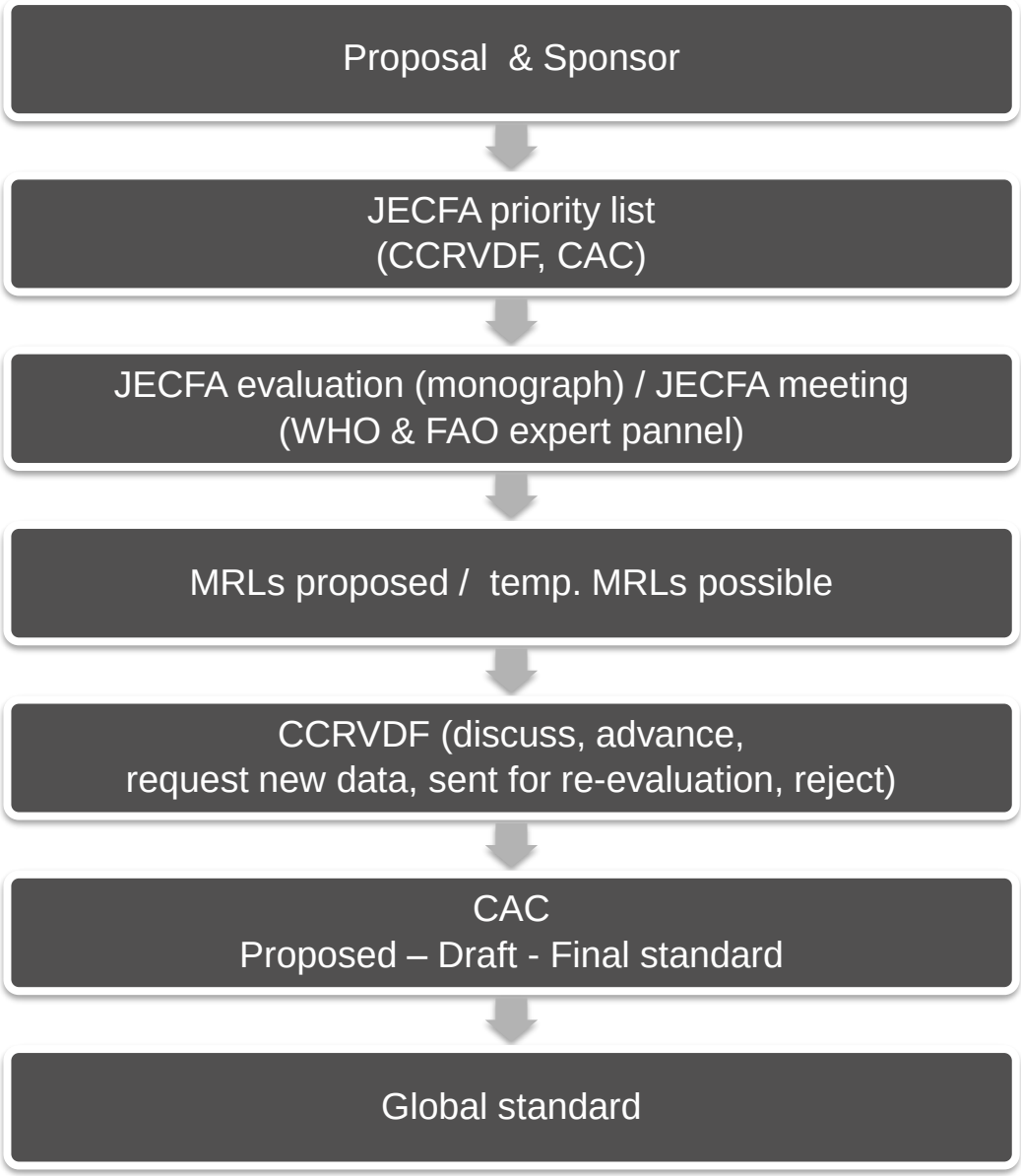
- Codex MRLs are a very important tool to have effective and internationally recognized food safety control measures which are used at port of entry inspections

➔ **Codex MRLs are an important element ensuring trade compliance especially in markets without local tolerance levels or MRLs**

# Codex Alimentarius MRL Process

- Goal Codex MRL: Protect consumer health and ensure fair practices in trade
- Codex MRLs are internationally adopted food standards

- Stakeholders:
  - World Health Organization (WHO)
  - Food & Agriculture Organization (FAO)
  - Codex Alimentarius Commission (CAC)
  - Codex Committee on Residues of Vet. Drugs in Foods (CCRVDF)
  - Joint Expert Committee on Food Additives (JECFA)
  - Observers (NGOs)
  - Product sponsors
- Codex Procedure described in Codex Procedural Manual

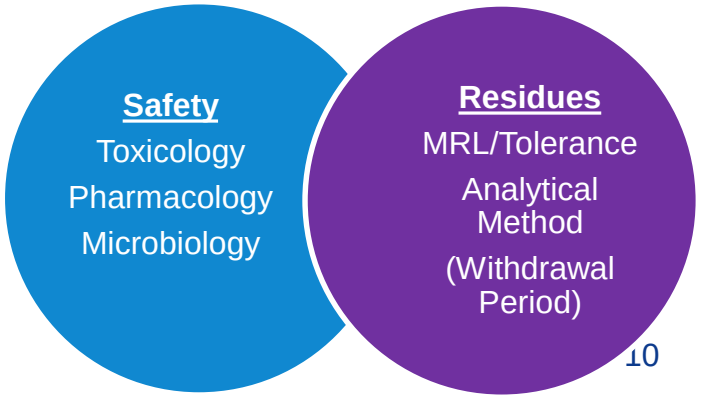


# Human Food Safety Evaluation

- Purpose: determine when edible tissues from food-producing animals treated with an animal drug are safe for human consumption
- Evaluation of safety is based on risk assessment principles

**Risk = Hazard x Exposure**

- **Hazard** (Toxicity) ➔ **ADI** = Acceptable Daily Intake
  - Estimate of the amount of residues in food that can be consumed daily over a lifetime without appreciable health risk
- **Exposure ➔ MRL** = Maximum Residue Limit
  - Maximum concentration of residues that is acceptable in food and considered to be without toxicological hazard for human health
  - Exposure from all food sources must be ≤ upper limit of the ADI



# JECFA Codex MRL - Scientific Procedure

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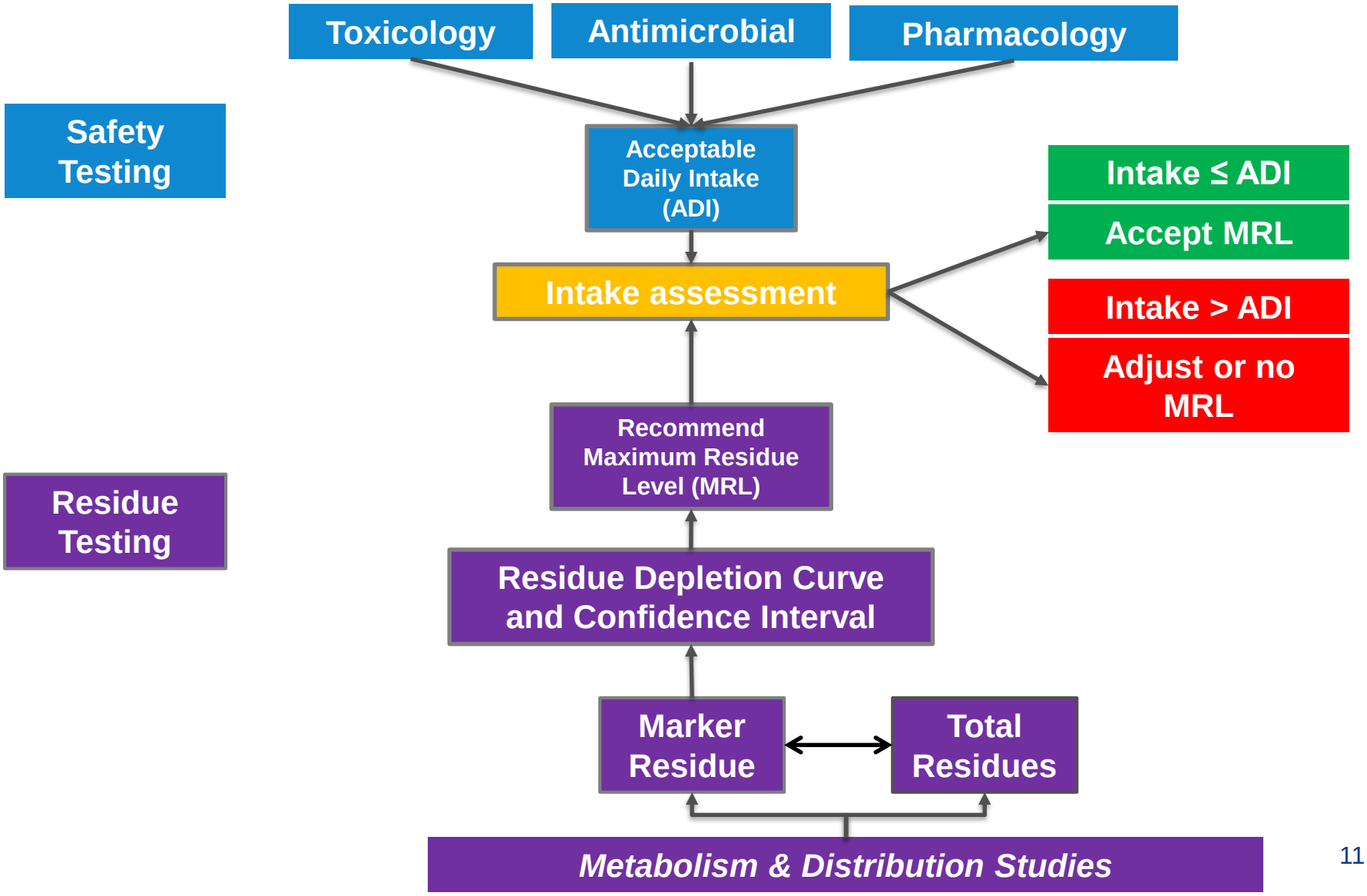

# Human Food Safety - Safety

Health for Animals
global animal medicines association

**Safety**
Toxicology
Pharmacology
Microbiology

## Objective

- Estimate of the amount of residues in food that can be consumed daily over a lifetime without appreciable health risk

## Deliverables

- Identification of the suitable model species
- Identification of the lowest No-observed-(adverse)-effect-level (NO(A)EL) in the most sensitive species
  - Toxicology
  - Pharmacology
  - Antimicrobial activity (if relevant)

## Goal

- Determination of the ADI on which subsequently MRLs are based derived from NO(A)EL and the use of safety factors

# Concept of Safety Testing – I


## Toxicology

- Toxicity is any adverse or unwanted condition that may effect health
- Any substance may exhibit a toxic effect in animals and humans
- Toxicity of a substance depends on the amount of the substance consumed or the extent of exposure (i.e. the dose or dose rate)
- Investigated in various laboratory animals
- Relevant toxicity studies:
  - Acute Toxicity
  - Subchronic and Chronic Toxicity
  - Mutagenicity and Carcinogenicity
  - Reproduction and Developmental Toxicity
  - Special Effects (e.g. Neurotoxicity, Immunotoxicity)
  - Toxicokinetic as part of subchronic and chronic toxicity studies
  - Etc…

# Concept of Safety Testing – II


## Safety Pharmacology

- Not mandatory but investigated if there are indications that the API might produce pharmacological effects in the absence of a toxic response or at doses lower than those required to elicit toxicity
- Core Study Battery (Central Nervous, Cardiovascular and Respiratory System)

## Antimicrobial Activity

- For compounds with antibacterial properties, information to determine the effects of residues of the drug on the human intestinal flora and resistance development is required
- VICH GL 36 defines standardized test systems (in vitro and in vivo) and recommends procedures to derive a microbiological ADI

# Concept of Toxicity – from animals to humans

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**Safety**
Toxicology
Pharmacology
Microbiology

- **Hazard identification** ➔ Is the product toxic?
- **Hazard characterization** ➔ NO(A)EL in most sensitive species
- To establish the **ADI** for humans, the data from laboratory animals are extrapolated to humans

  ➔ Use of appropriate multiplier of safety factors to apply to animal model studies

  - Interspecies extrapolation
  - Intraspecies extrapolation
  - Subchronic to chronic extrapolation
  - Absence of a NOAEL, etc.

} Usually factors of 10 (in some cases factor of 2 or 3)

**ADI [mg/kg bw] = No Observed Effect Level / Safety Factors**

# Concept of Safety Testing – Outcome


**Toxicological, pharmacological and microbiological (if relevant) ADI calculated based on the lowest NO(A)EL plus applying appropriate safety factors**

**The overall ADI should be established on the lowest of the pharmacological, toxicological or microbiological ADI that has been determined**

# Safety testing – Costs and timelines

| Study Type | Species |
|---|---|
| Acute Toxicity (oral/dermal single dose, irritating and allergenic potential) | Rat or Mouse |
| Subchronic and Chronic Toxicity | Rat and Dog (28 and 90 days, 52 weeks) |
| Mutagenicity | In vitro and in vivo (Mouse) |
| Carcinogenicity (if needed) | Rat and Mouse |
| Reproduction and Developmental Toxicity | Rat and Rabbit |
| Special Toxicity | Rat or Mouse |
| Pharmacokinetic (incl. Method development) | Rat, Dog, Mouse (as part of Toxicity Studies) |
| Microbiological Activity | In vitro |
| Pharmacology | Rat and Dog |

**Safety**
Toxicology
Pharmacology
Microbiology

**Total costs:**
**~ 4.500.000 USD ***
(Safety studies)
**+ ~ 1.000.000 USD ***
(technical development API)

**5.500.000 USD ***

**Duration full package:**
**4-5 years**

- Studies performed using the API according to Good Laboratory Practice (GLP) and appropriate OECD Testing guidelines

# Human Food Safety - Residues

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global animal medicines association

**Residues**
MRL/Tolerance
Analytical Method
(Withdrawal Period)

- Foodstuffs obtained from animals treated with veterinary medicinal products must not contain residues of the medicine or its metabolites which might constitute a health hazard for the consumer
  - ➔ Establishment of maximum residue limits (MRLs) for veterinary medicinal products in foodstuffs of animal origin
- Definition MRL:
  "The maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg or µg/kg) which may be accepted to be legally permitted or recognized as acceptable in or on a food"
- MRLs are derived from the ADI under the assumption that the average person consumes, on a daily basis:
  - 500 g of meat (300 g of muscle, 100 g of liver, 50 g of kidney and 50 g of fat)
  - 1.5 L of milk
  - 100 g of eggs or egg products.
  - Allowance is also made for the consumption of poultry, fish and honey

Food Basket*

  - ➔ **The total amount of residues present in this daily food basket is not allowed to exceed the ADI**

**JECFA is currently considering a new approach using different consumption figures (GEADE + GECGE)*

# MRL setting - Target tissues

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**Residues**
MRL/Tolerance
Analytical Method
(Withdrawal Period)

- Defined by species:

| | |
|---|---|
| Mammals (excl. pigs): | muscle, fat, kidney, liver |
| Pigs : | muscle, skin+fat, kidney, liver |
| Poultry: | muscle, skin+fat, kidney, liver |
| Fish: | muscle +skin |
| Lactating ruminants: | milk |
| Laying poultry : | eggs |
| Bees: | honey |

- Tissue having the highest residues or the slowest depletion rate to its MRL are most appropriate for surveillance monitoring
- Some countries have some additional tissues which are consumed and therefore must be investigated. e.g. intestine, lung, tribe etc. (= variety meats)

# MRL setting – Application routes

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**Residues**
MRL/Tolerance
Analytical Method
(Withdrawal Period)

- Nature of metabolites, distribution and magnitude of residues depends on route of administration
- ORAL – single dose, continuous by in-drinking water or in-feed
- INJECTABLE – intra-muscular or subcutaneous (sometimes IV)
- DERMAL – pour-on, spray-on, dipping (transdermal and oral uptake)
- OTHER – ear-tag, intra-mammary, intra-uterine...
- INDIRECT – via application to housing (transdermal and oral uptake)

| | |
|---|---|
| ORAL uptake | transit first through liver following absorption in intestine rapid metabolism, high residues in liver |
| DERMAL uptake | initially high residues in subcutaneous fat under skin |

# MRL setting – Absorption, Distribution, Metabolism, Excretion

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**Residues**
MRL/Tolerance
Analytical Method
(Withdrawal Period)

Most drugs are:

- **Absorbed** (so that they can act on target organs or organism)
- **Distributed** into organs/tissues driven by chemical nature of drug, e.g.
  - Lipophilic un-ionized drugs accumulate in the fat
  - Polar ionized drugs go to the kidneys for elimination via urine
- **Metabolized** (transformed chemically) in-vivo, (oxidation, conjugation) so that they can be eliminated
  - Rates of metabolism can vary widely from “none” to “extensive”. Highly drug dependent.
- **Eliminated** via
  - Feces, bile
  - Urine, generally very polar conjugates
  - Other: e.g. milk, lanolin, ‘growth dilution’, expiration

# MRL setting – Absorption, Distribution, Metabolism, Excretion

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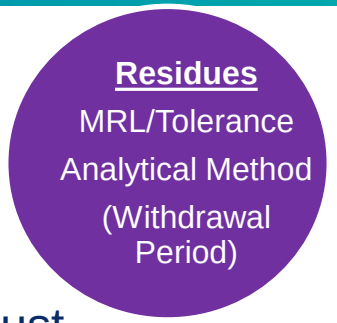
**Residues**
MRL/Tolerance
Analytical Method
(Withdrawal Period)

- ADME studies are conducted with drug substance containing a radioactive label to track progress of the drug through animal's body irrespective of metabolism: Carbon 14 or hydrogen 3
- ADME studies should be conducted in
  - In vitro (hepatocytes and microsomes from target species, toxicity test species) ➔ same metabolism?
  - Lab animals (usually rats), dosed by oral route with active substance
  - Target animal, dosed with close-to-final formulation via intended route
- Metabolites in target and lab animals must be compared AND major metabolites found in edible tissues of target animal MUST be present in lab animals (otherwise independent toxicological testing and assessment of ingested metabolites is needed)

# MRL setting – Marker Residue




- In residue studies and for MRL compliance monitoring, a **marker residue (MR)** is determined which would be representative for the total residue of toxicological concern
- MR must be able to be measured and reference standard of MR must be available
- MR can be:
  - parent compound
  - metabolite
  - combination of metabolite and parent
  - a substance to which parent and/or metabolites can be converted
- Ratio of MR to TRR (Total Radioactive Residue) will generally decrease with time (100% → 0%) and needs to be defined at the time of expected withholding period

# Residue Depletion – Determination of WHP

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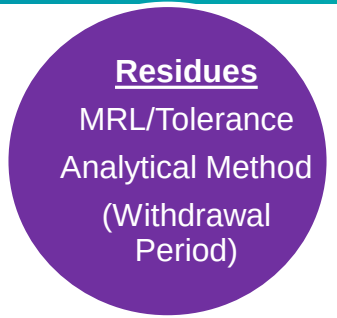


- **Establishment of WHP is not in the scope of the CODEX MRL process**
- Residue levels in food commodities derived from animals treated with drug product need to be at or below MRL
- Normally some period needs to elapse before commodities are safe = withholding period (WHP)
- The clinical use of the product needs to be established:
  - Residue studies consistent with dose and dose regimen
  - Route of application (use of field application method)
- **Basic Study Design**
  - Groups of animals are treated with final product (GMP) using field application method at maximum dose, maximum number and duration of treatments
  - Tissues are collected at various timepoints after treatment
  - Samples are analyzed for the marker residue using a validated analytical method
  - Residues are subjected to statistical analyses to set WHP

# MRL and WHP testing – Costs & timelines

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| Study Type | Species |
|---|---|
| Synthesis radiolabeled API ($^{14}C$ or $^{3}H$) | |
| Analytical Method Development and Validation - Tissue (typically LC-MS/MS) | |
| Analytical Method Development and Validation - Plasma, Test Article (e.g. in-feed) | |
| Comparative Metabolism in vitro (radiolabeled) | Hepatocytes and liver microsomes from target species and toxicity test species |
| Pilot studies (Pharmacokinetic, Radiolabeled Metabolism, Residue Depletion) | Target species |
| Pivotal Radiolabeled Comparative Metabolism Study in Laboratory Animals | Rat |
| Pivotal Radiolabeled Metabolism Study in the target species (Determination of Quantity and Identify the Nature of Residues) | Target species |
| Pivotal Marker Residue Depletion Studies (Establish Product WHP) | Target species |

**Residues**
MRL/Tolerance
Analytical Method
(Withdrawal Period)

**Total costs:**
**~ 1.900.000 USD ***
**(variable costs depending on type of product, application route, species, chemical and metabolic properties, etc.)**

* Cost estimate 1Q 2018

**Duration full package:**
**~ 2 years**

- Studies performed according to Good Laboratory Practice (GLP)

# Concluding observations

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## Elements that impact decisions to develop scientific inputs for Codex standards

1. There are significant benefits to countries of Codex MRLs
2. Applicants investment (approx. **7-8 Million US$ over 6 years**) – Return of investment consideration
3. Investment in developing data competes against opportunities for other medicines
4. Innovation companies are increasingly developing products where no MRL is required (i.e. biologics, proteins), factors influencing this include:
    - Market place is evolving faster than MRLs or Import Tolerances can be developed
    - National authorities' MRL approval periods are requiring more time and complexity
5. The decision to develop data for Codex is based on a projected ROI for the full product lifecycle – from R&D until end of marketing

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# Thank you

# Back-up

# JECFA Codex MRL: Submission to Approval

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global animal medicines association

- Submission and Approval Process

24 months

- Call for data by JECFA Secretariat about 10-12 months prior to JECFA meeting date
- Invitations to contributing experts about 6-9 months prior to meeting date
- Assignments to drafting experts about 6 months prior to meeting date
- First drafts of monographs and working papers submitted by drafting experts to FAO Joint Secretary 6-8 weeks prior to meeting date
- Distribution by FAO Joint Secretary of draft monographs and working papers for review by other members and invited FAO experts about 6 weeks prior to meeting

- Submission of first draft of summary by drafting experts to FAO rapporteur at meeting opening
- Overview presentation by drafting expert at beginning of JECFA Meeting to identify key issues for discussion and decision by the Committee
- Discussions in working groups and full Committee during JECFA Meeting to resolve issues, finalize decisions
- Preparation of revised summary text by drafting expert to reflect discussions and decisions
- Provision of final summary text by the drafting expert to the rapporteur for final review and adoption by the Committee
- Adoption of final text of meeting report by the Members of the Committee

- Submission of final draft of monograph by drafting experts to FAO Joint Secretary by date established at JECFA meeting
- Publication of monographs and meeting report, typically about 6 months after meeting

# Safety testing – Costs and timelines

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| Study Type | Species | Costs [USD] * |
|---|---|---|
| Acute Toxicity (oral/dermal single dose, irritating and allergenic potential) | Rat or Mouse | 75.000 |
| Subchronic and Chronic Toxicity | Rat and Dog (28 and 90 days, 52 weeks) | 1.200.000 |
| Mutagenicity | In vitro and in vivo (Mouse) | 70.000 |
| Carcinogenicity (if needed) | Rat and Mouse | 1.500.000 |
| Reproduction and Developmental Toxicity | Rat and Rabbit | 900.000 |
| Special Toxicity | Rat or Mouse | Up to 500.000 |
| Pharmacokinetic (incl. Method development) | Rat, Dog, Mouse (as part of Toxicity Studies) | 150.000 |
| Microbiological Activity | In vitro | 100.000 |
| Pharmacology | Rat and Dog | 50.000 |
| **TOTAL** | | **~ 4.500.000**<br>**+ ~ 1.000.000 USD ***<br>(technical development API) |

**Duration** full study package: approx. **4-5 years**

* Cost estimate 1Q 2018

# MRL and WHP testing – Costs & timelines

Health for Animals
global animal medicines association

| Study Type | Species | Costs [USD] * |
|---|---|---|
| Synthesis radiolabeled API ($^{14}C$ or $^{3}H$) | | Up to 150.000<br>(depending on synthesis and required amount) |
| Analytical Method Development and Validation - Tissue (typically LC-MS/MS) | | Up to 200.000<br>(depending on type of method, number of tissues, etc.) |
| Analytical Method Development and Validation - Plasma, Test Article (e.g. in-feed) | | Up to 80.000 |
| Comparative Metabolism in vitro (radiolabeled) | Hepatocytes and liver microsomes from target species and toxicity test species | 70.000 |
| Pilot studies (Pharmacokinetic, Radiolabeled Metabolism, Residue Depletion) | Target species | Up to 500.000 |
| Radiolabeled Comparative Metabolism Study in Laboratory Animals | Rat | 100.000 |
| Radiolabeled Metabolism Study in the target species<br>(Determination of Quantity and Identify the Nature of Residues) | Target species | Up to 500.000<br>(depending on species, route of administration, etc.) |
| Marker Residue Depletion Studies<br>(Establish Product WHP) | Target species | Up to 300.000<br>(depending on species, route of administration, etc.) |
| **TOTAL** | | **Up to ~ 1.900.000** |

**Duration** full study package: approx. **2 years**

* Cost estimate 1Q 2018

# Safety Guidelines (VICH and FDA/CVM Guidance

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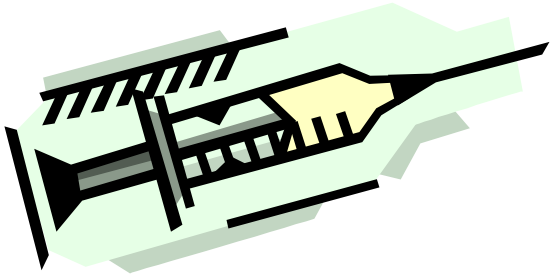
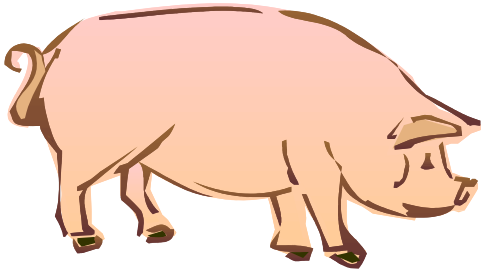
| VICH GL | CVM GFI | Subject |
|---|---|---|
| GL46 | GFI 205 | Metabolism Study to Determine the Quantity and Identify the Nature of Residues |
| GL47 | GFI 206 | Comparative Metabolism Studies in Laboratory Animals |
| GL48 | GFI 207 | Marker Residue Depletion Studies To Establish Product Withdrawal Periods |
| GL49 | GFI 208 | Validation of Analytical Methods used in Residue Depletion Studies |
| | GFI 3 | General Principles for Evaluating the Human Food Safety of New Animal Drugs Used In Food-Producing Animals |

# Study design (VICH GL 46)

[4 groups at different withdrawal times]

Dose at 1X intended rate
at proposed dose route (M/F)
for maximum duration (GLP)





Tissue
Collection

**Radiolabeled Drug [$^{14}$C]**

(1)

Combustion
Analysis

(2)

Metabolism

**TOTAL RESIDUES**

# Study design (VICH GL 48)

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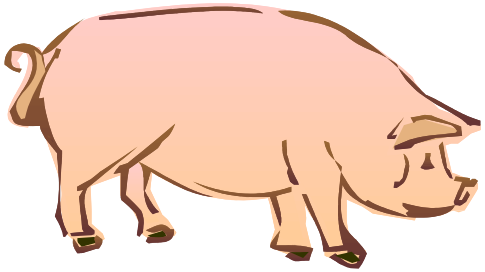
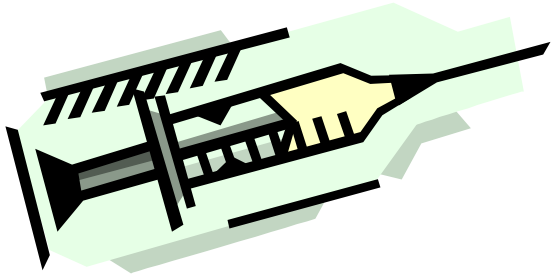
**[4 animals each at 4 different withdrawal times]**

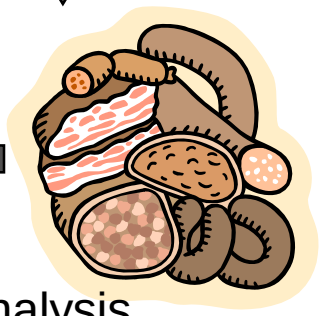
Highest commercial dose rate
and dose route (M/F)
for maximum duration



**Final Formulation**



**Target** Tissue Collection



**Marker**
Residue Analysis
Validated Method

**MARKER RESIDUES**

[Show residue depletion
to below **MRL or LOQ**]