



Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit



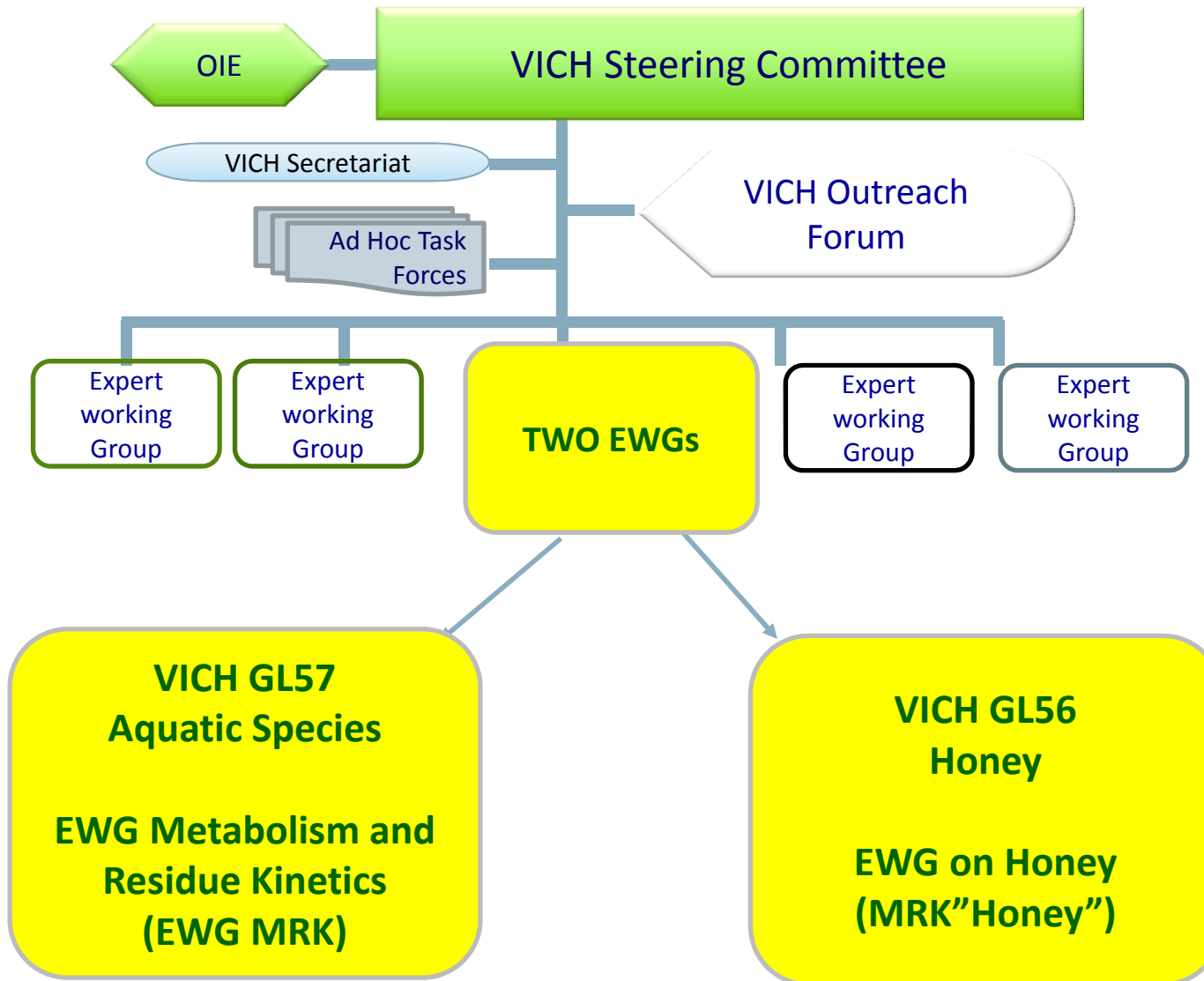
**New VICH Guidelines:
Bees/Honey and Aquatic Species
GL 56 & 57**

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"Veterinary Medicines"**

**Residues of Pharmacologically Active
Substances**

New VICH GLs: Aquatic Species and Honey



VICH Metabolism & Residue Kinetics GLs – The 4 original GLs

Guideline Series: „Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals“

- ✓ Metabolism study to determine the quantity and identify the nature of residues (VICH GL46) - February 2011 - Implemented in February 2012
- ✓ Comparative metabolism studies in laboratory animals (VICH GL47) - February 2011 - Implemented in February 2012
- ✓ Marker residue depletion studies to establish product withdrawal periods (VICH GL48(R)) - February 2015 - Implemented in January 2016
- ✓ Validation of analytical methods used in residue depletion studies VICH GL49(R) - January 2015 - Implemented in January 2016

The two new guidelines

- ✓ **VICH GL 57: Marker residue depletion studies to establish product withdrawal periods in aquatic species - for Consultation at Step 4/end of consultation 15 June 2018 – now ready for signatures at step 4/5**
- ✓ **VICH GL 56: Study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods (MRK) – for Implementation at Step 7 by June 2019**
- ✓ The 2 GLs are “spin-offs” from VICH GL 48 (“Marker residue depletion studies”)
- ✓ It turned out when drafting GL48 that studies in bees and aquatic species are different in too many aspects from mammalian/avian species and deserve consideration on their own

Expected benefits from VICH Metabolism & Residue Kinetics GLs

- Generation of high quality residue and exposure data (“state-of-the-art”)
- review of guidelines at least every 3 years and adaptation to the scientific progress (if needed)
- fewer studies needed (in total), less animals treated and sacrificed– 3R principles
- better use of resources (lower costs)
- better food safety to consumers
- data acc. to VICH GL are also accepted by other relevant international bodies (e.g., JECFA)



VICH GL 57 – Guidance Aquatic Species



Aquatic species considered

Fish

(Finfish, Eel)

Mollusks

(Snails, Clams)

Crustaceans

(Lobster, Shrimp)



VICH GL 57 – Guidance “Aquatic Species”

Scope

- Guidance addresses the recommendations on what should be provided for a **marker residue depletion study design for aquatic species**
- Guidance encompasses **all food-producing aquatic species** (principles of this guidance are also applicable to eggs from aquatic species)
- The GL complements VICH GL 48
- The GL can be used in combination with metabolism studies based on VICH GL 46 in aquatic species to identify a marker residue (although in aquatic species the marker is parent in many cases and total (radiotracer) residue studies are not required in most regions)

Fish Issues – Problems encountered

Drafting a GL for aquatic species complex and and difficult activity:

- more than 50 orders, great species diversity with hundreds of different edible species
- fresh vs salt water species
- environments in which fish are kept are highly variable (e.g. temperature, water quality)



Fish Issues – Problems encountered



- Aquatic species “cold-blooded” (poikilothermic)
- ADME correlated with water temperature (and other variable factors, e.g. oxygen, salinity, physical activity)
- Depletion of residues a function of time AND temperature (i.e. low(er) water temperature will result in lower(er) ADME activity, and vice versa)
- **In theory, each possible water temperature would require a separate study**
- **Number of studies can easily get “infinite” considering the number of species and the possible variability in conditions under which aquatic species are kept**
- **GL focused on the development of key concepts uniform/harmonised study design (rather than on technical details for individual studies)**

Two Key Concepts developed



- 1. Concept of “Worst-Case” study**
- 2. Concept of “Single Order Claim”**

Two Key Concepts developed



ad 1.) Concept of “Worst-Case” study

- ✓ **ONE STUDY** conducted under conditions of the worst case scenario (ideally) **sufficient to determine a withdrawal period**
- ✓ **WORST-CASE** study conducted at **lowest possible temperature**
- ✓ And, sponsor should demonstrate that the study conditions yield the worst case for residues
- ✓ The worst case withdrawal period may then be extrapolated
- ✓ Many regions recognize the concept of “degree days” where the “worst-case withdrawal period” is extrapolated to the “higher” temperature using the degree-day principle (withdrawal time x temperature = constant)
- ✓ it is also possible to provide additional data to further define the withdrawal period under alternate management conditions (e.g., higher temperature)

Two Key Concepts developed



ad 2.) Concept of “Single Order Claim”

- ✓ Study in **ONE REPRESENTATIVE SPECIES** can support a claim for withdrawal periods in an **ORDER**

- ✓ Selection of representative species (Table 2 of GL):
 - *similarity of metabolism assumption between in the same order*
 - *widely cultured in a certain region/country (or closely related to such a species)*
 - *residue depletion studies being able to be carried out at recommended (low) water temperature*
 - *however, residue data in a second species to confirm the withdrawal period recommended*

Orders/Species Single Order Claim



Order	Representative Species	Recommended Temperature (°C)
Salmoniformes	Atlantic salmon (<i>Salmo salar</i>) Coho salmon (<i>Oncorhynchus kisutch</i>) Rainbow trout (<i>Oncorhynchus mykiss</i>)	5-10
Cypriniformes	Carp (<i>Cyprinus carpio</i>) Common bream (<i>Abramis brama</i>)	15-20
Perciformes	European seabass (<i>Dicentrarchus labrax</i>) Hybrid striped bass (<i>Morone saxatilis</i> X <i>Morone chrysops</i>) Red sea bream (<i>Pagrus major</i>) Yellowtail (<i>Seriola quinqueradiata</i>) Walleye (<i>Sander vitreus</i>)	15-20
Scorpaeniformes	Mebaru (<i>Sebastes inermis</i> / <i>Sebastes cheni</i> / <i>Sebastes ventricosus</i>)	10-15
Siluriformes	Channel catfish (<i>Ictalurus punctatus</i>) Mudfish (<i>Clarias anguillaris</i>)	16-21
Osmeriformes	Ayu (<i>Plecoglossus altivelis</i>)	13-18
Anguilliformes	Eel (<i>Anguilla japonica</i>) European eel (<i>Anguilla anguilla</i>)	20-25
Pleuronectiformes	Bastard halibut (<i>Paralichthys olivaceus</i>) Summer flounder (<i>Paralichthys dentatus</i>)	15-20
Tetraodontiformes	Japanese pufferfish (<i>Takifugu rubripes</i>)	13-18
Acipenseriformes	Siberian sturgeon (<i>Acipenser baerii</i>)	14-19
Gadiformes	Atlantic cod (<i>Gadus mohrua</i>)	5-10
Shrimp or prawns in the order of Decapoda	Japanese tiger prawn (<i>Penaeus japonicus</i>) Whiteleg shrimp (<i>Penaeus vannamei</i>)	18-23



Study Design:

Number of fish in study:

- Terrestrial animals 4 per time point (minimum)
- Larger numbers needed for fish due to higher variability
- Residue data from a minimum of **10 animals per time point** are recommended



Study Design (contd):

- Study conducted under commercial growing conditions (or mimicking commercial conditions)
- animals representative of the commercial species/target animal population, if used at various stages of development, then in animals representing the highest development stage
- Animals raised in water that has quality and quantity appropriate for their development stage as per commercial conditions
- If more than one housing condition is used the study should be conducted under conditions that would result in the worst case scenario for tissue residues (up to the sponsor)



Study Design (contd):

Table 1. Critical Study Design Parameters

Critical Parameter	Options	Choice
Water Temperature	High or Low within the test animal's recommended water temperature range	Choose the temperature that results in the worst case for residues
Salinity	Salt or Fresh Water	If applicable choose the one that results in the worst case for residues
Housing	Recirculation or flow-through or net pens	If applicable choose the one that results in the worst case for residues

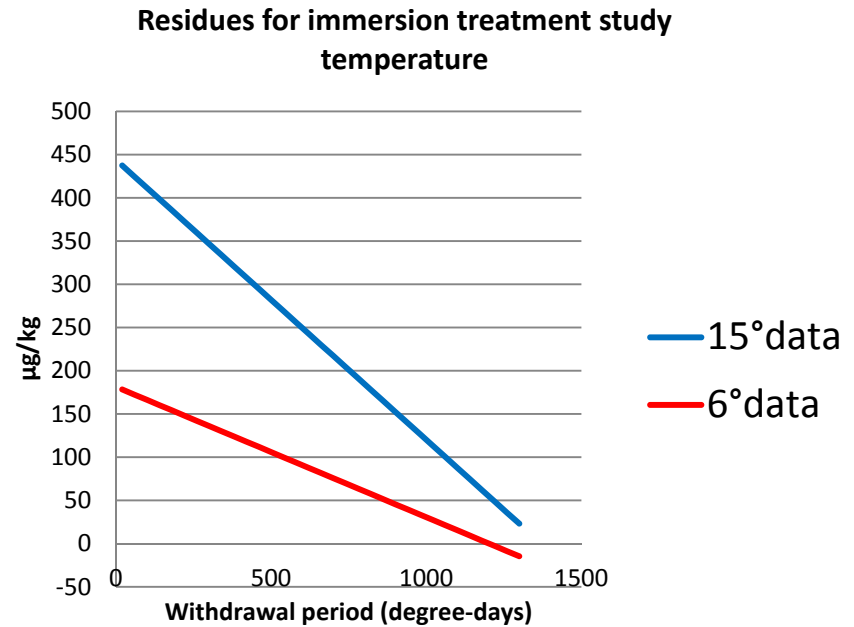
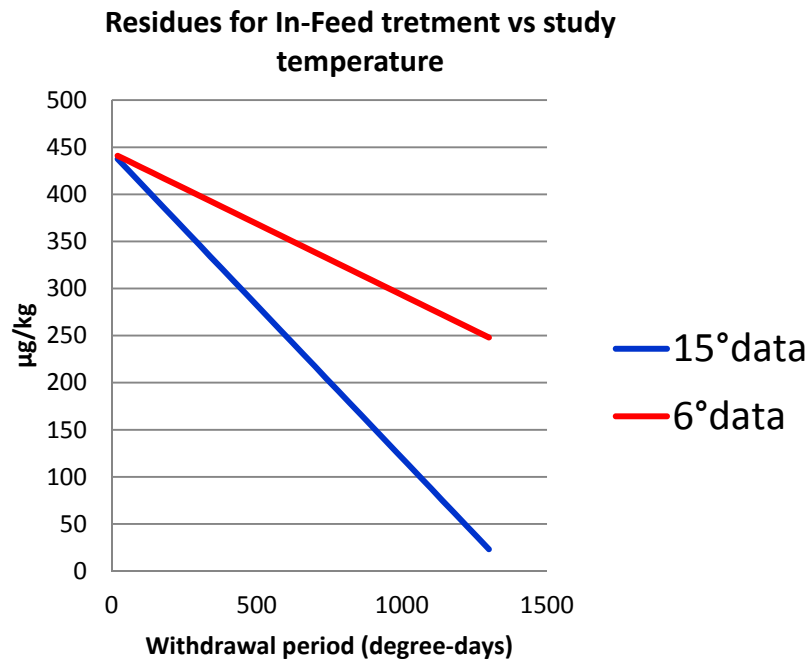


Study Design (contd):

- In-Feed treatment: Acceptance of study in VICH regions if conducted within the lowest range of temperatures
- Injectable treatment: Acceptance of the study in VICH regions if conducted within the lowest range of temperatures
- Immersion treatment: “atypical” absorption behavior possible where high(er) water temperature result in a worst case scenario for tissue residues. Here: sponsor should demonstrate that the conditions of the study yield the worst case for tissue residues



Residue profiles in-feed vs immersion treatment (example)



here: Steepness of slope reverses for immersion treatment



Sampling of (major) edible tissues for aquatic species

Aquaculture Species	Edible Tissue Samples
Fish with edible skin	Muscle including skin in natural proportions, which is the entire fillet with the overlying skin from one or both sides of the fish (scales can be included or excluded based on consumption and practicality of removal)
Fish with inedible skin (Channel catfish, threadsail filefish)	Muscle, which is the entire fillet from one or both sides of the fish
Mollusks	Soft tissue excluding shell.
Crustaceans with hard (inedible) shell	Soft tissue including mid-intestinal gland, excluding shell.
Crustaceans (during molting) with soft (edible) shell	The entire animal including the shell is considered as the edible tissue. The edible tissue for shrimp includes the mid-intestinal gland and shell.



Additional tissues to address specific national/regional requirements:

- Organs of fish and crustacean are generally eaten in certain countries, except fin, scale, and bone
- One additional tissue that has been shown to have the highest concentration or slowest depletion of residue among the tissues of visceral organs or the offal mixture of available liver, kidney, spleen, stomach, and intestine



VICH GL 56 Bees and Honey



VICH GL 56 Bees and Honey



Full title: “Study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods”

Study may be used to:

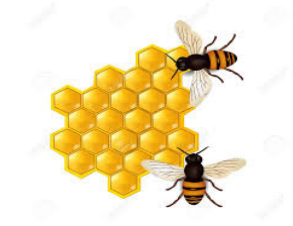
- determine the residues in honey
- generate data suitable for establishment of appropriate Maximum Residue Limits (MRL)
- justify the withdrawal period for a veterinary drug product in accordance with an existing MRL and/or generate data suitable for the establishment of risk-management measures (e.g. use restrictions) in order to address consumer safety concerns

Bee and Honey Issues



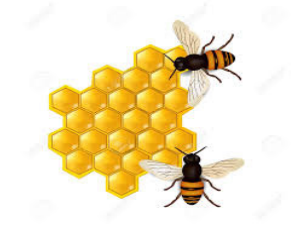
- ✓ Bees (honey) differ in many respects from other food producing species
- ✓ There is practically no (pharmacokinetic) depletion of residues in honeybees and (no/minimal) metabolism of xenobiotics
- ✓ When bees are treated, residue concentrations in honey are reduced mainly by dilution as more honey is produced during the honey flow
- ✓ Honey production rate depends on factors such as temperature, rain, season of the year, climatic zone, food source/type and honeybee species/subspecies.
- ✓ Residue concentrations can be influenced by thermal degradation (as temperature inside the hive reaches 32-36 °C), acidic hydrolysis (honey pH ranges 3.4 – 6.1) or other chemical reactions with honey matrix components

Bee and Honey Issues



- ✓ Metabolic or total residue studies using radiolabelled drugs are not requested for MRL assessment/approval of veterinary drug products used in honeybees
- ✓ It is anticipated that in most cases the (marker) residue to monitor is the parent drug
- ✓ However, additional information is needed on (putative) transformation and/or degradation products
 - *physicochemical properties of the active drug substance and other scientific information can be used to predict possible transformation/degradation*
 - *additional (in-vitro) studies recommended to determine stability of the active ingredient in honey. Variables to be tested include pH, temperature, time and exposure to (UV)-light*
- ✓ If data indicate transformation or degradation, an alternative residue or combination of residues may need to be monitored in the residue study

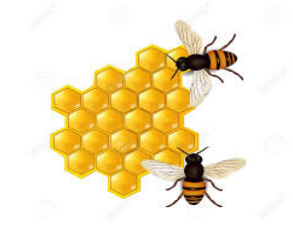
Bee and Honey Issues



The withdrawal period in honey should ideally be “zero” because:

- variables contributing to the residues in honey are difficult to predict and may change from one treatment to another and from one geographical region to another
- difficult to determine a “universally” applicable numerical withdrawal period
- Studies covering a reasonable range of commercially possible treatment situations are needed to support this “zero” withdrawal period

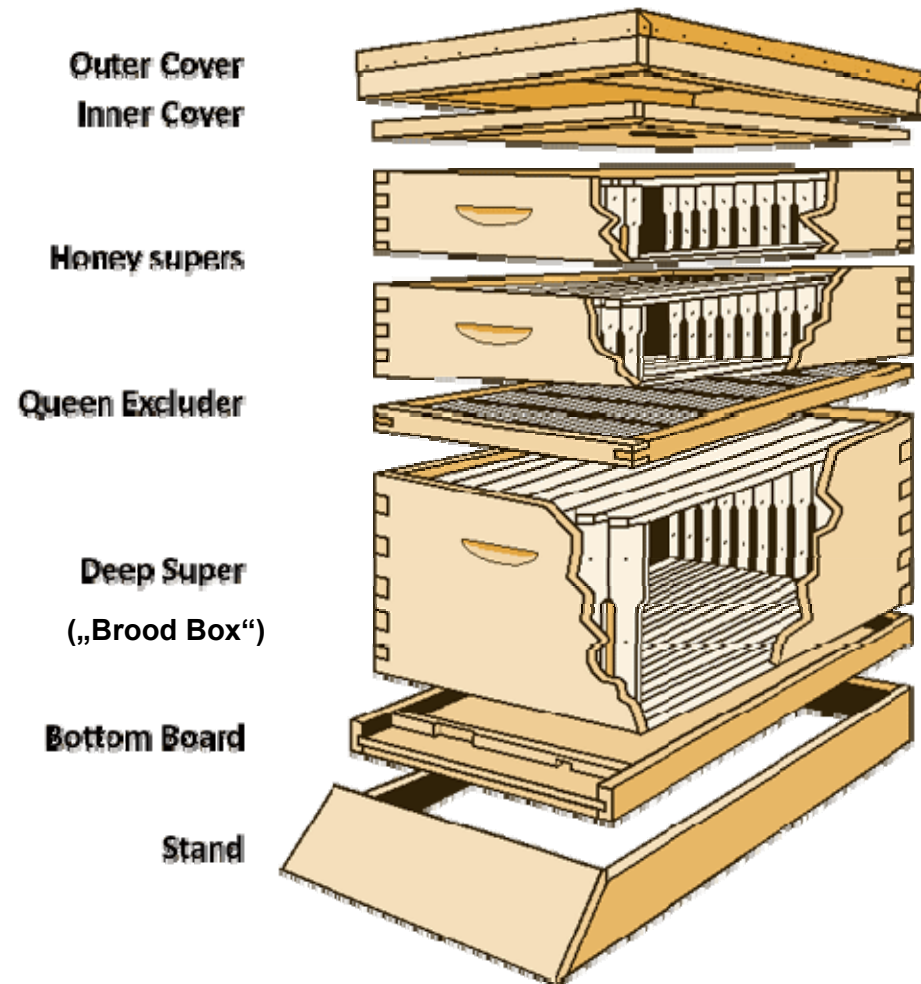
VICH GL 56 Bees and Honey



Study design:

- The test article (the veterinary drug product) used for the study should be representative of the commercial formulation and the design should cover the maximum treatment regimen
- Healthy and strong colonies should be used
- The hives should consist of one brood box only and a super box with frames added at the start of honey flow.
- Neither the colonies, boxes, nor frames should have a history of exposure to the veterinary drug
- Treatments are generally applied once per year after honey harvesting and should be completed before honey flow commences

Structure of beehive



VICH GL 56 Bees and Honey



Study design (contd.)

- Residue studies should be conducted in four sites of differing agro-ecological areas within one or more regions
- Six colonies per site should be treated, resulting in 24 colonies per residue study
- If the residue studies are intended to support an application for a national license, then depending on the country of application (size, variety of landforms and climatic conditions), two to three sites (of differing agro-ecological areas) may be considered sufficient

New sampling concept developed



Worst case design:

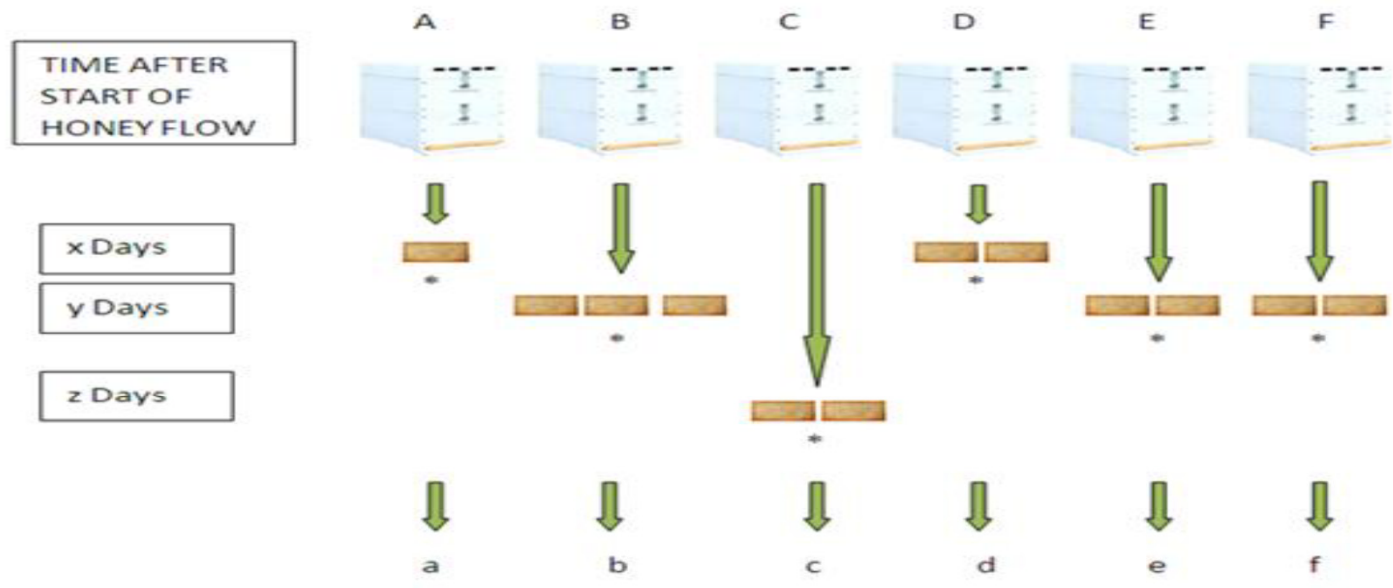
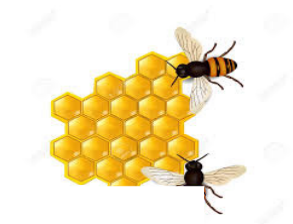
- **A single sampling time point** per colony is considered appropriate
- This is the **first time point when honey from a colony is ready to be harvested for human consumption** (only super honey from one or more frames)
- Honey harvest refers to the collection of honey from the honeycombs once they are filled with capped honey; at least 75% of the honeycells in a frame should be filled and capped

New sampling concept developed



- The honey is extracted, filtered, mixed to produce **one pooled sample for each colony**
- Sample processing (all activities after sampling and up to analysis) should take into account the stability properties of the residues
- For lipophilic compounds pooled wax sample collected per site from the last colony harvested (lipophilic = $\log K_{ow} \geq 3$)
- In cases of veterinary drug products that could be used during the honey flow, the basic study design should be followed. *Here:* The sponsor should provide justification for modifications to the basic study design. Points to consider are transfer of the veterinary drug to existing and newly produced honey

New sampling concept developed



$x \text{ days} < y \text{ days} < z \text{ days}$

*: Number of frames collected per hive

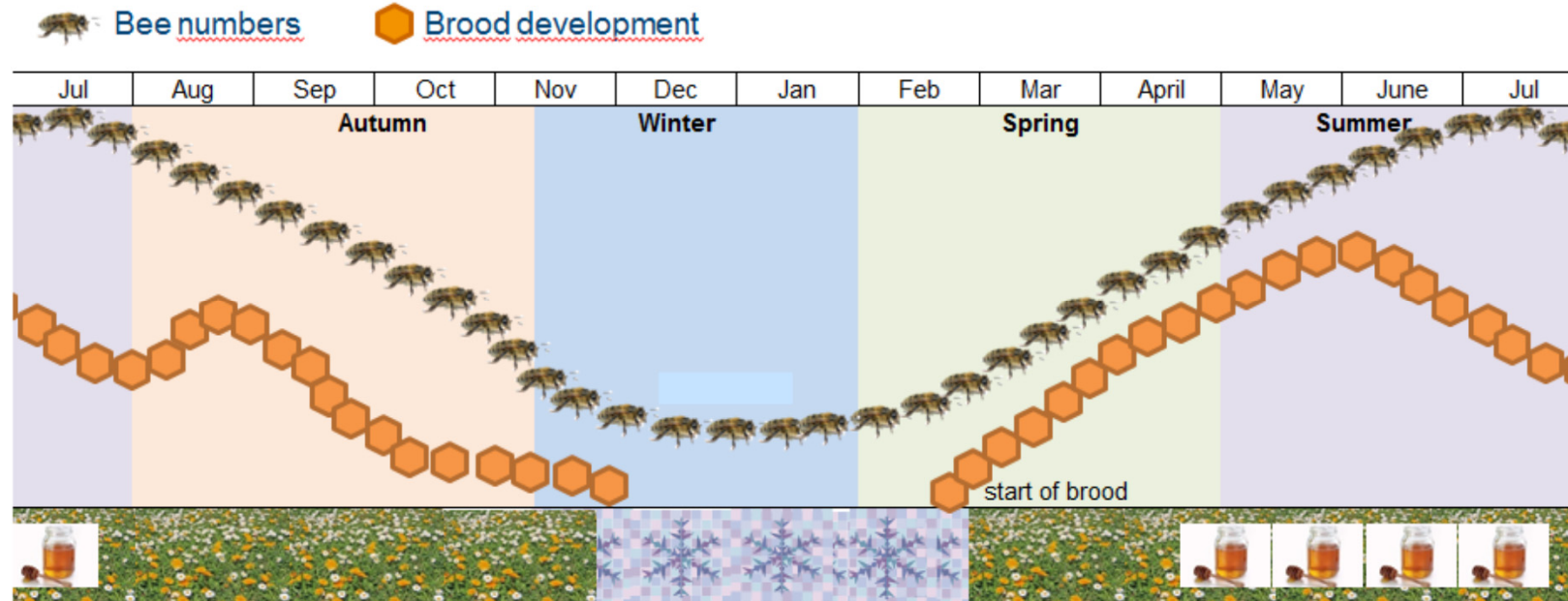
a-f: Pooled honey samples from the collected frames of each hive

Under 2.3.6.2. (lipophilic compounds) a pooled wax sample should be collected following honey extraction of c honey sample, as in this figure C colony is the last colony harvested

- A single sampling time point per colony (when honey from colony is mature)
- First honey harvest considered the worst case
- Number of mature honeycombs per colony usually varies from hive to hive



Insertion: Bee numbers and honey harvest in different seasons



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Thank you for your attention!

