Information Sheet on How to Determine Withdrawal Periods

Setting a withdrawal period is a multi staged scientific process.

**STEP 1**
Identify NO(A)EL (No Observed (Adverse) Effect Level)
The highest dose that does not cause adverse effects is identified.

**NO(A)EL**

**STEP 2**
Determine the ADI (Acceptable Daily Intake)
Estimated by dividing the NO(A)EL by an “uncertainty” factor to allow for variables.

**ADI**

**STEP 3**
Establish MRLs (Maximum Residue Limits)
The ADI is divided between edible tissues and foodstuffs. A limit for residues is set for each tissue and foodstuff to establish MRLs ensuring that the ADI is not exceeded.

**MRLs**

**STEP 4**
Determine Withdrawal Periods
The rate at which residues deplete (after treatment) to below the MRLs in all edible tissues and foodstuffs is measured and the withdrawal period calculated.

**Withdrawal Period**
The first 3 steps of this scientific process are conducted at a European level by the European Medicines Agency (EMEA). The VMD is involved in this work as the UK’s Veterinary Medicines Regulatory Agency and member of the EU Committee for Medicinal Products for Veterinary Use (CVMP). Step 4 is conducted both at National and European levels and the VMD is involved in the determination of withdrawal periods for all veterinary medicinal products authorised for use in the UK.

**Step 1 Identify NO(A)EL (No Observed (Adverse) Effect Level)**

A range of scientific studies (in laboratory animals) is conducted using the active substance that will be used in a veterinary medicinal product and from the results of these studies the highest dose (of the active substance) that does not cause observed adverse effects is identified; this is referred to as the No Observed (Adverse) Effect Level or NO(A)EL.

**Step 2 Determine the ADI (Acceptable Daily Intake)**

The NO(A)EL is divided by an “uncertainty factor”, typically 100-1000. This uncertainty factor is to allow for extrapolation between species and differences between individuals and compensate for other uncertainties in the data. The figure determined is referred to as the Acceptable Daily Intake or ADI. The ADI is the amount of a residue that is considered safe for a person to eat every day over a lifetime.

**Step 3 Establish MRLs (Maximum Residue Limits)**

The Maximum Residue Limit (MRL) is then set by dividing the ADI amongst all the edible tissues (muscle, liver, kidney fat/skin) and edible products, (milk, eggs, honey), taking account of:

- how much of a particular food may be eaten each day: this is called the “food basket”
- how much of the active substance and/or its metabolites occur in each food substance, i.e. how it is distributed in the animal's body
- how and how much of the active substance is metabolised in the animal's body
- identifying the appropriate “marker” for intake calculations – this may be the parent compound or a metabolite; this is referred to as the “marker residue”.

A limit is then set for the marker residue in each edible tissue and edible product ensuring that the ADI is not exceeded – these limits are the MRLs.

**Step 4 Determine Withdrawal Periods**

The time that must elapse after the last treatment of a veterinary medicine before an animal can be slaughtered, or the animal product can be taken, for human consumption is calculated from data collected in scientific studies. These studies determine how rapidly the marker residue is depleted from edible tissues and edible products and how quickly the levels of the marker residue fall to below the MRLs. Sometimes an “uncertainty factor” is included in the determination to allow for inconsistencies in the data and differences between individual animals. This period of time is referred to as the Withdrawal Period. A withdrawal period is set for each veterinary medicinal product intended to be used in food producing species so that the residues in each food will be below the relevant MRL and, therefore, ensure no risk to consumer health.