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ELEMENTAL IMPURITIES STATEMENT

TO WHOM IT MAY CONCERN

With the purpose to identify the potential elemental impurities present in **PYRANTEL PAMOATE API**, has been consulted the ICH Q3D (step 4, December 2014) and the compendia general chapters USP <232> and <233>. Both, the guideline and general chapters, describe the elements that should be considered in the quality risk analysis in order to ensure product compliance.

According to ICH Q3D, different potential sources of metal impurities must be assessed. These sources are: metals intentionally added, metals known or suspected being present (contaminants or naturally occurring), metals known or suspected being introduced from equipment and metals that are known or suspected of being leached from container closure systems. Similarly, USP <232> also refers to these kinds of potential sources. Regarding metals coming from the container closure systems, ICH Q3D describes that the probability of metal leaching into solid dosage forms is minimal and it is not required further consideration in the assessment.

Hence, regarding manufacturing process of **PYRANTEL PAMOATE API**, the following considerations must be taken into account:

1. The administration route is **oral**
2. No elemental impurities are added intentionally to the process in the final steps. In the synthetic routes of starting materials the following metal reagents are used: **Cd, As, Pb, Hg** (Class 1) **Co, V, Ni** (Class 2A).
3. Regarding the potential elemental impurities from the environment pollution risk: **Cd, As, Pb, Hg** (Class 1), **Co, Ni, V** (Class 2A)

Regarding the potential elemental impurities from UQUIFA manufacturing equipment: According to the Quality Risk Assessment "QRA-ING-16-001", the list of elements contained in the materials of the process equipment at concentrations higher than 0.5% are the following: : **Co, Ni, V** (Class 2A), Cr, Mo (Class 3), Al, Fe, Mn, W (Other Elements).

Considering that the class 3 elements do not need to be considered during the risk assessment if they have not been intentionally added and that the guideline do not describe limits for "Other Elements", the elements coming from the manufacturing equipment that will be included in the assessment are: **Co, Ni, V.**

A method (ICP-MS, Inductively Coupled Plasma - Mass Spectrometry) to determine elemental impurities content in **PYRANTEL PAMOATE** has been developed. The purpose of the study was to demonstrate that every elemental impurity required (Class 1 and 2A) is below the 30% of the PDE indicate by ICH Q3D Guideline, considering a **Maximum Daily Intake of 1000 mg** of product and the intended route administration, **oral**. The limit set for each element, performing the required calculations are in the table below. The evaluation has comprised the study of the following parameters:

a) Specificity, demonstrated by the accuracy results at the limit concentrations and the evaluation of blanks (set at 30% of the PDE).

b) Limit of Detection, verified at 50% of the limit concentration, in this case 15% of the PDE.

Therefore, taking into account all the considerations previously exposed, the potential elemental impurities analysed in three representative batches of **PYRANTEL PAMOATE** is the following:

Element	LIMIT OF CONCENTRATION (30% of the PDE)	LIMIT OF CONCENTRATION (30% of the PDE)	LIMIT OF DETECTION -LOD- (15% of the PDE)	RESULTS OF 3 BATCHES
	µg/día	ppm		
Cd	1.5	1.5	0.8	≤ LOD
Pb	1.5	1.5	0.8	≤ LOD
As	4.5	4.5	2.3	≤ LOD
Hg	9	9	4.5	≤ LOD
Co	15	15	7.5	≤ LOD
V	30	30	15.0	≤ LOD
Ni	60	60	30.0	≤ LOD

September 4th, 2018

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