

Alcobendas, October 13<sup>th</sup>, 2016

Dear Customer,

With the objective of aiding your efforts in assessing compliance with the ICH guideline Q3D on elemental impurities, Qualicaps Europe, S.A.U. and Qualicaps Romania, S.R.L. have completed an evaluation of elemental impurities that could be present in our capsule products, Quali-G<sup>™</sup> and Quali-V<sup>®</sup>, considering as potential sources raw materials as well as the manufacturing process and equipment. As a reminder, the ICH guideline Q3D went into effect for new marketing authorization applications this past month of June, while it will be instituted for authorised medicinal products in December of 2017.

The following are the summarized conclusions of our assessment:

- Neither of the Class 1, 2, 3 elements as defined by the International Conference on Harmonisation (ICH) Guideline for Elemental Impurities Q3D, nor metal catalyst or reagents are used in the manufacturing process of Empty Hard Shell Capsules (Quali-G<sup>™</sup> and Quali-V<sup>®</sup>) at Qualicaps Europe, S.A.U. and Qualicaps Romania, S.R.L.
- A limited number of representative capsule formulations were analysed and in all cases Class 1, Class 2A and Class 3 elements were below the amounts reported in the *Permitted Oral Concentrations of Elemental Impurities* for Option 1 from the guidance document.
- Both Qualicaps Europe, S.A.U. and Qualicaps Romania, S.R.L. will perform process monitoring for the elements listed as Class 1, Class 2A and Class 3. The limits for the monitoring tests have been established according to the amounts reported in the *Permitted Oral Concentrations of Elemental Impurities* for Option 1 from the guidance document:
  - Class 1 elements: cadmium, lead, arsenic and mercury → limits of 0.5, 0.5, 1.5 and 3.0 ppm, respectively.
  - Class 2A elements: vanadium, cobalt and nickel → limits of 10, 5 and 20 ppm, respectively.
  - Class 3 elements: lithium, antimony, barium, molybdenum, copper, tin and chromium → limits of 55, 120, 140, 300, 300, 600 and 1100 ppm, respectively.

I hope you find this information satisfactory; however, should you require further assistance, please do not hesitate to contact Qualicaps<sup>®</sup>.

Attentively,



Federico García Sagrado, PhD  
Vice President of QC/QA & Regulatory, EMEA