Dear Sir or Madam,

Today we would like to provide further information about the following topics:

We are at your disposal, should you require assistance or have further questions.

Best regards

The DiaMed Team

1 REVISED ICH Q3D GUIDELINE ON ELEMENTAL IMPURITIES

On April 26, 2022, Revision 2 of the ICH Guideline for Elemental Impuritis (Q3D) was adopted. The last revision concerned

- corrections (increases) of the PDEs for gold, silver and nickel (see Table 1) and
- the addition of appendix 5 to establish limits for elemental impurities by the cutaneous and transcutaneous route

The cutaneous PDEs given in Table A.5.1 of the Guideline are greater than or identical to the oral PDEs. In order to take into account sensitization effects on cobalt and nickel, a cutaneous and transcutaneous concentration limit (CTCL) of 35 µg/g was defined for each of these elements, which must be taken into account in the risk analysis.

Table 1: PDE changes from Revision 1 to Revision 2

Element	Class	Oral PDE µg/day	Parenteral PDE µg/day	Inhalation PDE µg/day
Ni	2B	200	20	~~5~~ 6
Au	2B	~~100~~ 300	~~100~~ 300	~~1~~ 3
Ag	2B	150	~~10~~ 15	7

2 EXTENSION OF THE REPORTING OBLIGATION IN THE LUCID PACKAGING REGISTER TO ALL PACKAGING

As already mentioned in previous circulars (October 2017 and September 2018), manufacturers have been obliged since 1 January 2019 to register with the Central Packaging Register (ZSVR) in the LUCID packaging register before distribution of packaged goods and to transmit data on packaging relevant to system participation.
From 1 July 2022, this registration obligation will be extended to all packaging - including packaging that is not subject to system participation, such as

- Transport packaging
- Sales and outer packaging that typically does not occur as waste by end users after use
- Sales and outer packaging for which system participation is not possible due to system incompatibility according to section 7 subsection 5
- Sales packaging of products containing harmful substances
- Reusable packaging

If producers have not met this registration requirement by then, their packaged goods must no longer be distributed in Germany from above date.
For further information see Registration at a glance (verpackungsregister.org)

3 ORDINANCE AMENDING THE ORDINANCE ON MEDICINAL PRODUCT WARNING (ARZNEIMITTEL-WARNHINWEISVERORDNUNG) PUBLISHED

On April 29, 2022, the Ordinance Amending The Ordinance On Medicinal Product Warnings (Arzneimittel-Warnhinweisverordnung Amwarnv) And The Pharmacy Operating Regulation (Apothekenbetriebsordnung Apbetro) was published in the Federal Law Gazette.

The AMWarnV has so far nationally regulated the application of a warning label if medicinal products contain the substances ethanol (from a quantity of 0.05 g per single dose) for internal use in humans or tartrazine for use in humans. The wording of the AMWarnV deviates in some points from the Excipients

Guideline, which specifies uniform texts at European level, and no longer represents the state of scientific knowledge.

Therefore, in the future, the requirements for the application of the warnings are to be regulated exclusively by the provisions of the Excipients Guideline and the national "Besonderheitenliste" published by BfArM. For this purpose, there will be a joint announcement of the BfArM and the PEI, which will be published in the Federal Gazette.

The current regulations will now be replaced by two transitional regulations and one regulation on expiry. The amending ordinance to the AmWarnV and the ApBetrO will enter into force on June 1, 2022. A revised version of Besonderheitenliste is expected no later than June 1, 2022.

According to the transitional periods stipulated in the updated regulations, pharmaceutical entrepreneurs may continue to market finished medicinal products bearing a warning label in accordance with the AMWarnV on the date of entry into force of this ordinance for three years after the ordinance enters into force.

In concrete terms, this means that finished medicinal products bearing a warning label in accordance with the provisions of the AMWarnV on June 1, 2022, in the version applicable on May 31, 2022, may continue to be placed on the market with this warning label by the pharmaceutical entrepreneur up to and including June 30, 2025. Wholesalers and pharmacies may continue to place them on the market after this date.