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ETAD note on Standard EN ISO 10993
Information on cytotoxicity of colorants used in medical devices

Background

The Standard EN ISO 10993:1 "Biological evaluation of medical devices document" specifies the general principles governing the biological evaluation of medical devices within a risk management process as well as the correct evaluation of existing data/creation of new ones.
An important requirement of the safety of medical devices regards the cytotoxicity; according to EN ISO 10993:1 "cytotoxicity tests employing cell culture techniques can be used to determine the cell death (e.g. cell lysis), the inhibition of cell growth, colony formation, and other effects on cells caused by medical devices, materials and/or their extracts. If testing is performed, it shall be conducted in accordance with ISO 10993-5".

Information on colorants' cytotoxicity

The tests described in ISO 10993-5 are only applicable to the final article, i.e., the medical device itself, since they need that the specific cultured cells are in contact with a device and/or extracts of a device either directly or through diffusion.
Nevertheless, **colorant manufacturers can provide useful information** on the cytotoxic properties of their products based on the results from the testing of substance-specific endpoints. Even though cytotoxicity is not usually determined as single endpoint, this information is provided as part of in vitro studies, where different cell lines are used. These methods are also officially recognised. Some **examples** are:

- In Vitro Bacterial Reverse Mutation Test (OECD 471)
- In Vitro Mammalian Chromosomal Aberration Test (OECD 473)
- In Vitro Mammalian Cell Gene Mutation Tests using the Hprt and xprt genes (OECD 476)
- In Vitro Mammalian Cell Micronucleus Test (OECD 487)
- Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells in vitro (OECD 482)
- In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene (OECD 490)

Any additional information from available studies/literature can also be provided, if helpful to clarify the colorants cytotoxicity.

Recommendations for colorant manufacturers

If colorants manufacturers are requested by their customers about the cytotoxicity of their products, we thus **recommend providing an overview of relevant information from existing sources**. This will assist the medical devices manufacturers in fulfilling their obligations, since the final medical device still must prove compliance to its specific standard according to the prescribed requirements.