European Federation of Pharmaceutical Industries and Associations

Deletion of test for abnormal toxicity from European pharmacopoeia

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About EFPIA

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 42 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world.

EFPIA Response

On 3 April 2017, the European Pharmacopoeia Commission asked for public feedback on its proposal to remove the requirements for a test on abnormal toxicity (ATT) from 49 monographs of the European Pharmacopeia.

EFPIA is fully supportive of this proposal because of the following key reasons, which were already published by EFPIA as a position paper (1) in 2013/2015:

- The Abnormal Toxicity Test (ATT) was developed at a time (early 1900s) when production processes and quality control for biological products was only poorly established (2). In today's modern pharmaceutical production and manufacturing facilities defined and specific quality measures to control and detect contaminants are in place in compliance with Good Manufacturing Practice (GMP) (2).
- From a scientific point of view, an *in vivo* ATT to identify potentially harmful batches is highly questionable. Numerous reviews of historical test results have revealed that no reliable

conclusions can be drawn from ATT (3, 4). Furthermore, the ATT cannot be validated according to today's validation characteristics such as specificity, reproducibility and detection limit. The test is highly variable, has issues with intra- and inter-laboratory reproducibility, and lacks specificity (2, 3).

- The requirement of ATT causes unjustified use for a substantial number of animals without any benefit with regards to demonstrating product safety. Using live animals in ATT does not comply with animal welfare and the 3Rs principle because of lack of a sound scientific rationale and justification.
- Last, but not least, various organizations and regulatory agencies have removed the request for ATT. (a) ATT has no longer been mandatory in the monographs of the European Pharmacopoeia for vaccines, sera and antibiotics (5,6). (b) US FDA has removed the general safety test (GST, = abnormal toxicity test in US) requirements for biological products as being both outdated and not supported by data (7).

References

1. EFPIA, position paper: rationale for removing abnormal toxicity testing (22 June 2015)
2. Garbe, JHO et al. (2014). Historical Data Analyses and Scientific Knowledge Suggest Complete Removal of the Abnormal Toxicity Test as a Quality Control Test. J. Pharm. Sci. 103: 3349-3355.
3. Kraemer, B et al (1996). Is the abnormal toxicity test still relevant for the safety of vaccines, sera and immunoglobulins?. ALTEX 13(1):7–16.
4. Duchow, K and Kramer B (1994). Abnormal toxicity - a relevant safety test under GLP- and GMP-conditions in the production of vaccines? ALTEX 11 (5).
5. EDQM: Updated Work Programme of the European Pharmacopoeia (June 2016)
6. Schwanig M et al (1997). Elimination of abnormal toxicity test for sera and certain vaccines in the European Pharmacopoiea. Vaccine 15: 1047-1048.
7. US FDA. Rules and Regulations. Implementation of revocation of general safety test regulations that are duplicative of requirements in biologics liscense applications. Federal register 80: 127, 2 July 2015.


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