PROPOSAL TO DISCONTINUE THE TEST
FOR UNDUE TOXICITY (CHAPTER 3.7)
IN THE INTERNATIONAL PHARMAPOEIA
(September 2019)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (schmidt@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by 10 October 2019.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link. If you wish to receive our draft guidelines, please send your email address to jonesi@who.int and your name will be added to our electronic mailing list.

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### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/19.822:

**PROPOSAL TO DISCONTINUE THE TEST FOR UNDUE TOXICITY**

*(CHAPTER 3.7) IN THE INTERNATIONAL PHARMACOPOEIA*

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<td>First draft prepared.</td>
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<td>Discussion at the informal Consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines.</td>
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<td>Presentation to the WHO Expert Committee on Specifications for Pharmaceutical Preparations.</td>
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PROPOSAL TO DISCONTINUE THE TEST FOR UNDUE TOXICITY
(CHAPeROF 3.7) IN THE INTERNATIONAL PHARMAPOEIA

At its Sixty-ninth meeting, held from 29 October to 2 November 2018, the World Health Organization (WHO) Expert Committee on Biological Standardization (ECBS) recommended to discontinue the inclusion of the innocuity test in future WHO documents on vaccines and other biologicals to be published in the Technical Report Series (TRS) (including WHO recommendations, guidelines and manuals). In addition, the inclusion of this test in previously published WHO TRS documents should be disregarded:

The scientific rationale and evidence for performing the innocuity test (also called the “abnormal toxicity test” or “general safety test”) as a measure of the safety of vaccines and other biological products, for the purpose of marketing authorization and lot release, were discussed by the Expert Committee. Current manufacturing processes, which include the implementation of Good Manufacturing Practices (GMP) and comprehensive quality control measures (including in-process controls), were considered to be more appropriate than the innocuity test in assuring the quality and safety of vaccines and other biological products. The Expert Committee reviewed the historical inclusion of the innocuity test in the documents published in the WHO TRS and concluded that its complete omission would not compromise the quality and safety of vaccines and other biological products. Therefore, the Expert Committee recommends the discontinuation of the inclusion of the innocuity test in all future WHO recommendations, guidelines and manuals for biological products published in the TRS, and that a clear indication be made in its report that the inclusion of this test in previously published WHO TRS documents be disregarded.¹

The principle of the test consists of injecting the product under investigation into guinea pigs and/or mice. The sample passes the test if no animal shows any signs of illness, relevant body weight changes or dies within a certain period. The exact test design and name varies between the different pharmacopoeias and requirements.

¹ Text reproduced from main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 29 October to 2 November 2018 (https://www.who.int/biologicals/expert_committee/ECBS_Executive_Summary_final_20_NOV_2018.1K.pdf?ua=1).
In *The International Pharmacopoeia*, the test is referred to as the test for undue toxicity (chapter 3.7) and stipulated in the monographs on Kanamycin acid sulfate and Kanamycin monosulfate.

Following the decision of the WHO Expert Committee on Biological Standardization (ECBS), it is proposed to omit chapter 3.7, “Undue Toxicity” in *The International Pharmacopoeia* and its reference in the monographs on Kanamycin acid sulfate and Kanamycin monosulfate (see below: changes from the current text/monographs are indicated by *insert* or *delete*). Users of *The International Pharmacopoeia* are invited to provide their comments on this proposal.

### 3.7 Undue toxicity

The test is used to determine the absence of undue toxicity of antibiotics intended for parenteral administration.

#### Recommended procedure

Use healthy mice of a single strain that have not previously been used for any test. Select 5 mice, each weighing between 18 g and 22 g. Prepare the solution of the test substance as specified in the monograph. Inject a test dose of 0.5 mL intravenously into a tail vein at a uniform rate, the injection occupying 5 seconds. Keep the mice under observation for 48 hours after the injection. The product meets the requirements for freedom from undue toxicity if no animal dies within 48 hours.

If 1 or 2 mice die within the observation period, repeat the procedure once, using respectively 5 or 15 mice, healthy and not previously used for any test, each weighing between 19.5 g and 20.5 g. The product under test meets the requirements for freedom from undue toxicity if no animal dies in the repeat test within the observation period (48 hours).
Monograph on Kanamycin acid sulfate

Manufacture

Kanamycin acid sulfate is produced by methods of manufacture designed to eliminate or minimize substances lowering blood pressure. The method of manufacture is validated to demonstrate that the product, if tested, would comply with the test as described under 3.7 Undue toxicity, using 0.5 mL of a solution containing 2 mg per mL.

Monograph on Kanamycin monosulfate

Manufacture

Kanamycin monosulfate is produced by methods of manufacture designed to eliminate or minimize substances lowering blood pressure. The method of manufacture is validated to demonstrate that the product, if tested, would comply with the test as described under 3.7 Undue toxicity, using 0.5 mL of a solution containing 2 mg per mL.

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