3.6 TEST FOR HISTAMINE-LIKE SUBSTANCES
(VASODEPRESSOR SUBSTANCES)

Draft proposal for revision in The International Pharmacopoeia
(August 2020)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmith@who.int) by 18 September 2020.

Working documents are sent out electronically and they will also be placed on the WHO Medecines 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 e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/20.856:

3.6 TEST FOR HISTAMINE-LIKE SUBSTANCES
(VASODEPRESSOR SUBSTANCES)

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<td>Proposal drafted base on a recommendation made at the Consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.</td>
<td>May 2020</td>
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<td>Draft proposal sent out for public consultation.</td>
<td>August-September 2020</td>
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<tr>
<td>Presentation to the 55th WHO Expert Committee on Specifications for Pharmaceutical Preparations.</td>
<td>October 2020</td>
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<td>Further follow-up action as required.</td>
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[Note from the Secretariat. Comments are sought on the proposal to suppress chapter 3.6 Test for histamine-like substances (vasodepressor substances) in The International Pharmacopoeia and the references to this chapter in the monographs on Bleomycin sulfate, Spectinomycin hydrochloride, Streptomycin sulfate. The proposals follows the strategy to phase-out animal testings where possible and justified.

The test for vasodepressor substances is carried out in cats by comparing the depression of arterial pressure caused by the test solution with that obtained after administration of a solution of histamine.

Changes from the current chapter are indicated in the text by insert or delete.]
3.6 TEST FOR HISTAMINE-LIKE SUBSTANCES
(VASODEPRESSOR SUBSTANCES)

3.6 Test for histamine-like substances (vasodepressor substances)

The test for vasodepressor substances is carried out in cats by comparing the depression of arterial pressure caused by the test solution with that obtained after administration of a solution of histamine.

Recommended procedures

Use healthy, adult cats, either males or non-pregnant females.

Determine the weight of the animal and place under general anaesthesia by injection of chloralose R or a suitable barbiturate that allows the maintenance of uniform blood pressure.

Protect the animal from loss of body heat and maintain it so that the rectal temperature remains within physiological limits. Introduce a tube into the trachea. Surgically expose the common carotid artery and by blunt dissection separate it completely from all surrounding structures, including the vagus nerve. Insert a cannula filled with heparinized saline TS into the artery and connect it to a mercury manometer or another suitable device arranged for making a continuous record of blood pressure. Surgically expose the jugular or the femoral vein and insert into it another cannula filled with heparinized saline TS through which can be injected solutions of histamine and of the test substance.

Determine the sensitivity of the animal to histamine in the following way: Start the recording kymograph or a similar recording device and inspect the tracings for amplitude of excursion and relative stability of blood pressure. Inject into the jugular or femoral vein histamine TS, in doses of 0.05 μg (dose A), 0.1 μg (dose B) - repeated at least 3 times - and 0.15 μg (dose C) of histamine base per kg of animal weight. Administer the second and subsequent injections not less than 1 minute after the blood pressure has returned to the level recorded immediately before the previous injection. Repeat this series of injections until, disregarding the first series of readings, a relatively uniform decrease in blood pressure is obtained after doses B of histamine. The animal should be used for the test only if the decrease after doses B is not less than 2.7 kPa.
(20-mm Hg) and, moreover, if dose A causes smaller responses than doses B whereas dose C gives greater responses than doses B.

Prepare the test solution as described in the monograph. During the course of the test, take care to maintain a uniform rate of injection for both the test solution and the standard solution. If the jugular vein is used, care should also be taken that the injection of test solution and histamine standard are given in equal volumes to avoid volume effects on blood pressure. When a common cannula is used for both the standard and test solutions, each injection of the standard and test solution should be immediately followed by an injection of approximately 2.0 mL of saline TS to flush any residues from the tubing.

Inject a dose B of the standard solution followed by an injection of the specified amount of the test solution and then another dose B of the standard solution. The second and third injections are given not less than 1 minute after the blood pressure has returned to the level recorded immediately before the preceding injection. If the response to the test solution is greater than that given previously by dose A, repeat the series of injections twice and conclude the test by giving dose C of standard solution. If the response to dose C is not greater than that to dose B, the test is invalid.

The animal may be used in the test as long as it remains reasonably stable and responsive to histamine and provided that (a) an injection of test substance did not cause a greater depressor response than that caused by dose C and (b) the response to dose C of the standard solution given after the administration of the test substance does not become lower than the mean response to doses of B previously injected.

The substance passes the test if the response or the mean of the responses after the injection of the amount specified in the monograph is smaller than the mean of the corresponding responses to dose B of the standard solution (0.1 μg of histamine base per kg of animal weight), and no one single dose of the test solution causes a greater depressor response than dose C of the standard solution (0.15 μg of histamine base per kg of animal weight).
Reference to 3.6 Test for histamine-like substances in monographs:

**Bleomycin sulfate (Bleomycini sulfas)**

**Manufacture.** The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

**Histamine-like substances.** Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using 1 mL per kg of body mass of a solution in saline TS containing a quantity equivalent to 500 IU per mL.

**Spectinomycin hydrochloride (Spectinomycini hydrochloridum)**

**Histamine-like substances.** Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using 1 mL per kg of body mass of a solution in saline TS containing 25 mg of the substance to be examined per mL.

**Streptomycin sulfate (Streptomycini sulfas)**

**Manufacture.** The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

**Histamine-like substances.** Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using, per kg of body weight, a solution containing 3 mg of streptomycin base in 1 mL of saline TS.

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