§ 650.1

Subpart A—Diphtheria Toxin for Schick Test

§ 650.1 Diphtheria Toxin for Schick Test.

The proper name of this product shall be Diphtheria Toxin for Schick Test, which shall be a preparation of a diphtheria toxin obtained from the growth of Corynebacterium diphtheriae.

§ 650.2 U.S. Standard preparation.

The U.S. Standard Diphtheria Toxin for Schick Test shall be used to determine the Schick test dose of the product. The Schick test dose of the standard is that amount of the standard that, when mixed with 0.001 unit of the U.S. Standard Diphtheria Antitoxin and injected intradermally in a guinea pig, will induce an erythematous reaction of 10 mm. in diameter.

§ 650.3 Manufacture of Diphtheria Toxin for Schick Test.

(a) Propagation of bacteria. The culture medium for propagation of the Corynebacterium diphtheriae for preparation of the parent toxin shall not contain ingredients known to be capable of producing allergenic effects in human subjects.

(b) The parent toxin. Diphtheria Toxin for Schick Test shall be prepared from a parent toxin which has been demonstrated to be stable and which contains no less than 400 minimum lethal doses per milliliter or 400,000 minimum reaction doses per milliliter. A minimum lethal dose is the smallest amount of toxin that will kill a guinea pig weighing approximately 250 gm. on the fourth day after its subcutaneous injection. A minimum reaction dose is that amount of toxin which when injected intradermally into a guinea pig induces an erythematous reaction 10 mm. in diameter.

§ 650.4 Potency test.

The dermal reactivity of each lot of the product shall be determined from the results of simultaneous guinea pig intradermal potency tests of the product under test and of the standard. The test shall be performed as follows:

(a) Guinea pigs. At least four healthy female guinea pigs shall be used, all of the same strain and each of a size that will permit a random distribution of eight intradermal injections. The hair shall be removed from the back and both sides of each guinea pig without producing abrasions of the skin. The denuded skin of each animal shall be sectioned into four equal areas at right angles to the vertebral column to provide two injection sites in each of the four areas, one on each side of the vertebra. The test is not valid if the guinea pigs do not show a graded response to the graded dilutions of the Schick test dose of the standard toxin.

(b) Preparation of the test doses. Four dilutions, two of the product under test and two of the U.S. Standard Diphtheria Toxin for Schick Test, shall be prepared in sterile buffered saline pH 7.4 containing 0.2 percent gelatin. The low and high dilutions of the standard shall be those amounts of a Schick test dose of the standard which in a dose of 0.1 ml. are capable of eliciting graded erythematous dermal reactions between 10 mm. and 20 mm. in diameter. The low and high dilutions of the Schick test dose of the toxin under test shall be the same as those of the standard toxin and estimated to have the same dermal reactivity.

(c) Inoculation. The low and high dilutions of the product (chart designation P_L and P_H) and the low and high dilutions of the standard (chart designations S_L and S_H) shall be injected intradermally in a volume of 0.1 ml. into each of the four guinea pigs according to the following scheme, or in another scheme, provided it will permit comparable randomization of injection sites:

<table>
<thead>
<tr>
<th>Area</th>
<th>Guinea Pig Number</th>
<th>Left</th>
<th>Right</th>
<th>Left</th>
<th>Right</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>S_L</td>
<td>S_H</td>
<td>S_L</td>
<td>S_H</td>
<td>P_L</td>
<td>P_H</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>S_H</td>
<td>S_L</td>
<td>S_H</td>
<td>S_L</td>
<td>P_H</td>
<td>P_L</td>
</tr>
</tbody>
</table>
(d) Calculation of test results. Between 40 and 66 hours following injection, a diameter of the reaction for each injection site shall be calculated by averaging two diameters of the reaction measured at right angles to each other. The average reaction for each dilution for each animal shall be determined, then the average diameters of the reactions of all of the guinea pigs for each dilution shall be calculated. The ratios of the reactions are determined by dividing the average diameter of the low dilution of the product under test by the average diameter of the low dilution of the standard and by dividing the average diameter of the high dilution of the product by the average diameter of the high dilution of the standard.

(e) Potency requirement. The potency of the product under test is satisfactory if each calculated ratio of the reactions of the product under test and of the standard is 1.0. The potency of the lot under test is considered to be equal to that of the standard if the ratios are not lower than 0.77 or higher than 1.30, provided that in a single test the ratios are substantially the same.

§ 650.5 Stability test.

A sample of each lot of the product shall be held at 37°C for not less than 24 hours and then tested for potency as prescribed in §650.4. The stability of the product is satisfactory if test results of the sample meet the potency requirement prescribed in §650.4(e).

§ 650.6 Samples; protocols; official release.

For each lot of the product, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research:

(a) A protocol which consists of a summary of the history of manufacture of each lot including all results of all tests for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(b) A sample of no less than 20 milliliters of the product.

(c) The product shall not be issued by the manufacturer until written notification of official release of the lot is received from the Director, Center for Biologics Evaluation and Research.


Subpart B—Tuberculin

§ 650.10 Tuberculin.

The proper name of this product shall be Tuberculin, which shall be a preparation derived from Mycobacterium tuberculosis or M. Bovis.

§ 650.11 General requirements.

(a) General safety. Each lot of Tuberculin shall be tested for safety as prescribed in §610.11 of this chapter, except that the sample of tuberculin from multiple puncture devices shall be obtained by removing the tuberculin in a manner that will permit the injection of material from at least five devices into each of two guinea pigs and from at least two devices into each of two mice.

(b) Labeling. In addition to complying with all other applicable labeling provisions of this subchapter, the package label shall state the following:

(1) For Tuberculin for Mantoux testing, the number of U.S. units (TU) per dose.

(2) For Tuberculin for multiple puncture testing, a statement indicating that the activity per test is comparable to a stated number of U.S. units (TU) administered by the Mantoux method.

(3) The applicable type of Tuberculin placed immediately following and of no less prominence than the proper name, as follows:

(i) “Old,” or