Bibliography

5. R. Schmidt, Muenchen Med. Wochenschr. 67, 48 (1920)
6. F. B. Seibert, Amer. J. Physiol., 71, 621 (1924)
8. J. Butlion Sanderson, on the process of fever, Praetitioner, 16, 257 (1876)
12. F. B. Seibert, Amer. J. Physiol., 67, 90 (1923)
13. Seibert FB. The cause of many febrile reactions following intravenous injections, Amer. J. physiol., 71, 628
18. C.C.Mascoli and M.E.Weary, Limulus amebocyte lysate test for detecting pyrogens in parenteral injectable products and medical devices: Advantages to manufacturers and regulatory officials, J.Parenter.Drug Assoc. 33, 81-95 (1979)
48. J.F.Cooper and S.M.Pearson, Detection of endotoxin in biological products by the Limulus test, Dev.Biol.Stand.34, 7-13 (1977)
49. E.Centanni, chem. Zbl, 6, 587 (1894)


54. USP 24-NF, 2nd Supplement, 85 Bacterial Endotoxins Test, (The USP Convention, Rockville, MD, 1999), pp 2875-9.


56. F.B. Seibert. The causes of elimination of reactions after intravenous infusions, Amer.Surg..92,195 (1930)


64. J.F. Cooper, endotoxins test In: Microbiology in Pharmaceutical Manufacturing (ed. Prince R), Bethesda, MD, Parenteral Drug. Assoc., Godalming, UK, Davis Horwood International Publication, Ltd, 2001; 537-567
66. United states Pharmacopeial Forum, 26 (1), <85> Bacterial Endotoxins test (The united states Pharmacopeial Convention, Rockville, MD), 2000, p218
70. M. Jahnke; M. Weigand; H.G. Sonntag. Comparative testing for pyrogens in parenteral drugs using the human whole blood pyrogen test, the rabbit in vivo pyrogen test and the LAL test. Eur J Parenteral Sci 2000; 5 (2); 39-44.


80. The United States Pharmacopeia 23, <85> Bacterial Endotoxins Testa, I/U.S(166,545),(909,863)


GLOSSARY

1) LIMULUS AMOEBOCYTE LYSATE (LAL) - An aqueous extract of the circulating blood cells (amebocytes) of the American horseshoe crab, Limulus Polyphemus.

2) BET – BACTERIAL ENDOTOXIN TEST – A standardized gel-clot Assay described in supplement 8, the United States Pharmacopeia XXII.

3) BP - British Pharmacopoeia

4) CSE - CONTROL STANDARD ENDOTOXIN - A purified endotoxin which is standardized against the RSE (currently E.coli).

5) RSE – REFERENCE STANDARD ENDOTOXIN – The USP Reference standard Endotoxin (currently EC-6). EC-6 is the 6th filling of a lyophilized E.coli-derived endotoxin which is maintained by the FDA’s Bureau for Biologics.

6) CERTIFICATE OF ANALYSIS (CoA) – A Certificate giving the CSE/RSE calibration ratio lot specific for LAL and CSE.

7) ENDOTOXIN – A toxic complex molecule from the outer cell wall of Gram-Negative bacteria. Endotoxin is also referred to as LPS of lipopolysacharide and was formerly called Pyrogen because fever is one of its first signs of toxicity in humans and animals.

8) ENDOTOXIN LIMIT - The maximum amount of endotoxin allowed in a parenteral product or medical device. The Endotoxin Limit set by the FDA for drugs is 5EU/kg/hr or 0.2 5EU/kg/hr for intrathecal drugs. The limit for devices is 0.5EU/mL, based on a 40mL rinse or 0.06 EU/ml for intrathecal devices.

9) ENDOTOXIN UNIT (EU) or International Units (IU) – A standardized amount of endotoxin based on its reactivity in the LAL test (the LAL reactivity of 0.1 ng of EC-5). A vial of RSE contains 10000 endotoxin units.

10) ENDPOINT – The observed result of a timed test. In the Gel-clot method of LAL testing, the endpoint is reached after one hour of incubation at 37°C. A positive test is scored when the test tube shows a firm gel which holds through Inversion. A negative test is scored when the sample and reagent mixture remains liquid.
GLOSSARY

11) ENHANCEMENT – The process in which a product formulation or test sample increases LAL reactivity.

12) FDA – The U.S. Food and Drug Administration. Three branches of the FDA regulates LAL Testing. The Bureau of Medical Devices, the Bureau of Drug and the center for Biologics Evaluation and review (CBER).

13) GMP (Good Manufacturing Practices) – A set of federal laws which define how the process of manufacturing drugs and devices be organized, managed, documented and recorded.


15) INTERFERENCE – Any type of chemical or physical enhancement or inhibition condition which can alter the recovery of endotoxin in a test sample. Inhibition is the major reason why product specific Validation studies are required for LAL testing; the majority of inhibition problems can be solved by appropriate dilutions.

16) INHIBITION – The process in which a product formulation or test sample decreases LAL reactivity.

17) LARGE VOLUME PARENTERALS (LVP) – Refers to I.V infusion solutions and other drugs which are giving intravenously at doses of maximum of 10ml per kg of patient body wt per hour.

18) LABEL CLAIM CONFIRMATION – An assay of an LAL reagent by a standardized endotoxin which yields an endpoint that is equal to or within a two-fold dilution of the labeled sensitivity (\(\lambda\)).

19) LAMBDA (\(\lambda\)) – The symbol for LAL reactivity stated in EU/ml. for gel-clot assay, lambda is the labeled lysate sensitivity; for kinetic assays, lambda is the lowest point on the standard curve.

20) LAL REAGENT WATER (LRW) – Highly purified water, absent of detectable endotoxin in a LA test system.

21) LIPOPOLYSACCHARIDE (LPS) – Highly purified bacterial endotoxin, free of protein.

22) MAXIMUM VALID DILUTION (MVD) – A calculation used to determine how much a parenteral product or raw material can be diluted and
still detect the endotoxin limit. Appendix E of the LAL-test Guideline is an extensive list.

23) PARENTERAL DRUG – Refers to drugs which are giving intravenously or by hypodermic injection. Parenteral drugs are classified as large volume parenterals (LVP) and small volume parenterals (SVP) depending on how much is given to a patient in a one hour period. All parenteral drugs require endotoxin testing.

24) POSITIVE PRODUCT CONTROL (PPC) – An aliquot of test sample spiked with a known amount of endotoxin. This control serves as the inhibition control for gel-clot assay. In the kietic assay the PPC serves as a control for inhibition and enhancement.

25) USP – United States Pharmacopeia

26) IP – United States Pharmacopeia

27) VALIDATION – The process of documenting that a drug or device sample may be tested by the LAL method without inhibition or enhancement.