Status of the General Safety Test (GST) in the United States –
Final Rule Published 02-July-2015

Robin Levis, PhD
Division of Viral Products
US FDA/CBER/OVRR
September 15, 2015
History of the GST in the US

  - **Oct. 1901** – St. Louis, first death from tetanus-contaminated diphtheria antitoxin
  - **Nov. 1901** – Camden, first death from tetanus-contaminated smallpox vaccine
  - **Spring 1902** – Medical Society of District of Columbia called for legislation to regulate the sale of biologics, bill drafted by the District Commissioners
  - **June/July 1902** – Bill passed by congress and signed into law
    - Biologics Control Act of 1902 established board made up of Surgeon General of the Army, Surgeon General of the Navy, and Supervising Surgeon General of the Marine Hospital Service to issue, suspend, or revoke licenses of establishments
  - **February 1903** – the board implemented first set of regulations, which went into effect 6 months later. Laboratory examinations conducted by Hygienic Laboratory (US Public Health and Marine-Hospital Service)
  - **1909** – “It is now as much a routine practice of antitoxin producers to make what is known as safety tests as to make potency tests. A safety test is made by injecting about 5 c.c. of the serum into guinea pigs and observing the animal for some days, particularly for symptoms of tetanus.” J.F. Anderson. J Exp Med. 1909 September 2; 11(5): 656–658.
The CFR and the GST – The rise and fall

- **1938** – First CFR published, Safety Test (along with Identity Test) mentioned in 42 CFR 22.110

  - **1949** – Description of Safety Test added to CFR [42 CFR 73.70(c)(3)]

- **1974** – Biologics General Safety Test in 21 CFR 610.11

  - The General Safety Test “has been part of the biologics regulation since their original adoption.”
  - “The existing safety test for biological products is stated in very general terms. As a result, specific test procedures developed during recent years have been incorporated into the license requirements of each manufacturer on an ad hoc basis.”
  - “The principal goal of the Commissioner's proposal is to increase the sensitivity of the test. Therefore, the proposed regulation permits only the intraperitoneal route of administration of the product sample into the test animal, requires higher standards for test animals, and establishes greater specificity in test procedures and interpretation. In addition, the proposed regulation will provide an opportunity for a limited number of repeat tests to establish the safety of a product since test animals often reveal abnormalities which result from natural factors not caused by the test product.”
The CFR and the GST – The rise and fall


- The requirement for a GST test was originally intended as a means by which harmful extraneous toxins could be detected (41 FR 10888, March 15, 1976).
- The source of such toxins may be bacterial toxins that persist even after the bacteria producing the toxins had been removed by filtration or killed by sterilization, or formulation errors that result in harmful levels of certain substances, e.g., preservatives.
- The test continues to serve as a safety net to detect harmful contaminants that may enter or be introduced into the final container through undetected failures in the manufacture of biological products.
- After more than a decade of experience with these products, FDA found that it could evaluate many aspects of a biological product’s safety, purity, or potency with tests other than those prescribed in part 610.
- Many biological products are currently manufactured, or will be manufactured in the future, under highly controlled and rigorously monitored conditions. Therefore, under the amended rule, manufacturers of biological products that employ appropriate production controls and quality assurance safeguards would be permitted to apply for an exemption from the GST requirement.
- To further reduce the possibility that an undetected extraneous toxin could contaminate the product just before or during the final fill stage, a manufacturer may use production facilities and final fill equipment that can detect or enable the detection of any loss in the integrity of the production and fill processes.
- The value of the GST as a final assay for the presence of extraneous toxins may be diminished for certain biological products, such as vaccines containing recombinant or purified protein antigens.
The CFR and the GST – The rise and fall

- **2003** – Exemptions from GST, 68 F.R. 10157, March 4, 2003
  - Many biological products are currently manufactured, or will be manufactured in the future, under highly controlled and rigorously monitored conditions.
  - Therefore, under § 610.11(g)(2) we will permit biological product manufacturers who employ appropriate production and final filling controls and quality assurance safeguards to apply for an exemption from the GST requirement.
  - The request must include an explanation of why the GST is unnecessary or cannot be performed due to the mode of administration, the method of preparation, or the special nature of the product and must describe alternate procedures, if any, to be employed.

- **2011** – On January 18, 2011, President Barack Obama issued E.O. 13563, “Improving Regulation and Regulatory Review” (76 FR 3821, January 21, 2011). One of the provisions in the E.O. is the affirmation of retrospective reviews of existing significant regulations.
  - The existing codified GST requirements are duplicative of standards that are also specified in biologics license applications (BLAs), or are no longer necessary to be codified and are no longer appropriate to help ensure the safety, purity, and potency of licensed biological products.
The End Game -


- **2015** - Final Rule - Revocation of General Safety Test Regulations That Are Duplicative of Requirements in Biological License Applications, 80 F.R. 37971, July 02, 2015
  
  - Effective Aug 3, 2015
Why Now?

- The Agency, over time, periodically explored the utility and efficiency of the GST regulations.
- It became increasingly clear that the codified GST requirements are too restrictive for certain biological products because alternatives may be available that provide the same or greater level of assurance of safety.
- E.O. 13563, “Improving Regulation and Regulatory Review” gave an opportunity to go forward with a change in the CFR.
What follows the GST?

- The final rule will provide flexibility while maintaining product safety and effectiveness.
  - Appropriate controls will remain in place
  - Manufacturers and FDA will focus on developing alternative tests that are meaningful and best ensure product quality and safety
- Manufacturers of products derived from inherently toxic substances would be required to continue to use the safety tests that are prescribed in their BLAs to control and monitor toxicity.
  - These include products with concerns related to residual toxin activity/reversion to toxicity, or if the alternative method proposed is not deemed acceptable
  - For these products, manufacturers may choose to replace the GST with specific toxicity testing or maintain the current GST.
- For currently licensed products, if the requirement to perform a GST is part of their BLA, the GST requirement would stay in place until an official request is made to not do (or modify) the test.
  - FDA would review such requests on a case-by-case basis to ensure the request is acceptable.
  - If no alternate approaches to GST are available, request to decrease the overall amount of testing may be considered by FDA.