Elimination of the General Safety Test (21 CFR 610.11) US FDA Update

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Regulation of Vaccines in the U.S.

- The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) is the national regulatory authority in the United States (US) charged with the regulation of biological products including vaccines.
- The review of vaccine applications occurs among CBER's Office of Vaccines Research and Review, Office of Compliance and Biologics Quality, and Office of Biostatistics and Epidemiology.
- CBER's current legal authority for the regulation of vaccines derives primarily from Section 351 of the PHS Act and from certain sections of the FD&C Act.

Biologics Licensure

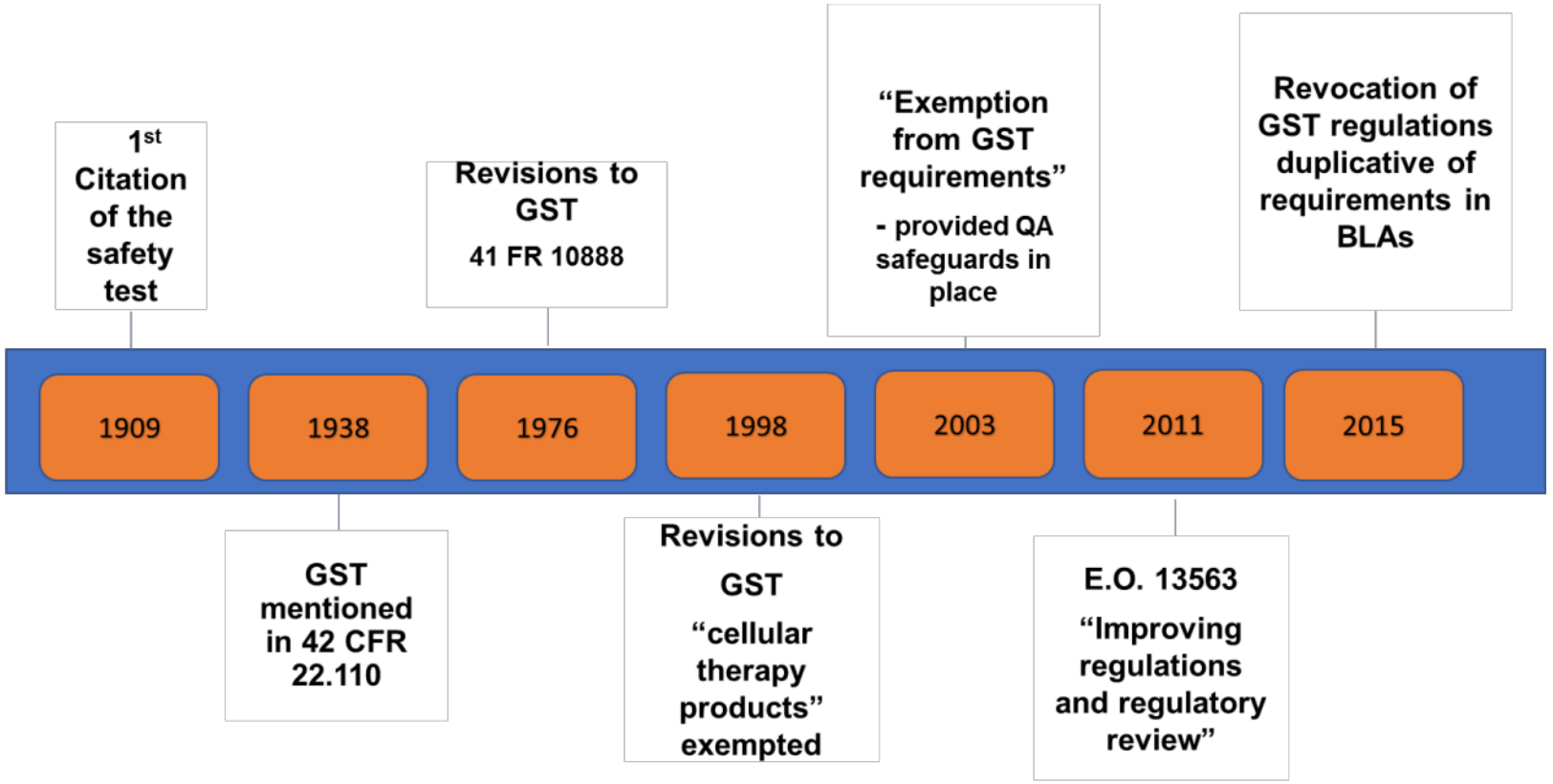
Section 351 of the Public Health Service Act, 42 USC 262:

- Licensure on the basis of a demonstration
  - that the biological product … is safe, pure, and potent; and
  - the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; ….
- Only those vaccines that are demonstrated to be safe and effective, and that can be manufactured in a consistent manner will be licensed by the FDA

Biologics Licensure

- Title 21 of the Code of Federal regulations (CFR) contains the regulations through which FDA implements the PHS Act and the FD& C Act
  - Legal definitions for safety, purity and potency are stated in 21 CFR 600.3
    - Safety is defined as "…the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at that time"
- All tests for safety, purity and potency for a particular product are documented in the license for the product
- One safety test, the General Safety test (GST) for detection of extraneous toxic contaminants, was described in the regulations (21 CFR 601.11) but was revoked in 2015

U.S. Regulatory History of the General Safety Test (GST)



Final Rules – 2003: Exemptions from GST
– 2015: Revocation of GST

- **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.

Final Rules – 2003: Exemptions from GST
– 2015: Revocation of GST (cont.)

- **2015** - Revocation of General Safety Test Regulations that are duplicative of requirements in Biological License Applications, 80 F.R. 37971, July 02, 2015
  - GST regulations are too restrictive …because they specify particular methodologies or requirements when alternatives may be available that provide the same or greater level of assurance of safety
  - ..the regulations may no longer reflect the best current testing procedures..
  - ..testing requirements should be specified in the biologic license application to enhance flexibility to make appropriate changes to testing methods.

Final Rule 2015 - Revocation of General Safety Test Regulations

- The final rule will provide flexibility while maintaining product safety and effectiveness.
  - Appropriate controls will remain in place
- 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.
  - For these products, manufacturers may choose to replace the GST with specific toxicity testing or maintain the current GST.

Final Rule 2015 - Revocation of General Safety Test Regulations

- 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.
  - Sponsor may request to decrease the overall amount of testing.
- Requirements for a licensed biological product manufacturer to report changes made to the product, production process, etc., that are established in the approved BLA are detailed in 21 CFR 610.12
- Accordingly, a manufacturer who desires to discontinue the GST in the approved BLA must submit a BLA supplement reporting the change under 21 CFR 610.12

Steps taken by Regulated Industry & FDA following Publication of the Final Rules of 2003 & 2015

- Since 2003 the OVRR has received numerous BLA supplements submitted by regulated industry requesting an exemption and/or elimination of the GST requirement from the finished product release specifications and stability testing for preventive bacterial and viral vaccines.
- OVRR has granted these requests and approved respective BLA supplements for all viral vaccine products and for the majority of bacterial products because
  - Appropriate process and environmental controls were put in place
  - History of passing GST
- For some products derived from toxins, i.e., diphtheria and tetanus toxins, OVRR approved replacing the GST with the specific toxicity test performed on final bulk and/or approved elimination of the GST because the specific toxicity test was already performed on final bulk
  - Of note, OVRR would consider eliminating these tests if adequate segregation of toxins from toxoided products is in place


THANK
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