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Potency Assays for Botulinum Products

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Potency Assays for Botulinum Products

- Focus on Use as a
  - Product Quality Test
  - Relation to Drug Product Immogenicity Testing
- Other Concerns May Arise as a Toxicology Test

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Tests for Potency: 21 CFR

§ 610.10 Potency.
Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency…..

§ 600.3
…Specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended to effect a given result

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Tests for Potency: PHS Act

PHS Act: 42USC262
(B) The Secretary shall approve a biologics license application - (i) on the basis of a demonstration that - (I) the biological product that is the subject of the application is **safe**, pure, and **potent**;

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Scientific Sense

- Higher Order Structure
- Consistency
- May be used for dosing
  - Mass Units Used More Frequently Now
  - Units of Activity Used When Accepted Standard
  - Special Circumstances

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For Biologics, FDA

- **DOES** Require a Potency Assay
- **DOES NOT** Recommend a Specific Test

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Potency Assay Attributes

Must be Suitable for Intended Purpose

- •Reflect its Clinical Mechanism of Action
- •Sensitive to Changes in Product Integrity
  - • Consistency on Lot Release
  - • Sensitive to Relevant "Stress" Conditions

Must be Validated for:

- • Sensitivity
- • Specificity
- • Reproducibility
- • Robustness
- • Statistically Confirmed

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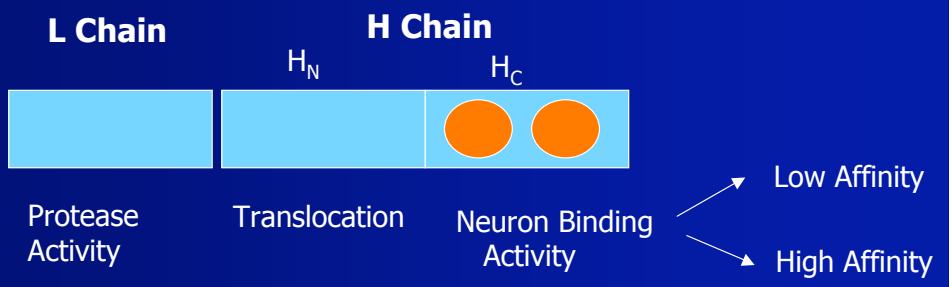
Botulinum Products: Potency Assay Concerns

Must be Suitable for Intended Purpose

- • Used to Determine Dose of Final Product
  Critical as Mass in Final Vial is Minute
- • Used to Compare Relative Activity of New Lots
  Compare to Reference Standard
- • Multiple "Working" Domains of the Toxin



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Enzyme Potency Assay Considerations

- Optimal enzymatic assays utilize physiologically relevant substrates.
- Important structural information is derived from determination of the kinetic parameters:
  - K_M (binding affinity for substrate)
  - k_{cat} (turnover of substrate)
- Enzymes may need more than one potency assay (i.e. receptor binding, etc.).

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Current and Future Concerns for Botulinum Potency Assays

Mouse LD50 Assay

Plus

- **Long History of Use for Dosing Patients**
- **Reflects Multiple Critical Product Activities**

Negative

- **Variable and Susceptible to Alterations in Assay Conditions (animal physiology)**
- **Death of Animals**

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Botulinum Potency Assays And Immunogenicity

- "Immunogenicity" section is a Part of the Package Insert for Biologic Products
  - Incidence
  - Titers
  - Binding and neutralization Assays

- A variation of Mouse LD50 Assay for Immunogenicity Testing of Botulinum Products
  MPA (Mouse Protection Assay)
  - Uses many animals
  - Insensitive
  - Other Assays Should be Considered

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Challenges to New Botulinum Potency Assays

- Sensitive (minuscule amounts of product)
- Reflect Critical Working Domains of Toxin
  (may require multiple assays)
- Reproducible and Robust (Statistical Analysis)
- Need for Validation
  - That it Works
  - Against Mouse LD50 Assay
  - Potentially In Clinical trials