Minimum Protective Dose (MPD)

How it is Established and What it Indicates

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Before we start...

“Minimum Protective Dose”

*is more accurately referred to as:

“Demonstrated Protective Dose”
Demonstrated Protective Dose:
So, where do we start?

• Challenge model
  – May be prescribed (9 CFR)
  – Often times developed by the firm
    • Balance between under-challenge vs. clinically relevant challenge vs. over-challenge.

  – A specific set of conditions
    • Genetics, age, class (breeding, etc.), environment (housing), immune status, virulence of challenge (route of administration, challenge strain, challenge dose), etc.
Dose Titration Study

• A dose titration study is not always done or necessary
  —The need for a dose titration study is determined on a case-by-case basis.
  —Considerations include: experience with the antigen, adjuvant, the need for judicious use of animals, facility limitations, complexity of challenge model and number of animals needed per group, etc.
Dose Titration Study

• How do we know what dose to start with?
  — Proof-of-concept studies (small scale; limited “power”, sometimes use surrogate markers).
  — Previous efficacy and/or safety experience with a similar antigen or the same antigen.
  — Experience with/expected effect of adjuvant.
  — Consideration of manufacturing constraints
    • Manufacturability -- yield, dose size, space for additional antigens, cost, etc.
    • May need to be overcome to ensure safe, efficacious and affordable product.
Dose Titration Study

**What are we looking for?**

- Clinically relevant protection – how to define??
- A dose response, including a “failing” dose.
  - May require $\geq 10X$ difference in potency between treatment groups.
  - Attempting to bracket the MPD.
  - May also serve as the pivotal efficacy study.
  - Value in potency test development and validation.
  - May be different for different challenge loads/models.
- What if we don’t see a clear dose response or a “failing” dose? Pick a dose? Repeat the study?
Determination of Potency

• How is potency of the immunogenicity serial determined?
  – The mean of replicate measures of potency.
    • Uses the proposed potency test.
    • Generally 5 or more replicates.
    • Pooling of clinical batch vaccine vials.
      – For potency determination and vaccination.
  – Determined at the time of vaccination or immediately prior to vaccination.
Demonstrated Protective Dose: Conclusions

• Dose titration studies are important and useful tools.
  – There are a number of variables that can influence the outcome.

• DPD is a critical and necessary number for the production, release and stability evaluation of veterinary biologicals.

• Methods used for immunogenicity serial potency determination (*i.e.*, the DPD) account for variation.
Demonstrated Protective Dose

Conclusions

• When assessing the risk to the animal (or the animal population) if a vial of vaccine has a potency below DPD, it is important to consider:
  – Protection is influenced by many factors.
    • Environment, age, genetics, challenge strain & dose, previous exposure (anamestic response), etc.
  – Protection is a continuum; it is not dichotomous.
    • A dose less than the DPD may still provide a beneficial level of protection.