21-22 Aug 2018 FDA Workshop Non-Traditional Antibacterial Therapies *Summary*

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John's high-level points

1. NT is very broad and requires qualification
   - NT *Structure* vs. *Goal* may help a bit
2. Current development tools are often suitable
   - Possible gaps around delayed (indirect) benefit
   - Possible gaps around combination products
3. The lack of a tool (or path) can be managed
   - New approaches have been / can be developed
4. The product's whole effect must be considered
   - Don't be seduced by a pretty mechanism
5. A high-level guidance document might be useful
   - But we're not ready to commit to many details

Details

1. NT is broad & language matters

"When I use a word," Humpty Dumpty said in rather a scornful tone, "it means just what I choose it to mean – neither more nor less." "The question is," said Alice, "whether you can make words mean so many different things."

- "Non-traditional" is too broad & needs qualification
  - "Alternatives to antibiotics" is no better
  - Non-traditional *Structure* vs. *Goals* helps a bit
- What buckets best delimit future conversations and provide development guidelines?
  1. Host-directed vs. pathogen-directed
  2. Direct (immediate) vs. indirect (delayed) clinical benefit
  3. Immunogenic vs. no immune response concerns
  4. Explicit combination vs. single entity
- *More on this later…*

2a: Current tools *often* work

- Current program designs often seen adequate
- Most of the challenges are not unique to NT
  - Small effects are hard to measure
  - Rare events (or pathogens) may require large trials
- Gap #1? Measures of indirect (or delayed) benefit
  - Microbiome/colonization seems important
  - Surrogate for future infection of self or others
  - There are already a few settings where we treat carriage as tantamount to an active infection (GAS in a surgeon, GBS in 3rd trimester, *N. meningitidis* in anybody)
  - Are there others such settings? What to measure?
    - Infection in self? Transmission to others? Infections in others?

GAS = Group A streptococcus, GBS = Group B streptococcus

2b: Current tools (continued)

- Gap #2?: Combinations require some thought
- How would you evaluate a mixture of 5-10 anti-toxin/virulence factors Mabs?
  - A factorial design is not really plausible
- Is it OK to simply accept a sponsor's mix of Mabs?
  - Treat this as effectively a polyclonal?
  - Safety is on the mixture, as is efficacy
  - The fact that dropping a Mab out might reduce COGS is the sponsor's problem
    - Ditto for dose (of any given component) that is too low or high
  - I'd wish to fully resolve all points (dose, role of each element), but if there is an effect then there is an effect

COGS = Cost of Goods Sold

2c: Current tools: Endpoints?

- Gap #3?: Are there other endpoints to consider?
- Consider an add-on product
  - Doesn’t improve on mortality effect of Base
  - Does improve Quality of Life or similar
- Are such measures strong enough to be compelling?

3. No path yet? Don’t panic!

- Using existing tools is desirable when possible
  - But, there won’t always be a path (yet)
- This is an opportunity for a sponsor to propose something new and innovative
- FDA is happy to have discussion(s) about how a program might progress
  - The sponsor needs to drive this with concrete suggestions
  - The sponsor knows more about the product than anybody else

4a: Consider the whole effect

- Hypothetical anti-toxin Mab
  - Consider result at right
- What to conclude?
  - The product did its bit (less *S. aureus* HABP-VABP)
  - But, did clearance of *S. aureus* open create other issues?
- This is a possibility that needs to be considered
- A similar problem arises with intercurrent mortality
  - We discussed this with the CDI case
- Personal view: Net effect in the enrolled population *(hopefully ≈ where will be used)* is what matters
  - This is not a regulatory problem!
  - If the effect does not show in real-life settings, the value proposition seems likely to be weak. DOOR as a path?

Anti-*S. aureus* Mab	Active	Placebo
S. aureus HABP-VABP	15%	25%
All-cause HABP-VABP	40%	30%

4b: Anti-virulence & whole effect

- Pathogenesis and immune response in animals is often different from that in man
  - Shanks N et al. "Are animal models predictive for humans?" Philos Ethics Humanit Med 4:2, 2009.
  - Uhl, E. W. and N. J. Warner (2015). "Mouse Models as Predictors of Human Responses: Evolutionary Medicine." Curr Pathobiol Rep 3(3): 219-223.
- And, (limits on) biodistribution may matter
- Personal view: A sponsor needs to maintain a skeptical attitude
  - We have to start with the preclinical models
  - Is this a worthy topic for a workshop?

5. High-level guidance document?

- Personal view:
  - If written, would need to be very general
  - Might have the effect of encouraging work
- That said, this conversation has shown that many details are not ready to be nailed down
- Some thoughts for future workshops (chose based on interesting products identified by CARB-X, FDA)
  1. Host-directed vs. pathogen-directed
  2. Direct (immediate) vs. indirect (delayed) clinical benefit
  3. Immune responses & pathogenesis: animal models vs. human illness

Thank you & remember that *All Art was once Contemporary!*

Over to Ed…

- Mechanism: Important, use for all it is worth
  - But, plan for patient-centered measures in Phase 3
- Enrichment vs. severity of illness in patient group
  - U-shaped curve – at extremes, co-morbidity may dominate
  - Practical considerations may limit scope
  - Competing risks also factor in here
- Animal models inform but have limitations
  - May help to confirm effect via multiple models
- Need to think about replacement pathogens in microbiome-focused products

Discussion (1)

- Logistics of pre-IND interactions?
  - Within practical limits, FDA will attempt to accommodate, including requests for serial conversation
  - Sponsor preparation drives the quality of the meeting
- Who supports products to benefit all of society?
  - Still need to know risk-benefit
  - Payor model is beyond scope of *this* meeting!
    - IDSA & BIO are good contacts for ongoing payor work
  - BARDA does have the role of USG's pharma company
    - CDC & NIAID are also active broadly in this arena

Discussion (2)

- How do we best define “net effect”?
  - No one answer: *Good to approach from a broad base*
  - FNIH-based work has helped define endpoints
  - CTTI has worked on making trials more efficient
  - Workshop on single-pathogen drugs led to funding opportunities for research to answer key questions
- About those buckets
  - Might add pathogen-specific as a bucket
  - At least one sponsor would be happy to use their program as the basis for a workshop!

Discussion (3)

- PK-PD became a strong tool based on many years of work (Craig, etc…)
  - Insights have grown, often due to program failures
  - Need to encourage open discussions of same
  - Perhaps look to Safety Management language (“near misses” and related) as a way to open conversations
- Microbiome-focused workshop(s) are of interest
  - 17 Sep 2018 NIAID workshop on Microbiome products
- CMC: Underestimated complexity, esp. for biologics
  - Delays here are troublesome – need to plan carefully
  - Must carefully manage contract manufacturing
  - Must anticipate significant costs, too

Discussion (4)

- More on CMC: Is consultation possible on GMP CMC issues? Facility design, etc.?
  - Yes, the Quality group can provide advice
- *C. difficile*: We've had failures here – would a workshop focus on C. difficile be useful?

- These slides will be available shortly!

Thank you!