(A) REGULATORY PERSPECTIVE ON ADAPTIVE DESIGN IN THE CONFIRMATORY PHASE

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

My goals

- Explain FDA's current thinking on confirmatory adaptive designs
- Dispel (or reaffirm?) some myths:
  1. FDA is not interested in adaptive designs
  2. FDA does not accept adaptive designs
  3. FDA does not accept Bayesian methods
- Give some advice on moving proposals toward regulatory acceptance

Outline

- Regulatory 101 for confirmatory adaptive designs
- A tour of FDA's draft guidance on adaptive designs
- Adaptive design submissions to FDA
- Some free advice

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Regulatory 101 for Adaptive Designs

Different centers, different approaches

- Three FDA Centers are responsible for regulating medical products for human use:
  - CDRH regulates most medical devices
  - CDER regulates drugs and some biologics
  - CBER regulates biologics, some devices, a handful of drugs
- Conceivable for same adaptive design proposal to get three different results
  - Different laws, different regulations, different guidances, different cultures

Same center, different approaches?

- Attitudes not necessarily monolithic within a Center
- Review offices and divisions may have distinct attitudes
  - Driven by indication, product class or even individual product-specific concerns
- Fundamentally, individual scientists are reviewing applications and may have individual viewpoints
- But: decisions should be backed by science and law

Regulatory basics for drugs and biologics

- Major interactions with FDA occur around investigational and marketing applications
- Marketing: New Drug Applications (NDAs) and Biologics License Applications (BLAs)
- Investigational: Investigational New Drug (IND) applications
- Devices:
  - Somewhat similar PMA / IDE process
  - Very distinct 510(k) process

NDA / BLA authority

- The result of an NDA / BLA application is:
  - Approval / licensure (along with labeling considerations)
  - Non-approval (Complete Response letters)
  - Refusal to file
- Depends on how the agency views design and conduct of confirmatory studies
- Considerable precedent for accepting various "traditional" study designs
- A given adaptive design may need to break new ground

Demonstrating effectiveness

- Effectiveness shown by "…evidence consisting of adequate and well-controlled investigations…." [A&WC]
- Important to believe FDA views your trial as potentially adequate & well-controlled…
  - …if you want to bring a product to market
- Strong convention that demonstrating effectiveness requires control of Type I error rate at 97.5%
  - Usually rejection of a null hypothesis of no difference at one-sided .025 significance level

IND authority

- An IND is required to transport or distribute an unapproved product across state lines
  - Usually requested for research purposes
  - This may or may not include your research (e.g. CER studies may not involve FDA)
- In one sense, IND protocol review is a binary decision: clinical hold or no clinical hold
  - Either way, you'll get lots of comments and free advice

IND clinical holds

- Lots of reasons a study can be put on clinical hold; notably:
  - Unreasonable and significant risk to subjects (all phases)
  - Clearly deficient in design to meet its stated objectives (phase 2 & 3 only)
- FDA could put a questionable confirmatory adaptive trial on hold, or…
- FDA could also allow the trial to proceed, noting reservations

Special Protocol Assessment

- Special Protocol Assessment (SPA) can be requested for a clinical trial that will form the basis of an efficacy claim in an NDA or BLA
- An SPA can lead to formal, written agreement on the design and size of a clinical trial
  - Simply allowing a trial to proceed under IND is not a formal agreement from FDA
- An SPA would be great for a novel design, but…
  - Review divisions have discretion with SPAs
  - Review timelines may be a concern

FDA Adaptive Design Guidance

FDA is interested in adaptive designs. Really.

- Easy to dispel the myth that the FDA is not interested in adaptive designs:
  - ADAPT-IT
  - The adaptive design guidance
  - Internal performance metrics

Guidance background

- *FDA Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics*
  - Released as draft for public comment February, 2010
  - *Many* comments, currently under revision
  - Signed by CDER & CBER, *not CDRH*
- Levels of policy:
  - Statutes: laws enacted by Congress
  - Regulations: binding interpretations of law
  - Guidances: non-binding descriptions of current thinking
  - Draft Guidances: current thinking not yet clear

Scope and definition

- Focus on confirmatory (i.e. A&WC) trials
- "…an *adaptive design clinical study* is… a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data… from subjects in the study"
  - Stress on *prospectively planned*
  - Detailed protocol and usually separate Statistical Analysis Plan prior to start of study

Not adaptive designs

- Modifications based on analysis of interim data that were not prespecified
  - That is, either analyses not prespecified or modifications not prespecified
  - Default position is “no” for this when modifications are substantial
- Modifications made based entirely on external information
  - Default position for reasonable proposals is usually yes, provided you can show no internal information involved

What about exploratory studies?

- The guidance distinguishes A&WC vs. exploratory
- Anything goes would be an overstatement, but…
  - The guidance strongly encourages experimentation with novel designs in exploratory studies
- Some examples:
  - CRM in Phase 1
  - Selection designs in Phase 2
- Major caution is to avoid misleading certainty

What can be adapted?

- Eligibility criteria
- Randomization procedure
- Treatment regimens
- Sample size
- Follow-up schedule
- Primary endpoints
- Secondary endpoints
- Analytical methods
- Etc.

General concern 1: False positives

- Type I error rate inflation
  - More paths to a "win" can mean more false positives
  - Control of this can be more or less straightforward
- Difficulty in interpreting results after a win
  - Does the effect size estimate account for design?
  - Is the population a moving target?
- Operational bias
  - Many adaptations require unblinded analysis
  - Can knowing results affect conduct?
  - Who knows what when?

General concern 2: False negatives

- Common to think of adaptive designs as more powerful
  - Not necessarily so
- Reduced time for "thoughtful exploration"
  - Seamless Phase 2/3 may limit modifications that would ordinarily happen post-Phase 2
  - E.g. not allowing survival data to mature

General concern 3: Time

- Adaptive designs increase efficiency, right?
  - Not if they take an extra year to plan
- FDA review time should also be considered
  - Novel proposals will receive more scrutiny
  - More time required on front-end for sponsor-FDA communication
- These concerns should be mitigated by increased experience and wider adoption over time

Who understands what?

- The guidance divides confirmatory adaptive designs into two categories:
  - Generally well-understood adaptive designs
  - Less well-understood designs
- "Generally well-understood" ≈ "FDA is familiar with these designs and is comfortable with their use in A&WC trials"
- "Less well-understood" ≈ "we're not confident error rate inflation and bias are controlled"

Well-understood designs

- Adaptations blinded to treatment effect, or
- "Traditional" group-sequential designs
- Examples:
  - Eligibility criteria adapted based on baseline data
  - Sample size re-estimation based on blinded analysis
  - Adaptations based on outcomes unrelated to efficacy
  - Group sequential designs implemented by DMC
  - Adaptations based on e.g. missing data, overall data distributions, etc.

Less well-understood designs

- All based on unblinded interim analysis of treatment effect
  - But remember group-sequential exception
- E.g.:
  - Dose selection designs
  - Response-adaptive randomization
  - Unblinded sample-size re-estimation
  - Population, endpoint adaptation based on treatment effect
  - Combinations of techniques
  - Non-inferiority study adaptations

Other guidance considerations

- Safety
- Content, format, documentation
- Interactions with FDA
- Simulations
- SOPs for data integrity, blinding and information sharing
- Reporting

A note about devices

- Medical device trials are not covered by the Guidance
- In some areas, CDRH has been faster than CBER and CDER to adopt new approaches
- FDA's *Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials* covers many related topics
  - Primarily used and developed by CDRH
  - CBER also a signatory

Adaptive Design Submissions to FDA

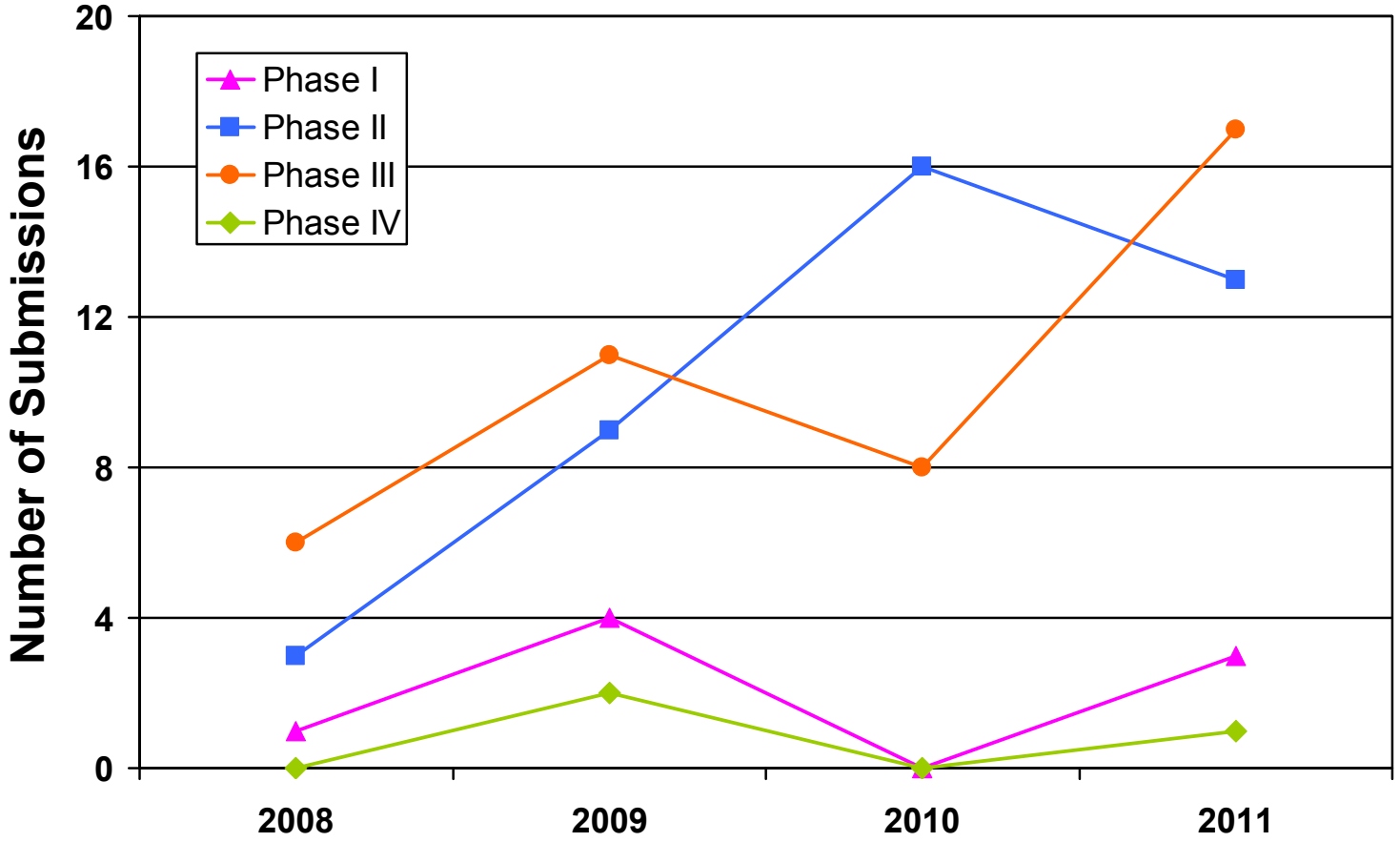
General trends

- More adaptive design submissions over time
- The more innovative proposals for drugs and biologics tend to be under IND as of now
  - Fewer approved examples
  - More in devices
- More design experimentation in early phases than in confirmatory trials

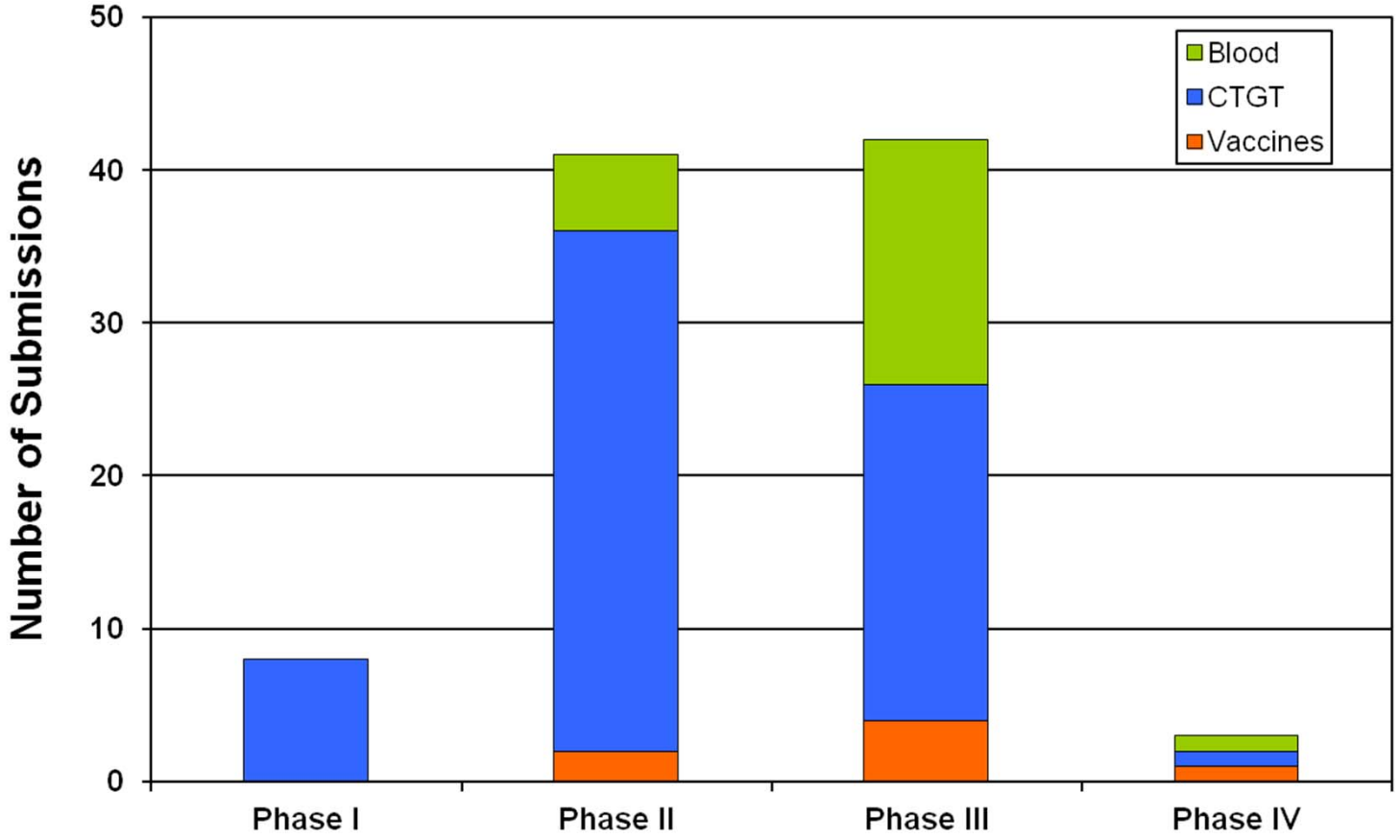
CBER's experiences

- Loose survey of IND and IDE statistical reviews from 2008-2011
  - All phases
  - Number of submissions requiring stat review: 7,030
  - Number of review memos screened: 958
  - Number of submissions involving adaptive design components: 94
- Results broken down by product office:
  - Vaccines (OVRR)
  - Blood (OBRR)
  - Cell, tissue, gene therapy (OCTGT)

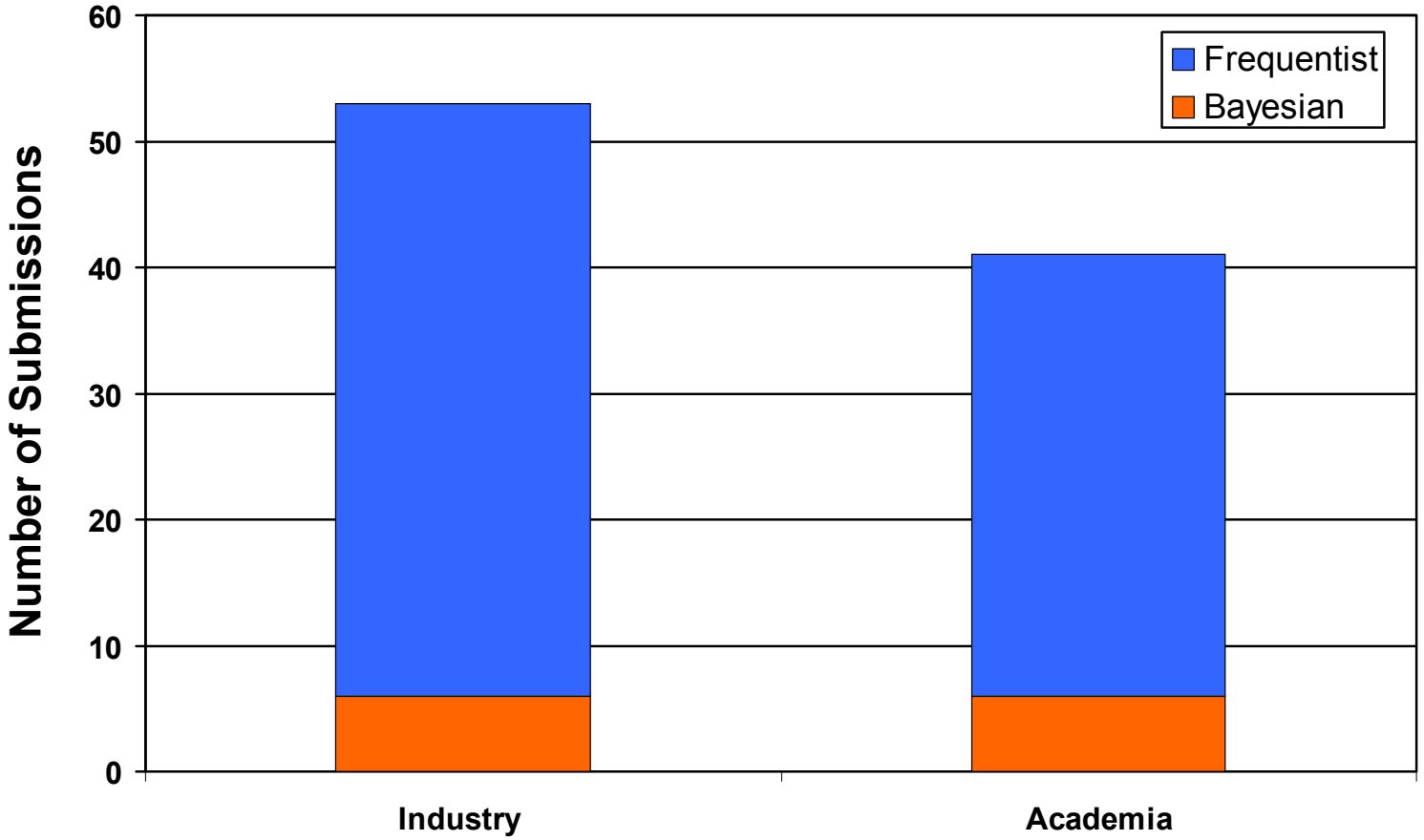
CBER adaptive trends by trial phase



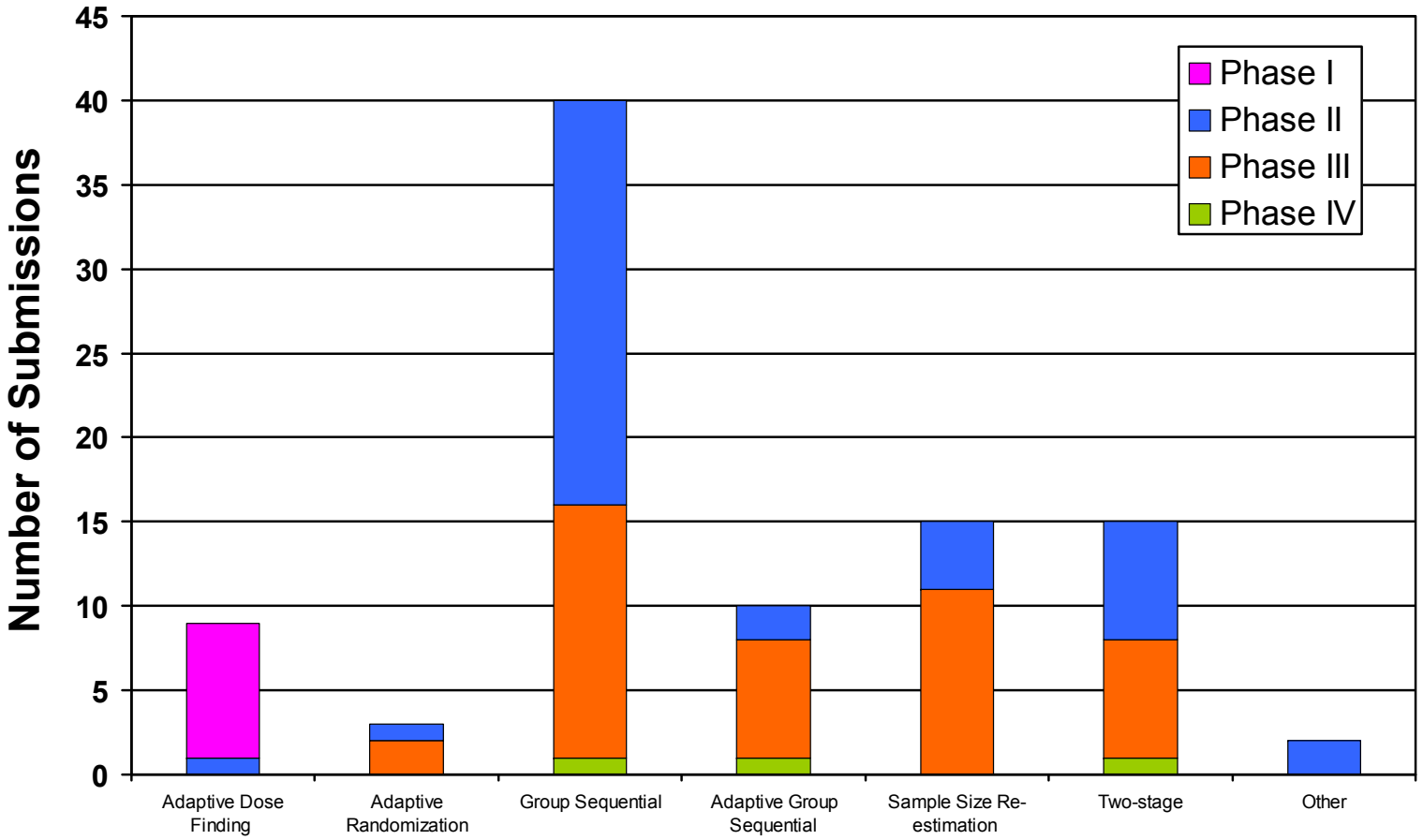
Phases by product class



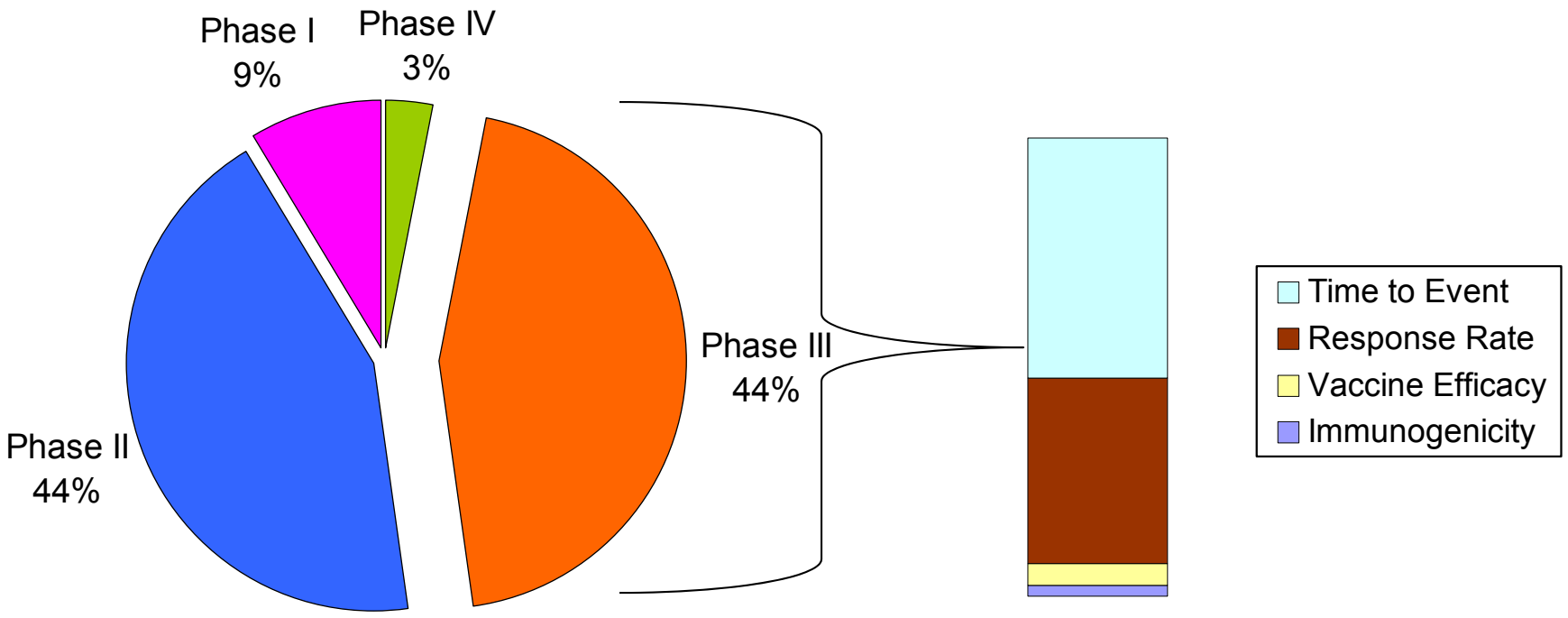
Sponsor by method / philosophy



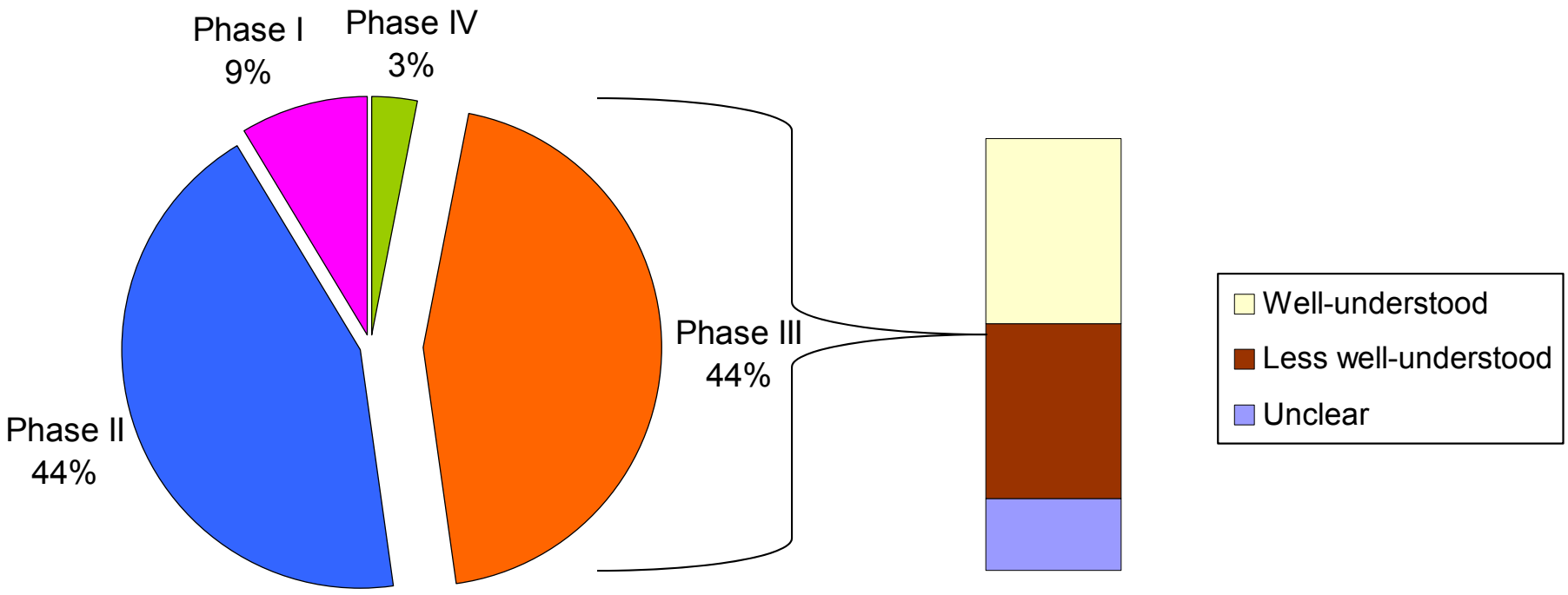
Adaptations



Phase III endpoints



Proportion “understood” in Phase III



CBER overview

- Trending upward, especially in Phase III
- Majority of Phase II and about half of Phase III proposals are in cell, tissue, and gene therapies
  - Large proportion of these are oncology
- Bayesian proposals are in the minority
  - Mostly used in CRM and other dose escalation or selection designs
  - Confirmatory Bayesian proposals can be counted on 1 hand
- Sample size re-estimation most common in confirmatory designs

CDRH experiences

- About 120 adaptive design submissions in past five years
- ~90% therapeutic, 10% diagnostic
- ~90% proposed protocols, 10% completed trials
- Some approved, some not
- Mostly sample size adaptations, some randomization adaptations
  - Large proportion of proposals Bayesian

Simulation

- The Bayesian device trial guidance discusses simulation for Type I error rates
  - Seen as fairly non-controversial at CDRH
- The adaptive guidance is more ambivalent
  - "Using simulations to demonstrate control of the Type I error rate, however, is controversial and not fully understood"
- CBER has accepted Type I error simulation
  - Not automatic
  - Evaluated on a case-by-case basis

Simulation issues

- Problems generally multidimensional
  - Not always obvious what parts of the parameter space need to be explored
- Review resources, expertise
  - No standardization of simulation methodologies, software
- Stochastic error

Some free advice

Interacting with FDA on AD

- DIA ADSWG 2011 survey respondents on whether regulatory acceptance is a barrier to adaptive design implementation:
  - ~45% Major barrier
  - ~45% Minor barrier
  - ~10% No barrier
- General advice: Try to make FDA an ally in your development program

Communication

- Clear and adequate communication in formal submissions (protocols, SAPs)
- Taking advantage of formal meeting opportunities with FDA
- Using informal contacts when possible
- Escalating when necessary (but don't shoot yourself in the foot on efficiency)

Documenting a novel AD proposal

- Describe technical aspects of the adaptation clearly
  - You're talking to two audiences: statisticians and clinicians
  - Keep in mind we're kind of obsessed with pre-specification
  - Type I error *will* come up in confirmatory studies
- Include literature when appropriate
- Describe the role of the trial in development plan
- Document chain of information-passing

Documentation cont.: justification

- Explain why you're making this proposal
- My personal hierarchy:
  - Ethics
  - Feasibility
  - Efficiency
- Compare the adaptive design proposal to other possibilities
  - Don't cheat!
  - Group-sequential designs are "well-understood"

Documentation cont.: simulation

- Provide a clear explanation of overall simulation strategy
  - Consider two versions: high-level for non-statistician audience and more detailed for statistical reviewers
- Provide detailed results
- Provide code
  - Can we run it? We don't endorse software, but you can ask specific questions…
  - Consider making at least toy version runnable by FDA
- C.f. AD & Bayesian guidances

Formal meetings with FDA

- Most important: End-of-phase 2 / Pre-phase 3 meeting
  - Have a draft protocol
  - Critical if planning an SPA
- Even at pre-IND stage, useful to talk about overall development program
- Type A meetings for stalled development programs
  - Includes failure to reach concurrence on SPA

Informal meetings with FDA

- You can ask for informal phone calls with review team
  - More likely to be granted if review team is convinced of public health importance and general scientific soundness of project
  - Better for simpler / discrete questions
  - Not binding but very useful
- Use public workshops and scientific conferences to sound out FDA staff on proposals
  - Very unlikely to get responses on specific submissions, but people often happy to opine in general terms
  - Not binding

Pushing back

- Speaking (unofficially) for CBER alone….
- If you get a response you disagree with, best first bet is usually to ask for an informal telecon
  - Explain clearly why you want the telecon
  - More likely to be helpful in cases of miscommunication; less likely if we just plain disagree
- Formal appeals process available
  - Contact center-specific ombudsman
- Understand what you are appealing:
  - Appealing clinical holds, CRs makes sense
  - Appealing “free advice” probably not useful

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