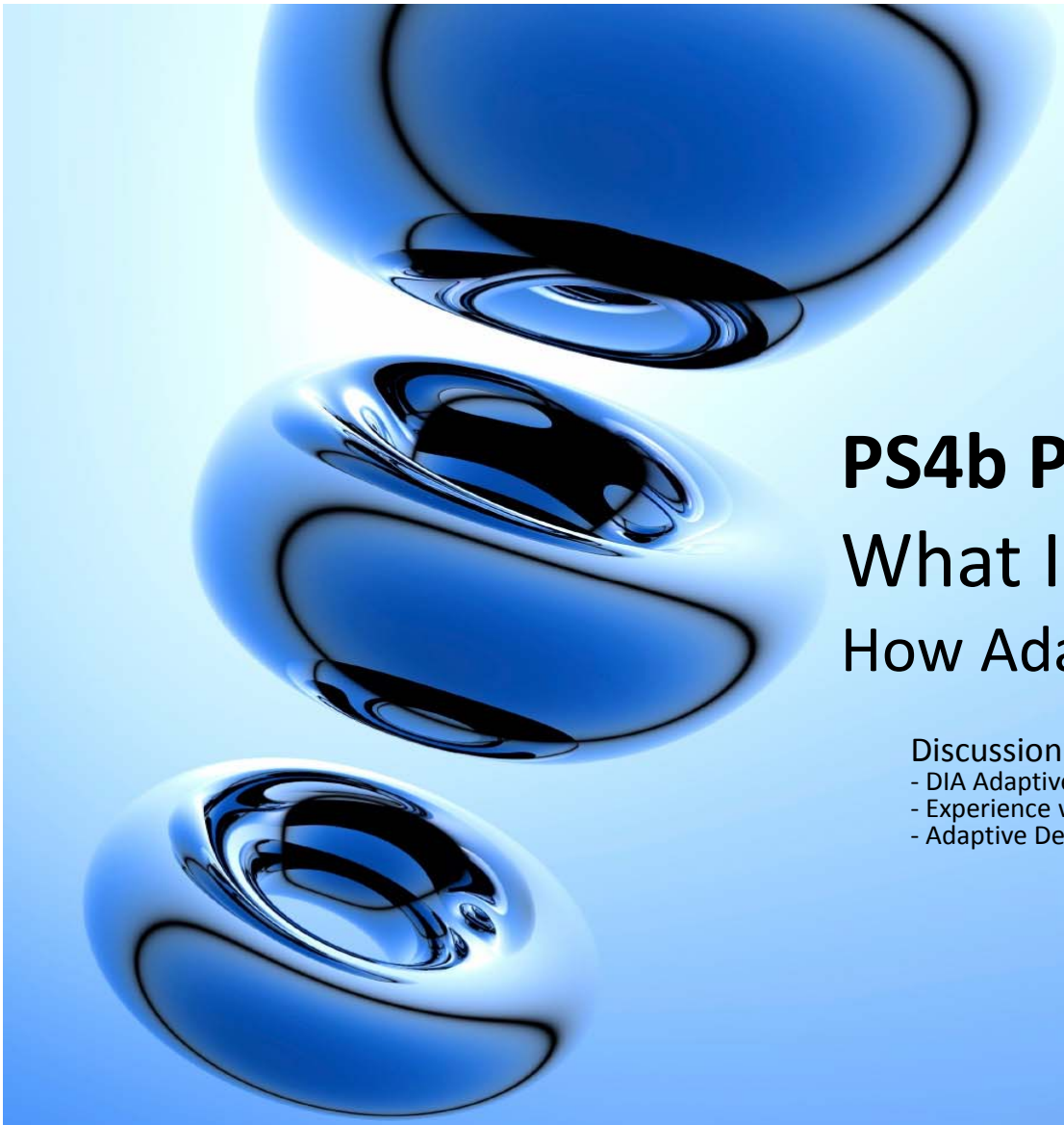


Cytel

PS4b Parallel Session

What Industry and FDA See:

How Adaptive Our Clinical Trials Are

Discussion

- DIA Adaptive Designs Scientific Working Group Survey Results, Alan Hartford
- Experience with Adaptive Design Clinical Trials in CBER, Annie Lin
- Adaptive Design Practice at CDRH, Xiting Yang

Caroline C. Morgan, Cytel Inc.

ASA Biopharmaceutical Section
Regulatory-Industry Statistics Workshop
Washington, DC
September 25-27, 2017

General Observations

- Considerable increase in ADs in the 2016 survey compared to the 2012 survey. However, no clear increase or decrease seen in the CBER and CDRH surveys. The FDA surveys also reflected the results of the registry survey carried out by the ADSWG survey subteam.
- Back in 2012 only 1 academic institution participated in the survey with no trials in the category "Other ADs" to report. In 2016, 7 institutions participated and reported 39 "Other ADs".
- General increases across all surveys in:
  - Exploratory adaptive designs
  - Population enrichment trials
  - Use of Bayesian methodology, particularly in exploratory and interim confirmatory setting.
  - Increased use of futility boundaries to improve the attrition rate in later Phase trials.
- Move away from the "less well understood" term employed in the 2010 guidance and misinterpreted somewhat by the industry, then dropped from later publications and the 2016 CDRH AD guidance.
- A persistent issue with the ADSWG survey is the difficulty for participants to obtain an overview of adaptive design use within their organizations.

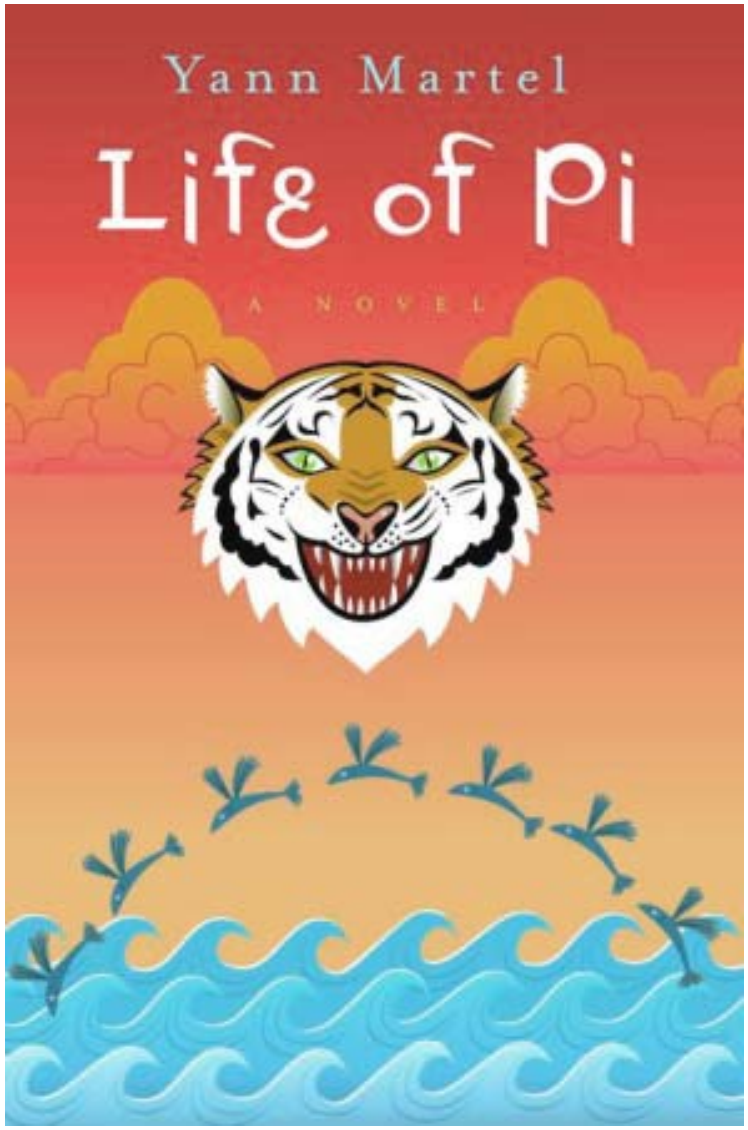
EMA Survey

- Systematic text search in scientific advice letters issued between January 1, 2007 and May 8, 2012 for relevant key terms.
- 59 scientific advices for Phase 2 and 3 AD trials (almost all were confirmatory Phase 2/3 or Phase 3 trials)
- Most frequently proposed adaptation was SSR, then dropping of treatment arms then population enrichment.
- Only 12 (20%) of the 59 proposals for an adaptive clinical trial were not accepted. 15 (25%) were accepted and 32 (54%) were conditionally accepted.
- The most frequent concerns raised by CHMP/SAWP were insufficient justifications of the adaptation strategy, type I error rate control and bias.
- The EMA continues to recommend early interaction with regulatory authorities since there is still relatively limited experience in the implementation and interpretation of adaptive clinical trials.

Elsäßer, A. et.al. Adaptive clinical trial designs for European marketing authorization: a survey of scientific advice letters from the European Medicines Agency. Trials (2014), 15:383
http://www.trialsjournal.com/content/15/1/383

Discussion

- Increase in population enrichment designs to target specific populations of interest, suggesting a real interest in personalised healthcare across the industry and academia.
- Despite improvements since the last survey, more emphasis needs to be given to ensuring that the appropriate simulations are performed for the designs and adequate firewalls are in place to minimize operational bias.
  - Allow adequate time for simulation guided clinical trial design in order to understand the operating characteristics and possible Type I error inflation, and ultimately increase information value and the chance of success.
- The perceived barriers of change management, regulatory acceptance and education remain a concern.
  - Education must continue and involve all levels (including senior management) so that there is alignment on expectations.
  - Communication on positive and negative experiences.
  - Early engagement with regulators to discuss the adaptive approach.



"All living things contain a measure of madness that moves them in strange, sometimes inexplicable ways. This madness can be saving; it is part and parcel of the ability to adapt. Without it, no species would survive."