What is the role of outcome studies in pulmonary drug development and what data can be collected during development to sufficiently characterize an agent so that an outcome study not necessary?

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PMRs and PMCs

- Post-marketing Requirement (PMR)
  - required under FDAAA
  - assess safety
- Post-marketing Commitment (PMC)
  - Sponsor agrees to conduct
  - assess safety (pre-FDAAA)
  - assess additional efficacy questions, quality issues

FDAAA

- Food and Drug Administration Amendments Act of 2007 (FDAAA)

- Provided FDA authority to require a post-marketing trial or study for any or all of the following purposes
  - To assess a known serious risk related to the use of the drug
  - To assess signals of serious risk related to the use of the drug
  - To identify an unexpected serious risk when available data indicate the potential for a serious risk
- At time of approval
- Post-approval if *new safety information*

FDAAA Trial vs. Study

- **Clinical trials -** prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects.

- **Studies** are all other investigations, such as investigations with humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.

FDAAA PMR

- Based on scientific data deemed appropriate by FDA, including information regarding chemically-related or pharmacologically-related drugs

- Before requiring a ***postmarketing study***, FDA must find that adverse event reporting and the new pharmacovigilance system will not be sufficient

- Before requiring a ***postmarketing clinical trial***, FDA must find that a postmarketing study will not be sufficient

- Purpose of the trial or study
  - assess a known serious risk, signal of serious risk or unexpected serious risk

PMR/PMC Examples from COPD Programs

- Fluticasone and Salmeterol Diskus (11/17/03 Approval ltr)
  - safety trial to evaluate effect on bone mineral density in COPD patients
  - efficacy trial to evaluate effect on COPD exacerbations
- Tiotropium HandiHaler (1/30/04 Approval ltr)
  - safety trial to evaluate effect on QT interval
- Arformoterol Inhalation Solution (10/6/06 Approval ltr)
  - safety trial to evaluate the risk of fatal and life-threatening respiratory events in COPD patients

PMR/PMC Examples from COPD Programs

- Formoterol Inhalation Solution (4/27/07 Approval ltr)
  - safety trial to evaluate the risk of fatal and life-threatening respiratory events in COPD patients
- Roflumilast (2/28/11 Approval ltr)
  - efficacy trial to evaluate roflumilast as an add-on therapy to ICS/LABA in severe COPD patients
- Aclidinium (7/23/12 Approval ltr)
  - safety trial to evaluate the risk of major adverse cardiac events with aclidinium bromide in COPD patients

Recent COPD Approvals without PMR/PMC

- Indacaterol inhalation powder (7/1/11)
- Fluticasone furoate and vilanterol (5/10/13)
- Umeclidinium and vilanterol (12/18/13)

Clinical Data in COPD Development Program

- Individual program considerations
  - mechanism of action and potential clinical toxicities
  - evaluate signals identified in early clinical trials or animal studies
  - size of safety database
- Allow patients with CV comorbidities (enrichment)
- Minimize missing data
- Deaths and serious adverse events
  - consider blinded adjudication
  - standardized definitions for events of interest

Clinical Data in COPD Development Program

- Thorough QT study
- Holter monitoring
- Electrocardiograms
- Heart rate and blood pressure
- Laboratory assessment
  - e.g. lipids (if relevant)

Will an outcome study be necessary?

- Cannot eliminate need for outcome study
  - signal in clinical program can trigger PMR
  - postmarketing signal may trigger PMR

- Minimize potential for outcome study
  - robust data collection
    - standardized assessment of events of interest, adjudication
  - adequate safety database
  - enriched patient population