Regulatory Advances and Challenges with Antibacterial Drug Development for HABP/VABP

Sumati Nambiar MD MPH
Director
Division of Anti-Infective Products
Center for Drug Evaluation and Research
FDA

ASM Microbe Meeting, New Orleans
June 03, 2017

Outline

- Background on HABP/VABP trials for antibacterial drugs
- Summarize key aspects of the draft guidance on developing drugs for HABP/VABP
- Summarize activities undertaken through public-private partnerships
- Ongoing work/next steps

HABP/VABP Trials

- HABP/VABP trials are challenging on several fronts
  - Enrollment challenges: Sick patients; issues with obtaining consent; often receiving antibacterial therapy prior to trial enrollment
  - Diagnostic challenges: Clinical, radiologic, and microbiologic criteria can overlap with other clinical conditions
  - Therapy is often empiric due to diagnostic uncertainty about the causative pathogens
  - The use of concomitant antibacterial therapies can confound assessment of treatment effect of the test drug

HABP/VABP Trials

- Over the last several years many activities have been undertaken to address challenges and find solutions for feasible and scientifically sound clinical trials in HABP/VABP
- Engagement of multiple stakeholders has played a key role in finding a path forward
- It is encouraging that some HABP/VABP trials are either underway/planned

Lessons Learned

- For some antibacterial drugs for which efficacy was demonstrated in certain indications, efficacy could not be demonstrated in HABP/VABP
  - Doripenem: Approved for cIAI and cUTI; higher mortality and lower cure rates in a VABP trial; trial terminated early due to these findings
  - Tigecycline: Approved for cIAI, cSSSI, CABP; efficacy not demonstrated in a HABP/VABP trial; higher mortality and lower cure rates in patients with VABP

Prescribing information for both drugs includes a warning about the higher mortality and lower clinical cure rates

- Ceftobiprole: Not approved in the US. In a HABP/VABP trial, lower cure rates and higher mortality in VABP patients

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm388328.htm
http://www.fda.gov/drugs/drugsafety/ucm369580.htm
Ambrose CID 2010; Udy Int J Antimicrob Agents. 2012; Awad et al. CID 2014

Regulatory Activities

Date	Event
March 31 and April 1, 2009	FDA co-sponsored workshop, "Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP); proceedings of the FDA co-sponsored workshop published in Clinical Infectious Diseases volume 51 Supplement 1
November 29, 2010	Draft HABP/VABP guidance issued
February 2011	14 docket comments in response to the draft guidance – overwhelming issue of greatest concern was that guidance was not practical to conduct trials in HABP/VABP
November 4, 2011	AIDAC meeting to discuss issues in clinical trial designs
May 7, 2014	Draft HABP/VABP guidance re-issued
August 2014	5 docket comments in response to second draft guidance
2015-2017	CTTI and FNIH Biomarkers Consortium public/private partnership begin and continue work on clinical trial designs and endpoints
2017-2018	Plans to convert the guidance to final

Guidance for Industry

Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Joseph Toerner, MD, MPH at 301-796-1300.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2014
Clinical/Antimicrobial
Revision 2

Trial Population

- Trial population can consist of:
  - Patients who have HABP only, or
  - Patients with VABP only, or
  - Patients who have either HABP or VABP; for an indication for treatment of HABP and VABP, approximately 50% of enrolled patients with VABP

Trial Population

- Inclusion criteria:
  - New onset or worsening respiratory signs/symptoms, hypoxemia, acute changes in ventilatory requirements
  - Temperature changes, elevated WBC/bands, leukopenia
  - Chest radiograph showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia
- Exclusion criteria:
  - Known or suspected CABP/viral pneumonia
  - > 24 hours of prior effective therapy in the 72 hours preceding enrollment

Trial Designs

- Noninferiority Trial:
  - Patients should have received ≤ 24 hours of effective non-study antibacterial therapy prior to enrollment
  - NI margin for all-cause mortality has been justified using historical data that show a treatment effect for antibacterial drugs
  - For a standard HABP/VABP indication, a 10% NI margin is recommended
- Superiority Trial:
  - Often difficult to demonstrate superiority against available therapies

Rex JH et al. Clin Infect Dis 2017

Endpoints

- Primary:
  - All-cause mortality evaluated at a fixed time point between day 14 and day 28 post randomization
  - All-cause mortality or disease-related complications (e.g., development of empyema; onset of acute respiratory distress syndrome; other complications) evaluated at a fixed time point between day 14 and day 28 post randomization
- Secondary:
  - Resolution of signs and symptoms of HABP/VABP at approximately 7 to 14 days after the completion of therapy
  - Days of hospitalization
  - Days on mechanical ventilation (for VABP and ventilated-HABP patients)

Analysis Populations

- Intent-to-treat (ITT):
  - All randomized patients
- Microbiological intent-to-treat (micro-ITT):
  - All randomized patients who have a baseline bacterial pathogen identified as the cause of HABP/VABP against which the investigational drug has antibacterial activity
- Per-protocol:
  - Patients who follow important components of the trial as specified in the protocol
- Per-protocol microbiologically evaluable:
  - Patients who follow important components of the trial as specified in the protocol and have a baseline bacterial pathogen identified as the cause of HABP/VABP

Addressing Trial Feasibility

- Allow for ITT as primary analysis population for drugs that have a broad spectrum of activity
- Allow receipt of up to 24 hours of prior effective therapy
- Allow the use of comparators that are considered standard of care, although not labeled for HABP/VABP
- Allow enrollment of ventilated HABP patients to be included in the VABP subgroup

Data Package

- For standard development programs, one adequate and well-controlled HABP/VABP trial is adequate if evidence of efficacy demonstrated in one or more other body sites of infection
- Usually HABP/VABP is a follow on indication studied after approval of an antibacterial drug for complicated intra-abdominal and/or complicated urinary tract infections

Data Package

- For drugs with activity against Gram-positive bacteria only
  - Supportive clinical data can be from indications such as ABSSSI, CABP
  - One practical challenge in HABP/VABP trials for drugs with activity against Gram-positive organisms only is the use of concomitant therapies for suspected/confirmed Gram-negative bacteria; generally such drugs also cover most Gram-positive bacteria

ABSSSI: Acute bacterial skin and skin structure infections
CABP: Community acquired bacterial pneumonia

Unmet Need Programs

- Examples of types of antibacterial drugs suitable for an unmet need development pathway
  - Act via new mechanisms of action
  - Have an added inhibitor that neutralizes a mechanism of resistance
  - Activity preserved in setting of resistance to other antibacterial drugs
- Smaller data package; greater uncertainty about risks and benefits
  - Single adequate and well-controlled trial may be adequate with supportive evidence

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm359184.pdf

Unmet Need Programs

- Adequate *in vitro* data and activity in relevant animal models of infection
- Evaluation of PK/PD relationships from animal models of infection
- Understanding the PK in patients with renal or hepatic impairment early in development
  - Generating these data early would facilitate enrollment of such patients as they often have important comorbidities
- Collection of PK data in clinical trials (e.g., informative sparse sampling in all patients enrolled)

Unmet Need: HABP/VABP

- Data package could include one HABP/VABP NI trial with a wider NI margin
  - Could enroll all-comers and not be limited to patients with a resistance phenotype of interest
  - Evidence of activity against phenotypes of interest can come from in vitro and animal models of infection
  - Robust PK/PD package

OR

- A superiority trial either in HABP/VABP or in a trial pooling across body sites; e.g., 50% HABP/VABP, 25% cUTI, 25% cIAI

Single-Pathogen Trials

- There is interest in developing antibacterial drugs that target only a single bacterial species such as *P. aeruginosa* or *A. baumannii*
- This topic was discussed at an FDA workshop in July 2016 and at the Antimicrobial Drugs Advisory Committee meeting in April 2017
- For such drugs, HABP/VABP is the most likely indication that will be studied as these organisms will most likely be identified in these infections

https://www.fda.gov/drugs/newsevents/ucm497650.htm
https://www.fda.gov/AdvisoryCommittees/Calendar/ucm551347.htm
Boucher HW et al. J Infect Dis 2017 May 5

Single-Pathogen Trials

- Similar principles apply as for unmet need programs in general; allow for wide NI margin, greater than that used in unmet need programs
- Animal models of infection play an even more important role in the development programs for such drugs
- Such development programs only apply for single-species products where conducting a clinical trial is extremely challenging or infeasible and not for products that have a broader spectrum of activity that includes organisms such as *P. aeruginosa* or *A. baumannii*

Adjunctive Therapies

- There has been interest in developing inhaled antibacterial drugs and monoclonal antibodies for treatment or prevention of HABP/VABP
- Trial design for such products will be superiority, assessing the superiority of the adjunctive treatment plus standard of care compared to standard of care; some examples:
  - Inhaled Amikacin Solution BAY41-6551 as Adjunctive Therapy in the Treatment of Gram-Negative Pneumonia (INHALE 1) https://clinicaltrials.gov/ct2/show/NCT01799993?term=amikacin+inhaled&rank=3
  - Aerosolized Amikacin and Fosfomycin in Mechanically Ventilated Patients With Gram-negative Pneumonia (IASIS) https://clinicaltrials.gov/ct2/show/NCT01969799?term=amikacin+fosfomycin&rank=1
  - Effort to Prevent Nosocomial Pneumonia Caused by *Pseudomonas aeruginosa* in Mechanically Ventilated Subjects (EVADE) https://clinicaltrials.gov/ct2/show/NCT02696902?term=medimmune+pneumonia&rank=1

HABP/VABP Trials

- Ongoing:
  - Imipenem/Relebactam/Cilastatin Versus Piperacillin/Tazobactam for Treatment of Participants With Bacterial Pneumonia (MK-7655A-014) (RESTORE-IMI 2); https://clinicaltrials.gov/ct2/show/NCT02493764
  - Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia (MK-7625A-008) (ASPECT-NP); https://clinicaltrials.gov/ct2/show/NCT02070757
  - Tedizolid Phosphate (TR-701 FA) vs Linezolid for the Treatment of Nosocomial Pneumonia (MK-1986-002); https://clinicaltrials.gov/ct2/show/NCT02019420
- Completed:
  - A Study Comparing Ceftazidime-Avibactam Versus Meropenem in Hospitalized Adults With Nosocomial Pneumonia; https://clinicaltrials.gov/ct2/show/NCT01808092;
  - Topline results: http://www.pfizer.com/news/press-release/press-release-detail/pivotal_phase_iii_study_underscores_efficacy_of_zavicefta_ceftazidime_avibactam_for_treatment_of_hospital_acquired_pneumonia_a_leading_cause_of_mortality_in_hospitals

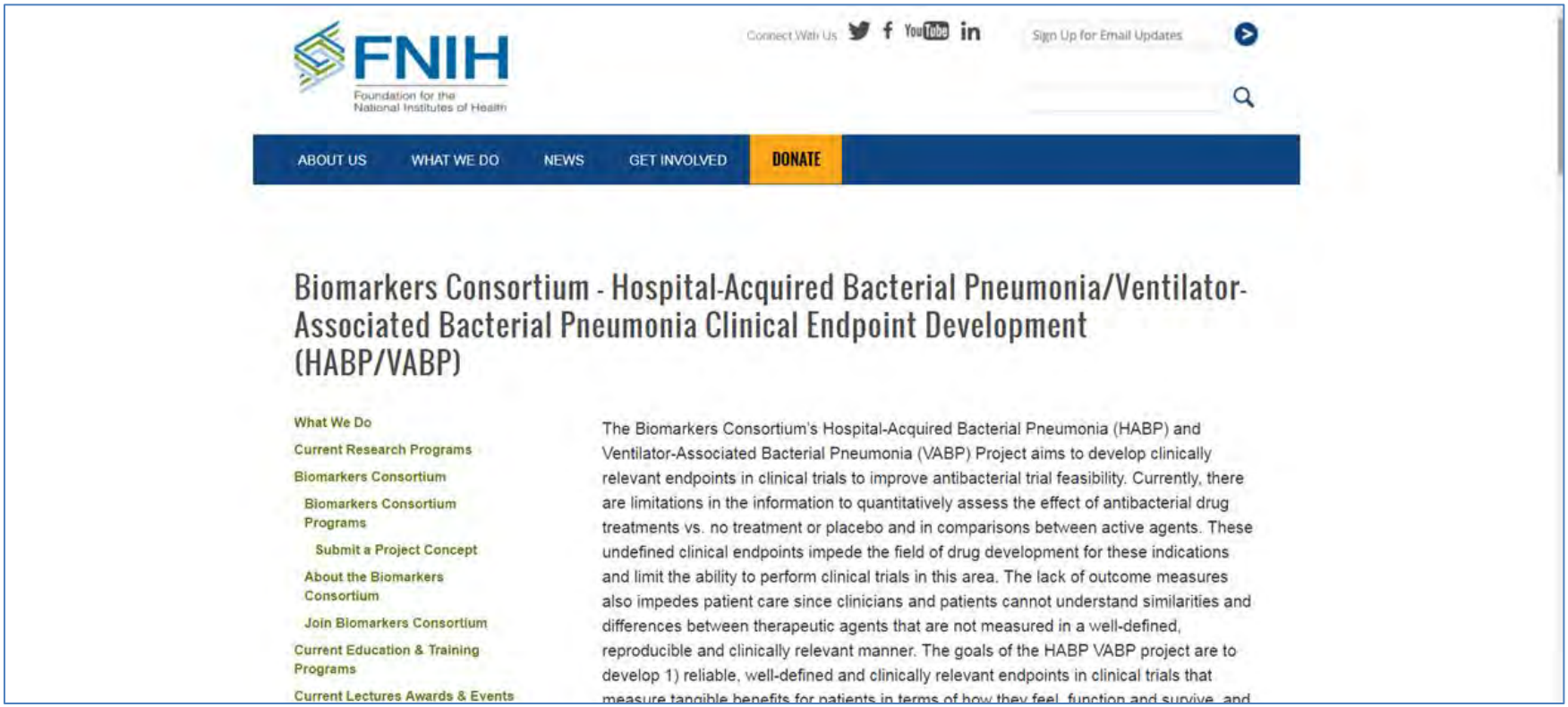
HABP/VABP Trials

- Planned (not yet recruiting):
  - Clinical Study of S-649266 for the Treatment of Nosocomial Pneumonia Caused by Gram-negative Pathogens (APEKS-NP): https://clinicaltrials.gov/ct2/show/NCT03032380?term=nosocomial+pneumonia&rank=41
  - A Study of Meropenem-Vaborbactam Versus Piperacillin/Tazobactam in Participants With Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (TANGOIII): https://clinicaltrials.gov/ct2/show/NCT03006679?term=nosocomial+pneumonia&rank=84

Public-Private Partnerships

- Foundations for the National Institutes of Health Biomarkers Consortium (FNIH) HABP/VABP Project
- Goals:
  - Develop reliable and well-defined clinically relevant endpoints that measure tangible benefits for patients in terms of how they feel, function and survive
  - Identify potential changes to study design and analysis that could improve the feasibility of HABP/VABP NI trials
  - Complete the content validity phase of a Patient-Reported Outcome (PRO) measure for HABP
- Interim recommendations: Submitted to the docket in 2013; update published in Clinical Infectious Diseases, March 2016
- Recommendations based on analyses of data from recent clinical trials will be submitted to the docket

https://fnih.org/what-we-do/biomarkers-consortium/programs/ventilator-acquired-bacterial-pneumonia

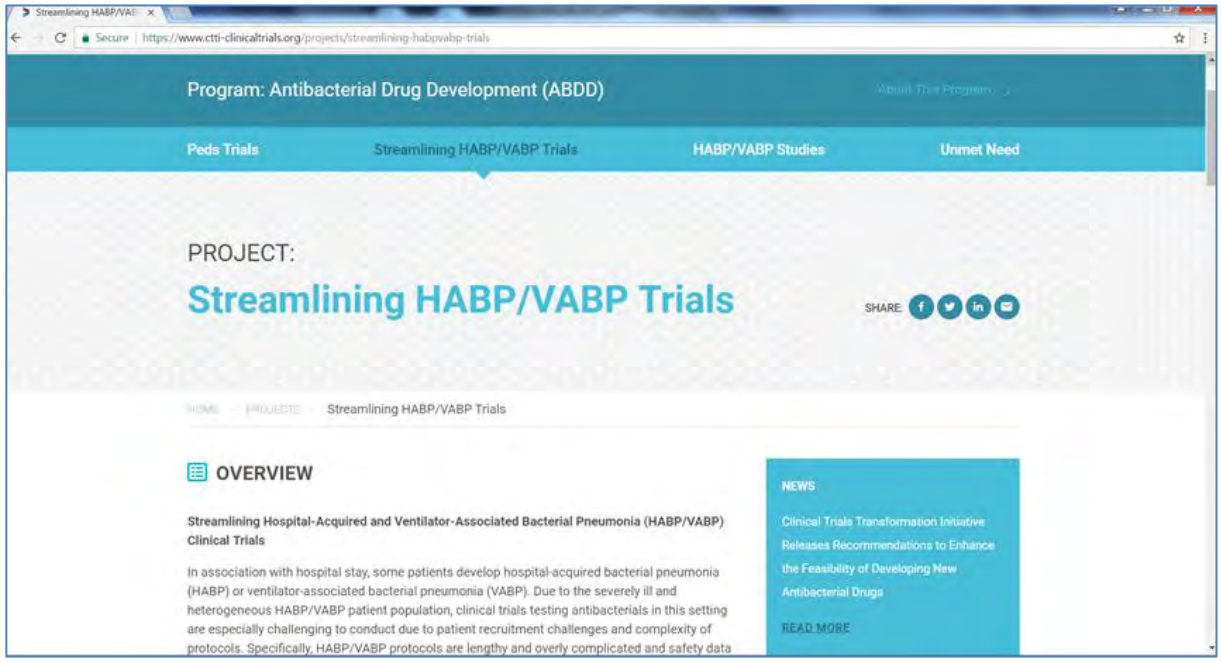


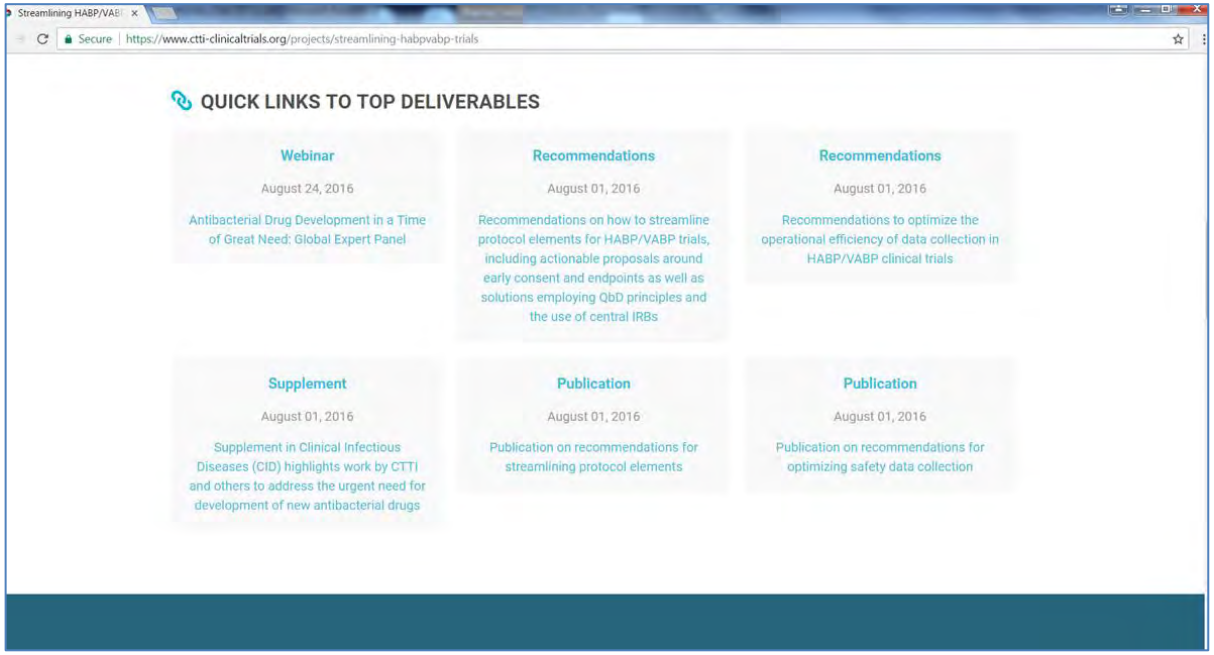
https://fnih.org/what-we-do/biomarkers-consortium/programs/ventilator-acquired-bacterial-pneumonia

Public-Private Partnerships

- CTTI HABP/VABP Project: Evidence-based recommendations for designing more feasible clinical trials
  - Strategies for streamlining protocol elements to increase enrollment and reduce trial complexity
  - Proposals around early consent and endpoint selection and solutions employing Quality by Design principles and the use of central IRBs
  - Methods to optimize operational efficiency in HABP/VABP trials by streamlining data collection

https://www.ctti-clinicaltrials.org/projects/streamlining-habpvabp-trials





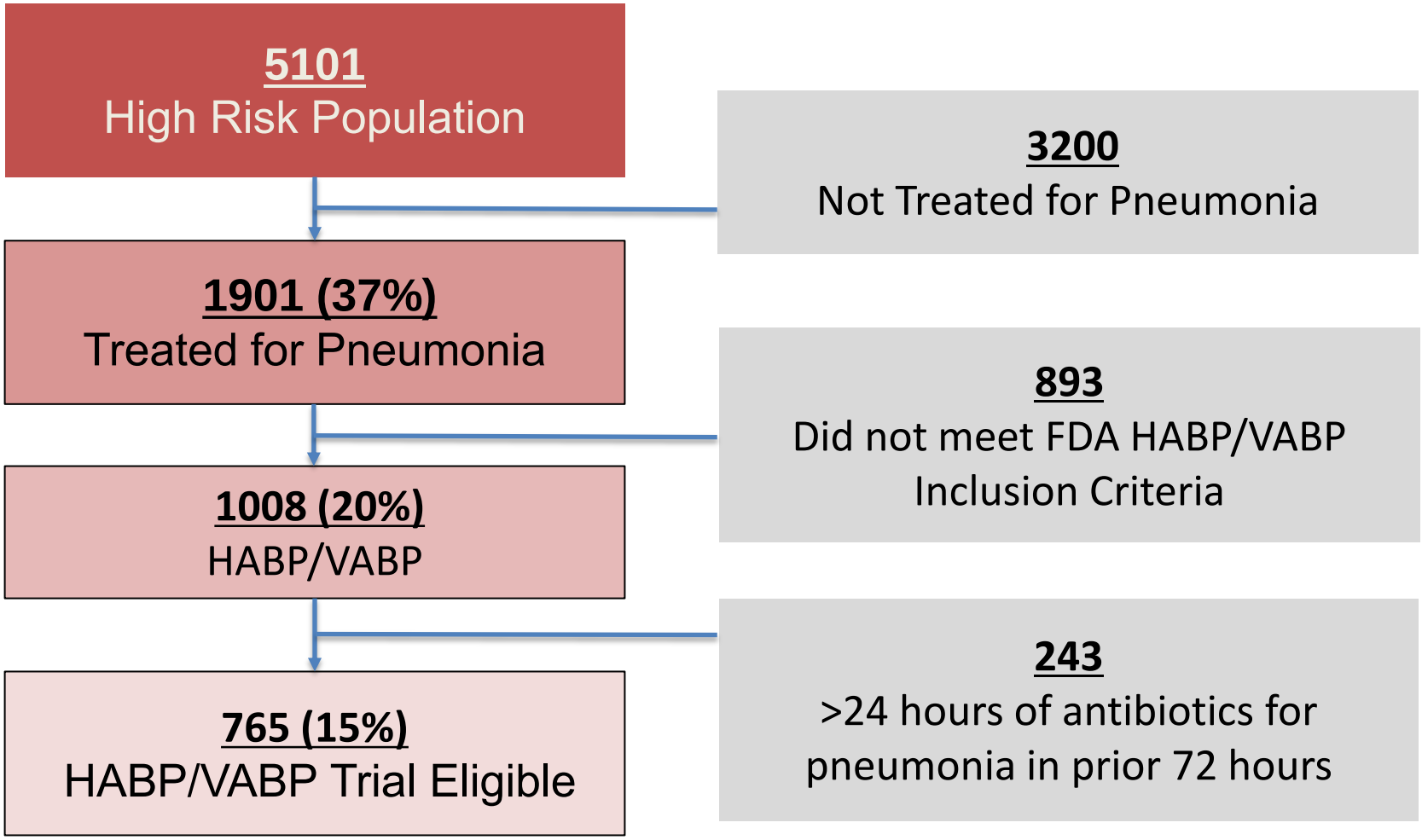
https://www.ctti-clinicaltrials.org/projects/streamlining-habpvabp-trials

Observational Study

- Multicenter, prospective, observational study conducted over 9 months in ICUs of 28 US hospitals
  - Estimate the rates of HABP/VABP among ICU patients considered high risk for pneumonia
  - Estimate the proportion of patients with HABP/VABP who would be eligible for a HABP/VABP trial

High risk: >12 hours of treatment with invasive mechanical ventilation, noninvasive ventilation , or high levels of supplemental oxygen within the past 7 days
Slide adapted with permission from May 21, 2017 ATS presentation by Bergin et al.

High Risk Population



Slide adapted with permission from May 21, 2017 ATS presentation by Bergin et al.

Common HABP/VABP Exclusion Criteria

Among HABP/VABP Trial Eligible Patients

Potential Exclusion Criterion	Proportion
Dialysis	44/865 (5%)
eGFR <10 mL/min/1.73m^2	33/865 (4%)
eGFR <30 mL/min/1.73m^2	218/865 (25%)
eGFR <50 mL/min/1.73m^2	364/865 (42%)
Severe Hepatic Dysfunction	90/865 (10%)
Receiving Chemotherapy	41/865 (5%)
Stem Cell Transplant	20/865 (2%)
Cystic Fibrosis	2/865 (0.2%)
Interstitial Lung Disease	28/865 (3%)
Seizures	64/865 (7%)
Enrolled in Another Clinical Trial	22/865 (3%)

Slide adapted with permission from May 21, 2017 ATS presentation by Bergin et al.

Ongoing Activities

- Patient Reported Outcome (PRO) for HABP:
  - Being developed by ICON in collaboration with FNIH
  - The instrument is being developed in accordance with the FDA Drug Development Tool qualification process
  - FDA funding has been provided to validate the PRO instrument
- Review of the FNIH docket submission
- Finalize the guidance document on developing antibacterial drugs for HABP/VABP
- Develop recommendations for evaluating single-species antibacterial drugs
- Advancing the development of animal models of serious infection caused by *P. aeruginosa* and *A. baumannii* (FDA BAA-17-00123N)

https://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm452292.htm
https://fnih.org/what-we-do/biomarkers-consortium/programs/ventilator-acquired-bacterial-pneumonia
https://fnih.org/sites/default/files/final/pdf/fda-coa-award.pdf

Summary

- Progress has been made in designing feasible and scientifically sound clinical trials for antibacterial drugs; some recent approvals and reports of successful trials
- While it is encouraging to see some antibacterial drug development for HABP/VABP, many challenges remain in studying this indication
- We appreciate the efforts made by the various stakeholders to facilitate antibacterial drug development for HABP/VABP
- Ongoing work and lessons learned from trials that are underway/recently completed will further help us understand some of the challenges and facilitate efforts to continue to refine trial recommendations

U.S. FOOD & DRUG ADMINISTRATION

Thank You


FDA
U.S. FOOD & DRUG
ADMINISTRATION