Interim Considerations for Clinical Trial Design for the Study of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

Foundation for the National Institutes of Health
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Executive Summary

- At FDA’s request, this Working Group has been constituted to provide recommendations to support FDA’s goal of articulating scientifically rigorous and clinically relevant hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) drug development based on a non-inferiority (NI) design.

- Despite the potential clinical trial implementation feasibility issues that have been raised with current FDA HABP/VABP Guidance, including an all-cause mortality (ACM) endpoint, most Working Group participants are comfortable with ACM as an endpoint, especially for VABP, if trial feasibility could be addressed by changing other parameters of study design.

- The outstanding questions for use of ACM relate to timing of its assessment, as well as to whether there are suitable intermediate clinical endpoints. One concern with ACM is its lower incidence in registrational trials versus “real life.” It is hypothesized that making exclusion criteria less restrictive, and thereby increasing the severity of illness in the enrolled population, has the potential to facilitate enrollment. The past practice of excluding those more ill patients who could have a poor outcome exacts a cost to a study of limited enrollment, lower ACM, and decreased generalizability. The practical consequence of this challenge is that when the mortality rate for enrolled subjects falls much below 15% to 20%, trial sizes rapidly enlarge based on a change to the odds-ratio metric. It is anticipated that enrolling a population with increased severity of illness would make trials more broadly generalizable while decreasing sample size of trials based on a risk-difference metric.

- All-Cause Mortality in VABP could be evaluated at day 14, or at day 28, or sometime in between (e.g., day 21); rates of ACM would be expected to be 10% to 15% (e.g., for day 14 ACM) and 20% to 25% (e.g., for day 28 ACM).

- For VABP sample size estimation and analyses, when mortality is at least 15% on the active control regimen, a risk-difference metric with an NI margin of 10% could be used.

- For HABP, a clinically meaningful endpoint of symptom improvement plus survival for non-ventilated patients could be based on the historical data for community-acquired bacterial pneumonia, for which there is a large treatment effect to day 7 of antibacterial drug therapy.

- There was some concern in the Working Group that mortality and other differences between HABP and VABP suggest these are different diseases, meaning that combining both in a single trial could raise methodological issues.

- A number of candidate changes to other aspects of trial design (e.g., primary analysis set) were identified as promising potential approaches to improving feasibility, while maintaining scientific validity.

- The Working Group remains very interested in evaluating the potential application of alternative endpoints (e.g., improved oxygenation) for VABP and considering how they could be evaluated and qualified as endpoints.

- The next step for the Working Group is to examine the data from a single HABP/VABP trial, contributed in kind, to understand the data that are available (e.g., prevalence of respiratory symptoms at trial enrollment and their severity, mortality rate over time).

- Subsequently, a formal statistical analysis plan will be drafted; data from a number of HABP/VABP trials contributed in kind will be analyzed, with the results used to inform the Working Group’s final recommendations to FDA.
Background

At FDA’s request, this Working Group has been constituted to provide recommendations to support FDA’s goal of articulating scientifically rigorous and clinically relevant HABP/VABP drug development guidance that is also feasible for sponsors to implement in terms of both financial cost and time. The HABP/VABP Working Group is building upon the work of the FNIH Biomarkers Consortium Community-Acquired Bacterial Pneumonia (CABP)/Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Project Team. Forthcoming recommendations will be based on an evidenced-based, hypothesis-testing endeavor through analysis of HABP/VABP clinical trial data contributed in kind. In addition to FDA, other likely beneficiaries include clinicians, investigators, and patients.

Working Group Goal and Processes

The goal of the HABP/VABP Working Group’s efforts is to identify potential changes to study design and analysis that could improve the feasibility—while retaining reliability, scientific validity, and meaningfulness for patients, caregivers, and clinicians—of HABP/VABP registrational clinical trials based on an NI design. HABP/VABP registrational trials based on a superiority design, as for narrow-spectrum antimicrobials intended to treat uncommon, multidrug-resistant pathogens, are not a focus of this group’s initial deliberations.

This goal will be achieved via the following process:

• Evaluating the medical literature to determine those HABP/VABP signs, symptoms, and measures of function that are clinically relevant to treatment outcome, including mortality;
• Identifying feasibility constraints imposed by clinical trial requirements other than the choice of the primary endpoint (e.g., definition of statistical analysis populations);
• Determining whether it is possible to identify non-mortality endpoints, with specific regard to their potential use as the primary endpoint or as part of a composite primary endpoint. Using hypotheses generated based on the medical literature followed by examination of data from modern-day clinical trials, work on this question will focus specifically on defining the variables in such endpoints and quantifying a treatment effect on how patients feel and/or function; and
• Performing sensitivity analyses to understand how certain assumptions (e.g., day of endpoint assessment) impact these parameters.

Primary Endpoint: All-Cause Mortality vs. Non-Mortality vs. Composite (ACM Plus Non-Mortality)

• In a review of the literature for non-mortality clinical endpoints in HABP/VABP, FDA found 16 papers providing historical evidence for sensitivity to drug effects on the ACM endpoint. Only two papers described non-mortality outcome measures: Luna et al. [i] showed that serial Clinical Pulmonary Infection Score (CPIS) values did not improve among non-survivors and that PaO2/FiO2 did not improve or worsened among non-survivors, and Dennesen et al. [ii] showed that PaO2/FiO2 correlated with clinical resolution. A discussion of non-mortality measures at the 2009 FDA co-sponsored workshop included PaO2/FiO2, time-on-ventilator (for VABP), and time-in-hospital. Subsequently, Esperatti et al. [iii] found that an increase in the Sequential Organ Failure Assessment...
score from day 1 to day 5 of treatment and lack of improvement in PaO2/FiO2 were independently associated with increased 28-day mortality.

- In November 2011, the Anti-Infective Drugs Advisory Committee reviewed the HABP/VABP mortality endpoint based on four studies with mortality data at days 14, 21, and 28 [iv]. In this set of data, a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score at baseline correlated with a higher mortality rate. The day 14 mortality rate is no more than 10% lower than 28-day mortality in a combined population. In HABP, mortality in treated patients ranged between 14% and 17% at day 14, and as expected, the VABP 14-day rate in treated patients was somewhat higher at 10% to 20%.

- However, data from trials recently conducted by one sponsor suggest a lower mortality rate can be observed (Rebecca Redman, written communication, June 2013). Evaluation of the data sets contributed in kind to the FNIH as part of this Working Group initiative should elucidate the mortality rate that has been observed in a broad range of modern-day trials using current enrollment criteria.

- The principal strengths of ACM are its simplicity of measurement (decreasing missing data) and unequivocal clinical relevance. ACM is, and will always remain, an acceptable choice as the primary endpoint in any nosocomial pneumonia trial. In addition, other endpoints cannot be evaluated independent of mortality since patients must be alive in order for measurements to be obtained (i.e., patients are not excluded from analysis due to death). Also, there is a clear and large treatment effect of antibiotics on ACM that justifies the NI trial design with an ACM endpoint.

- Concerns raised with ACM as an endpoint may include both competing risks (causes) of death and the timing of assessment. Potential concerns of some participants are that in some patients death may be caused a) by comorbidities that cannot be resolved by antimicrobial therapy and/or b) by withdrawal of care (especially for VABP). Some participants suggested that a day 28 assessment might enhance these potential concerns. Other participants countered that while these concerns would be relevant for superiority trials against active control antibiotics, they are not influential in the NI setting because the historical evidence, despite its modest size, establishes that the treatment effects of antibiotics are very large even in the presence of competing risks.

- Concerns were also raised that a smaller clinical trial sample size could result in meaningful imbalances between treatment groups for variables that impact mortality such as chronic health conditions, acute comorbid diseases, and pharmacological interventions. Other participants countered that such concerns would apply to all endpoints, not only to ACM.

- Some participants noted that while it is always important to measure mortality—and certainly a drug should not increase mortality—alternative endpoints can also provide important indirect or direct insights about benefits for patients. Data from recent HABP/VABP registrational trials provide evidence of a non-mortality endpoint that is sensitive to treatment effect and is correlated with ACM [v] [vi] [vii], although substantive evidence currently is not available to determine whether an estimated treatment effect on that non-mortality endpoint would provide reliable insights about the true effect of treatment on direct measures of how a patient feels, functions, or survives [viii].

- A composite endpoint that includes mortality could be clinically relevant; reflect how a patient feels, functions, or survives; and allow for more feasible clinical trials, although some noted that such an approach could have the undesirable effect of increasing clinical trial sample sizes and would still require justification of an NI margin.

- Global harmonization has suffered since, in general, the European Medicines Agency remains focused on non-mortality endpoints.
Statistical Considerations and Feasibility

- The decision to use either an odds-ratio or a risk-difference approach will have an impact on sample size requirements. If a fixed risk-difference margin is used, it will be important to indicate the lowest mortality rate at which the fixed risk difference would still be able to reliably demonstrate NI.
- The ACM endpoint is well defined, reliable, and clinically meaningful. Its strong level of clinical relevance justifies requiring only a single trial for registration, which in itself increases the feasibility of clinical trial conduct for this indication. Furthermore, when using absolute differences for an ACM endpoint, there is evidence-based justification for a 10% margin when mortality is at least 15% on the active control. Data reviewed by FDA from prior VABP trials confirm mortality should be in the range of 15% to 24% in the interval between day 14 to day 28. With the 10% margin and an active control survival of 15%, the total sample size would be approximately 544 patients in an intent-to-treat (ITT) analysis. Positive results would be obtained if the estimated ACM on the experimental regimen did not exceed that on the active control by at least 3.5%. ACM also allows cost savings due to the simplicity of measuring that endpoint and enhances trial integrity by reducing the risk of missing data.
- However, if a microbiologically confirmed ITT (micro-ITT) primary analysis population is required, the required number of enrolled patients becomes much larger.
- The question of feasibility of various endpoints and trial design characteristics remains the subject of active debate in the Working Group. For example, whether a 500-patient sample size is achievable depends on the type of patient and other factors such as enrollment criteria and choice of analysis population; e.g., 500 PORT V CABP patients would be difficult to enroll. Other important impacts on feasibility include the ability to capture information and subsequent missing data. For example, it is likely not feasible to collect information on a biomarker every hour in an intensive care unit setting. One benefit of the ACM endpoint is that it is an easy endpoint to capture, so discussion of a composite endpoint should include consideration of the feasibility of assessing the chosen endpoint and risk of missing data for that endpoint. It is expected that analysis of actual clinical trial data will facilitate consensus-building on these important considerations.
- Other elements of NI trial design beyond choice of endpoint impact feasibility: the NI margin, the primary analysis population to determine treatment effect, and the inclusion/exclusion criteria.
  - While the traditional outcome measure of clinical response is perceived by some experts as a subjective endpoint that is an indirect measure of patient benefit and currently cannot be used to set an NI margin, stakeholders agree that ACM is evaluated in any trial. ACM is a direct measure of patient benefit for which evidence exists to justify an NI margin. Further, ACM is a valid endpoint in that it is well defined and reliable and characterized by minimal ascertainment and measurement bias.
  - Concerns about a lack of clinical trial feasibility based on the sample size required for an ACM endpoint may be minimized if this endpoint is analyzed using the ITT as the primary analysis set.
  - Other endpoints may be considered, such as 14-day (or 21-day) ACM or a composite index, with the requisite requirements for validation and determination of the relationship between indirect and direct measures as well as justification of an NI margin. With regard to the NI margin, the 10% margin proposed by FDA is based on ACM in the ITT, not the micro-ITT, analysis population.
  - Either a 14-day or a 28-day evaluation is likely an informative time point for ACM. At 14 days, the proportion of deaths from “other causes” (e.g., comorbid conditions) may be lower. However, the mortality rate will be lower at 14 days than at 28 days, and this may lead to the need for a larger study if the odds-ratio metric is used. Furthermore, for a marginally effective antibacterial drug, the time to death from inadequate treatment of infection could be delayed.
beyond 14 days. If a 14-day ACM mortality assessment is chosen as the primary endpoint for
efficacy, evaluation of 28-day ACM would still be a key secondary efficacy endpoint and an
important safety assessment.

- Selection of the primary analysis set may well represent the greatest opportunity for
decreasing sample size while maintaining scientific validity. The primary analysis set is
defined as the population with the disease of interest in which a treatment effect will be
evaluated; however, there are no "gold standard" criteria for the diagnosis of VABP.
Diagnosis by lung histopathology and respiratory tract culture may lack sensitivity and
specificity and, accordingly, may not add value to the diagnosis of VABP. Issues with
microbiological confirmation include a large number of different sampling techniques, a high
rate of false-positives, inability to distinguish between colonizing and pathogenic bacteria,
and the lack of quantitative biotechnology sophistication at certain sites involved in a global
trial. Thus, microbiological documentation is viewed by some as an imperfect clinical tool
that justifies choice of an antibiotic against the possible causative pathogen isolated from the
respiratory tract but not as a diagnostic tool for the disease of nosocomial pneumonia in a
registrational trial. However, others expressed concern with this approach, citing a recent
analysis showing that patients with microbiologically documented HABP/VABP have
different baseline characteristics and different mortality rates than those without such
documentation [ix]. Specifically, following adjustment for potential confounders, patients
with positive microbiology at baseline had higher hospital mortality and lower 90-day
survival but, notably, a non-significantly lower 28-day survival. A proposed approach,
balancing these varied concerns, suggests that with the present state of the art regarding
microbiological diagnosis (e.g., availability of results with some meaningful delay), it makes
sense to assess ACM primarily in the ITT analysis set but to place a substantial emphasis on
results in the micro-ITT population. One option suggested is to require that a minimum
percentage of the ITT population be microbiologically documented (e.g., 50% of ITT be
micro-ITT), the results of which would be expected to be consistent with those in the primary
ITT analysis.

- Accordingly, various values of the microbiological evaluability rate (the 50% rate noted
above as well as alternative values) will be considered during the Working Group’s data
analysis, based upon previously observed data, and performance characteristics related to the
expected sample size in a microbiologically confirmed population (i.e., uncertainty in the
estimates received) will be used to provide a recommendation.

- Regardless, if employing ITT as the primary analysis population, it will be essential to ensure
that the patients enrolled do not have an etiology other than HABP/VABP (e.g., pulmonary
edema or venous thromboembolism).

- Overall, considering the ITT population as the primary efficacy set found broad support
within the Working Group, with the micro-ITT population as a key secondary subset for
sensitivity analyses.

- Using ITT as the primary efficacy set is most logical when the test agent is reasonably likely
to have utility in the bulk of the enrolled population. For agents with a reasonably broad
spectrum (e.g., an agent active against most gram-negative pathogens), this is a good
assumption. For a narrow-spectrum agent (e.g., an agent active only against \textit{Acinetobacter spp.}), population enrichment via enrollment based on rapid and sufficiently predictive
microbiologic tools would seem necessary.

- The impact of prior antibiotic use has been an area of much discussion in HABP/VABP and
other indications (especially CABP). Although allowing up to 24 to 48 hours of prior
antibiotic treatment before study enrollment may substantially enhance trial feasibility in this
indication, effective antibacterial drugs given promptly for the treatment of HABP/VABP
may result in interpretability and integrity issues for an NI trial design. Some participants
suggested that interpretability and integrity issues due to 24 hours of prior antibacterial drug therapy may be of less concern with a 28-day ACM endpoint. As a potential solution, trial sites should be encouraged to employ prompt or even “anticipatory” enrollment procedures so that for some patients the antibacterial drug therapy for HABP/VABP can be initiated promptly within the context of the trial. Regardless, the Working Group expects that available data sets could be used to further evaluate this issue.

- Finally, beyond ACM, all other potential alternative outcome measures will have to be “well defined and reliable,” define concepts of direct relevance to patients or have evidence that indirect benefits reflect direct benefits, allow justification of an NI margin, and prove useful for increasing trial feasibility. Study feasibility is defined not only based on the trial size but also the ability to be conducted globally, to obtain valid measurements with minimal missing data, and to reach completion within a reasonable timeframe while maintaining scientific validity. Furthermore, study costs should not preclude small companies from embarking on such trials. In short, the feasibility of the study will depend on considering all drivers of study design: outcome measure, enrollment criteria, NI margin, inclusion and exclusion criteria, primary analysis set, and meaningfulness of the design and results in providing benefits to patients. Lastly, as an extension to addressing issues related to the individual clinical trial, the Working Group will address feasibility and scientific validity considerations of conducting separate or combined trials for HABP and VABP as well as of conducting separate development programs in these two indications.

Endpoints for HABP vs. VABP Other Than ACM

The endpoint for HABP vs. VABP trials could well be different given the differences in patient populations, diagnostic modalities, and mortality. While the 2010 FDA Guidance advised separating the indications, comments posted to the docket discouraged this approach, and now the FDA in fact would consider proposed approaches to study both indications in a single trial, at least as a starting point. Nonetheless, there was concern among some members in the Working Group that mortality rate and other differences between the two infections may suggest these are different diseases, which means that for a single trial enrolling both populations, a sponsor may have to prespecify the hypotheses based on the proportion of patients who have VABP or HABP. Even within the VABP subset there may be a bimodal distribution of patients based on drug clearance, for example. Most notably, a small subset of VABP patients could alter conclusions from what is primarily a HABP study, or NI on HABP could mask differences in VABP patients.

Potential HABP Endpoints

An FDA review of historical papers for a CABP clinical endpoint included a cross-study comparison of patient recovery before the availability of antibiotic drugs versus after. These data demonstrate a large difference in clinical resolution of symptoms between treated and untreated patients that begins as soon as day 1 and extends to day 7. In this approach, historical “cross-study” comparisons represent the most appropriate data to justify a clinical recovery endpoint on symptoms for the NI trial design in HABP/VABP, specifically a clinical recovery endpoint up to day 7. Collection of carefully defined patient symptoms would fulfill the requirement to assess how a patient feels, functions, and survives. Since HABP is more severe than CABP, the treatment effect should be large. Recent evidence from older hospitalized patients with CABP with comorbidities (patients similar to those with HABP) shows substantial symptom burden in these patients [x].
**Potential VABP Endpoints**

For VABP, a different approach may be necessary given the inability of most intubated patients to reliably report symptoms.

- *A priori*, various parameters were seen as biologically plausible elements of an early endpoint, but the possible choices vary in their strengths and weaknesses. It was agreed that the CPIS criteria are not adequate in terms of following patients over time given existing evidence on the lack of reliability of this measure. (See Schurink et al. [xi] and Zilberberg et al. [xii]; CPIS and other severity scores were discussed at the 2009 FDA co-sponsored workshop [xiii].)

- Improvement in oxygenation was another focal point of discussion. While the literature to date suggests that oxygenation status is prognostic of outcome, no data are available to show that it is sensitive to antibiotic treatment effect or that it has been rigorously evaluated as a surrogate endpoint for mortality. Specifically, while there are valid clinical uses for markers such as oxygenation and temperature and although data on some of these measures show a relationship to death, correlation is not sufficient evidence for surrogacy. Comparator data are critical to establish the validity of a surrogate endpoint. On the other hand, this measure has significant face validity—it is not possible to survive if oxygenation does not ultimately improve. However, it is possible that patients could die despite improvements in oxygenation or that factors other than antibiotics might affect oxygenation. (See Guérin et al. [xiv]; improvement in oxygenation was discussed at the 2009 FDA co-sponsored workshop [xiii].)

- Similarly, although time-to-extubation or ventilator-free days could be endpoints of direct relevance to the VABP patient, the consensus was that variability in decisions to intubate and extubate could be problematic in developing these measurements into an endpoint, especially in a global trial with a multitude of investigator sites across which standards of critical care practice may vary. An additional requirement would be obtaining data on treatment effects for these measures to justify an NI hypothesis.

- For VABP, robust evidence defines a large treatment effect on the ACM endpoint, which thereby provides flexibility on the margin. Using an ITT analysis population, specifically for a broad-spectrum antibiotic trial, adds to the feasibility. On this basis, a single trial in VABP with a mortality endpoint at 21 to 28 days for a 10% margin on 20% mortality would require approximately 674 patients (337 per arm) at 90% power. A population with 15% mortality would require a sample size of approximately 544 patients. A sensitivity analysis in the micro-ITT population or any other relevant subgroups would not require formal demonstration of NI; it should also include an analysis of prior antibiotic use as another sensitivity analysis. Whether this sample size reflects a feasible study was a matter of some debate.

**Formulation of a Statistical Analysis Plan**

Steps to guide initial development of a statistical analysis plan (SAP) include the following:

- Examining the definitions of various outcome measures in current trials;
- Examining the sensitivity to treatment effect of an earlier (e.g., 14-day or 21-day) ACM endpoint and its relationship to later time points like 28-day mortality;
- Exploring other potential alternative clinical endpoints such as symptoms (for which treatment effects are already known) for HABP and VABP by determining the frequency of the proposed parameter(s) at baseline and then over time during treatment;
- Evaluating potential indirect measures of treatment effects, including their definitions, timing, relationship to direct benefits, and effect sizes;
• Determining the impact on sample size of a potential new endpoint, including ACM at 14 days (or 21 days), an ITT primary analysis population, and altered inclusion/criteria such as prior antibiotic use (e.g., allowing 24 hours of prior therapy specifically for non-28-day ACM), increased severity of illness at baseline, and subgroups with and without receipt of prior therapy;

• Examining differing NI margin requirements;

• Examining performance characteristics related to the expected sample size in a microbiologically confirmed population;

• Standardizing the definition of pneumonia across the various databases for easier comparability (e.g., American Thoracic Society/Infectious Diseases Society of America criteria); and

• Identifying a set of prognostic factors (e.g., APACHE-II) based on the literature to estimate the association with mortality.

Significant discussion centered on how best to analyze the data to assess mortality, particularly in terms of understanding whether assessment can reasonably occur at an earlier time point, to avoid some of the possible attenuation of treatment effects due to non-infection-related deaths at day 28. Options included seeking evidence that allows a comparison of the survival curves between active agents and either a non-specific therapy control or a control that has inferior effect on mortality. For these comparisons, from randomization to day 28, the goal would be to seek to identify where they diverge as well as examine instantaneous risk of mortality between groups at slices of time.

Determining attributable mortality was discussed, but it was generally agreed that attribution in a clinical trial setting is so challenging that it cannot be done in this context. Most participants considered that attribution is not necessary given the large treatment effects of antibiotics (M1) relative to the surrogate estimate of placebo effect via inadequate or delayed treatment [xv]. However, others were concerned that rates of non-attributable mortality could be so high as to reduce assay sensitivity of ACM [xvi]; it was also noted that the historical evidence of treatment effect derives from a relatively small data set [xv].

As noted above, one hypothesis can be based on the approach in ABSSSI and CABP. Given the biological and clinical similarities of HABP and CABP, assessing the quality of the data sets to support a CABP-like 4-point symptom measure for HABP seemed a reasonable starting point to most participants as an interim outcome measure. What is needed for HABP/VABP is to understand when deaths occurred and also, using information on baseline prevalence of symptoms, when these symptoms changed over time, and the distribution of outcomes/rates. The effect of changing the number of symptoms, the amount of improvement required over baseline, and/or the timing of assessment will be examined. With regard to VABP, it was noted that the work done in ABSSSI relied on a historical data set to establish the marker of erythema. Similarly, the oxygenation ratio as a marker tracks with the mortality outcome and was argued by some to be on the causal pathway of disease. However, others cautioned against extrapolating the strategy of ABSSSI to establish oxygenation as a surrogate endpoint for VABP given that lesion size is a clinician-reported outcome with a demonstrated relationship to patient pain while oxygenation is a biomarker whose relationship to direct measures of benefit remains to be defined.

Next Steps

• The first step will be a high-level descriptive statistical analysis of the available data to inform development of the formal SAP.

• The group accepted that a preliminary hypothesis for HABP is that a symptom plus mortality-based endpoint built on the model of CABP could perform well. To that end, the first pass
through the data can assess whether these symptom data exist and, if so, what was their severity and distribution at baseline and the frequency of measurement and rates over time.

- For VABP, a working hypothesis is that the ACM endpoint could be assessed at an earlier time point; thus, the first review of the data sets will be with an eye toward determining if the data can support that hypothesis. In addition, other clinical markers of interest in VABP will be explored (e.g., improvement in oxygenation).

- These exploratory descriptive analyses will be performed on a single HABP/VABP trial available to the Working Group.

- Thereafter, a formal SAP will be articulated, approved by the Working Group, and implemented using all the in-kind clinical trial data sets. The focus will be on understanding the impact of differing outcome definitions, outcome timing, analysis population assumptions, and enrollment criteria on the feasibility of HABP/VABP trial conduct.
Working Group Members

The conclusions described within this document represent the work of the FNIH Biomarkers Consortium HABP/VABP Working Group:

- Jeff Alder, Ph.D. (Bayer)
- Partha Bagchi, Ph.D. (Johnson and Johnson)
- Steve Barriere, Pharm.D. (Theravance)
- Helen W. Boucher, M.D., FACP (Tufts University, IDSA)
- Laurie Burke, R.Ph., M.P.H. (FDA)
- Becky Coleman, Pharm.D. (Theravance)
- Lynn Connolly, M.D. (Achaogen)
- Edward Cox, M.D. (FDA)
- Aaron Dane, M.Sc. (AstraZeneca)
- Anita Das, Ph.D. (InClin)
- Dennis M. Dixon, Ph.D. (NIH/NIAID)
- Michael Dudley, Pharm.D. (Rempex)
- Barry Eisenstein, M.D., FACP, FIIDSA (Cubist)
- Thomas File, M.D. (Summa Health System)
- Tom Fleming, Ph.D. (University of Washington)
- Dean Follmann, Ph.D. (NIH/NIAID)
- David Friedland, M.D. (Cerexa)
- Ian Friedland, M.D. (Cubist)
- Kenneth Hillan, Ph.D. (Achaogen)
- Alan Hopkins, Ph.D. (Theravance)
- Nicholas Kartsonis, M.D. (Merck)
- Charles Knirsch, M.D., M.P.H. (Pfizer)
- Mark Kunkel, M.D. (Pfizer)
- Chin-Yu Lin, Ph.D. (Achaogen)
- Lily Llorens, Ph.D. (Cerexa)
- Daniel Meyer, Ph.D. (Pfizer)
- Roger Novak, Ph.D. (Sanofi)
- Elektra Papadopoulos, M.D. (FDA)
- John Powers, M.D. (NIH)
- Philippe Prokocimer, M.D. (Trius)
- Rebecca Redman, M.D. (Johnson and Johnson)
- John Rex, M.D., FACP (AstraZeneca)
- Dan Rubin, Ph.D. (FDA)
- Ashley Slagle, Ph.D. (FDA/CDER, CTR)
- Judy Siuciak, Ph.D. (FNIH)
- Will Stubbings, Ph.D. (now Achim Kaufhold, M.D.) (Basilea Pharmaceutica, Ltd.)
- Anthony Suffredini, M.D. (NIH/CC/CCMD)
• George H. Talbot, M.D., Co-Chair (Talbot Advisors, IDSA)
• Joe Toerner, M.D., Co-Chair (FDA)
• John Tomayko, M.D. (GSK)
• Antoni Torres, M.D. (Catedràtic de Medicina Hospital Clínic, Barcelona, Spain)
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xiii Meeting materials, “Clinical Trial Design for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia,” a public workshop co-sponsored by the FDA and professional societies. Available at: http://www.fda.gov/Drugs/NewsEvents/ucm169877.htm

