HAP / VAP Clinical Trials: Can we reduce complexity to reduce cost while improving the quality of the data and inferences we make?

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Knirsch Disclosure

Employee of Pfizer and compensated with equity

This presentation does not reflect an official position of Pfizer

Does reflect the views of a physician/investigator deeply concerned about the current state of antibacterial discovery and development

Overview

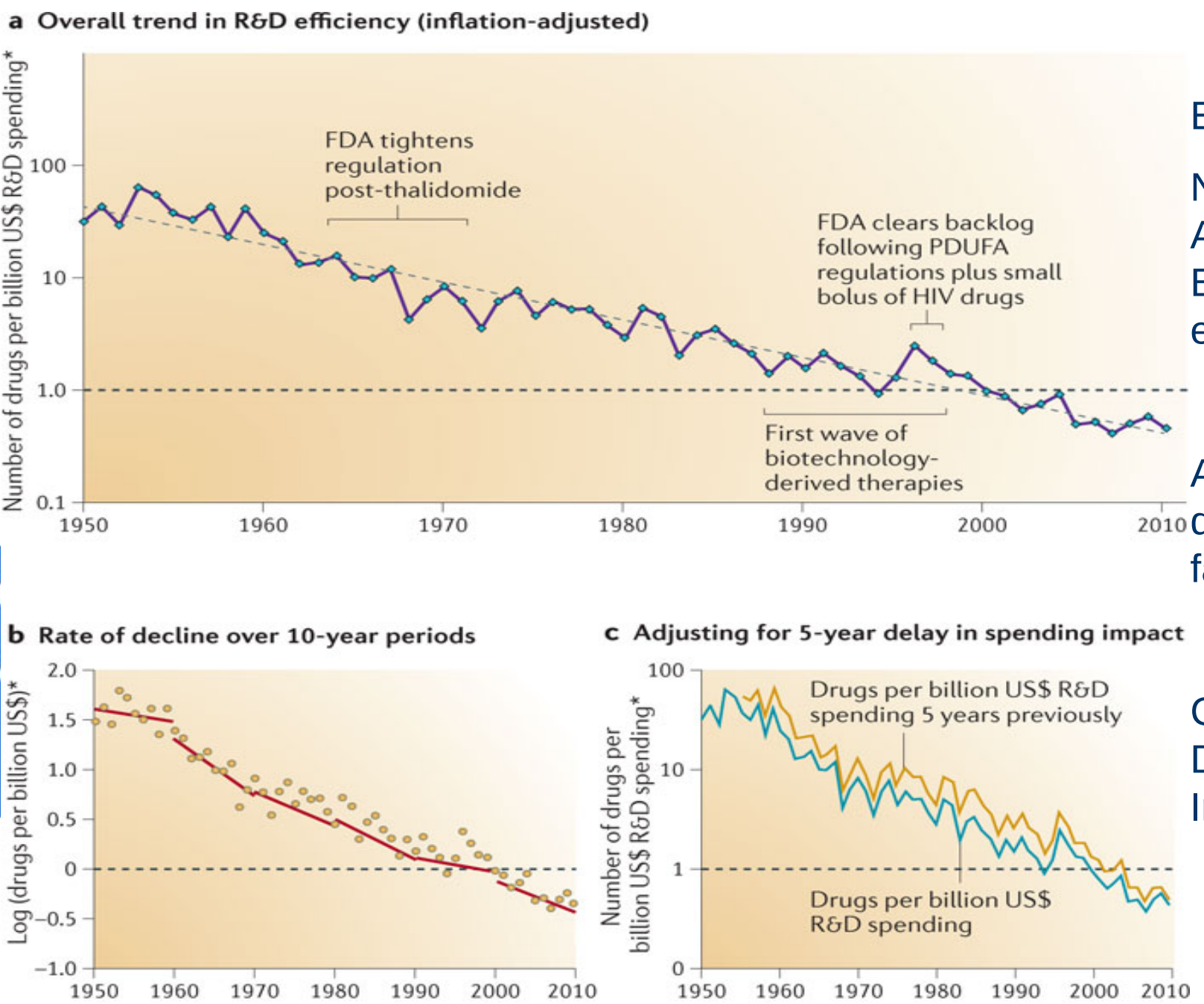
Problem Statement from a Drug Developers POV

Anti-bacterial discovery and development are *in extremis* so a good place to start; generalisable to the clinical trial ecosystem that is at risk

Academia (IDSA) alone will not solve this; Public Private Partnership eg CTTI is more likely to succeed

The Industry has committed in 3rd party convened fora, time and effort to the thought experiment and discussed, presented and published our work

Last Gasp



Eroom's Law:

New FDA Approvals / Billion $: halved every 9 years

Anti-bacterial discovery failures

Confirm Development Inefficient

Nature Reviews | Drug Discovery **Scannell et al 2012**

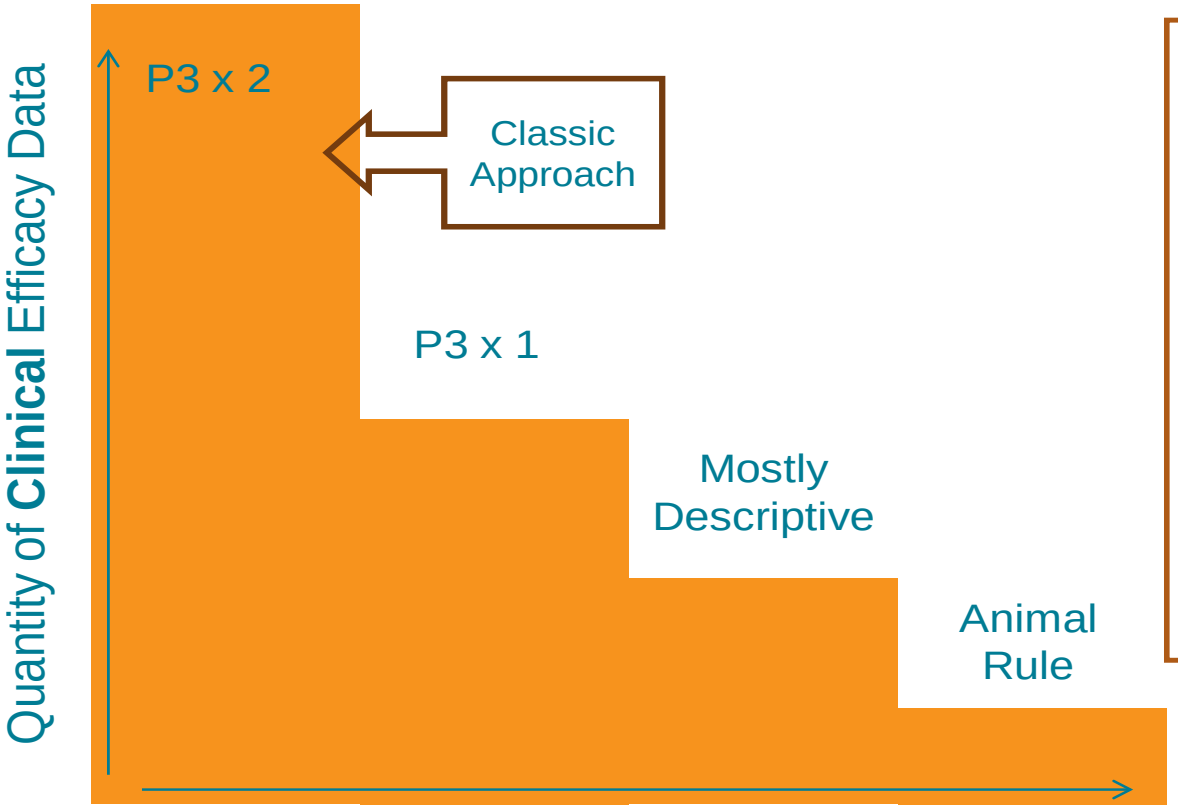
Simple Substantive Steps Now
Knirsch CTTI 2012 Workshop Summary

- **Increased Funding for basic bacterial laboratory work**
- **Infrastructure and network for clinical trial excellence particularly learn phase development at leading academic medical centers**
- **Enhance GAIN or other mechanisms (Foundations, NGO's) for discovery and early development incentives**
- **Continue and commit to the progressive Regulatory stance we have heard at this meeting and comments in other fora eg PCAST**
- **Not relaxed standards but efficient development to bring much needed medicines to the clinic faster with robust pharmaco-vigilance and stewardship**
  - Use of existing expedited Regulatory Pathways (Sub-part H and PV Guidance)
- **Progressive value models eg LSE report from the Swedish Presidency**
  - http://www.se2009.eu/en/meetings_news/2009/9/17/conference_innovative_incentives_for_effective_antibacterials.html

The paradigm gap

- For registration, we traditionally expect
  - Two substantial trials per indication (e.g., two UTI trials)
  - Typical size/trial: ~1,000 patients
- This presumes ready availability of substantial numbers of patients with the target disease
- But, what if the target disease includes a less common, but important, pathogen or type of resistance?
  - Less common pathogen: *Pseudomonas*
  - Emerging form of resistance: KPC or Metallo-ß-lactamase
- When only limited clinical data for these important subsets are possible, current paradigms give no easy way forward
  - Waiting for widespread resistance means we can't anticipate the epidemic

A tiered approach: Aligning feasibility and the quantity of clinical data with the unmet medical need

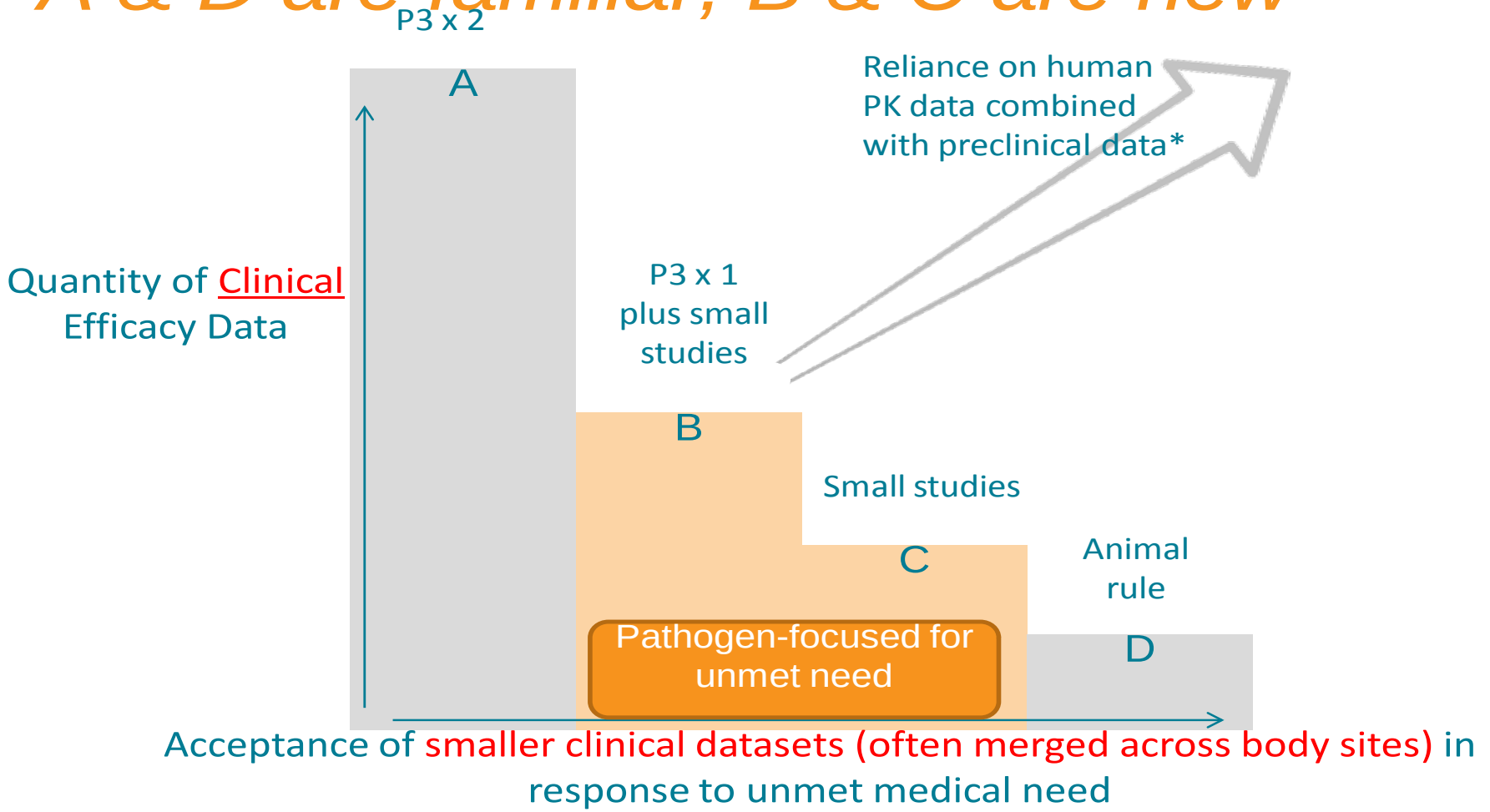


- The need for a tiered approach is real – there are real products at each tier that need a path forward
- Determination of the appropriate tier should be based on ***context***:
  - Feasibility
  - Unmet medical need
  - Strength of the preclinical data
  - By utilizing the totality of data, ***existing*** regulatory requirements can be met at each tier

Eisenstein - Tier B-C overview, EMA workshop 25-26 Oct 2012

Rex et al Lancet ID 2012

A & D are familiar, B & C are new



Rex et al Lancet ID 2012

It’s all about Benefit-Risk

- High unmet need for new MDR therapies justifies accepting more uncertainty regarding efficacy and safety in product development.
  - Without this, we’ll see a continuing increase in unmet need
  - These greater levels of uncertainty can be managed & described
- Efficacy
  - Increased utilization of pre-clinical and early clinical data
  - At least some controlled data in the clinical trials
- Safety
  - Usual preclinical assessments
  - Safety data from all trials to identify AEs in the 0.5-1.0% range
- SmPC to focus on situations where both potential benefit and tolerance of unexpected safety events are greater

Summary

- MDR development focuses on an unmet need
- A totality of evidence approach expedites development while enhancing the strength of evidence supporting the new drug
- Development approaches must anticipate the problem of Drug #2: To meet the challenge of evolving resistance patterns there must be feasible pathways for both the initial and subsequent drugs that do not require a demonstration of superiority on a hard endpoint
- To provide these new therapies it will be necessary to accept greater uncertainty regarding efficacy and safety but some of the associated risk can be mitigated
- Harmonization of regulatory requirements is an essential component of this paradigm

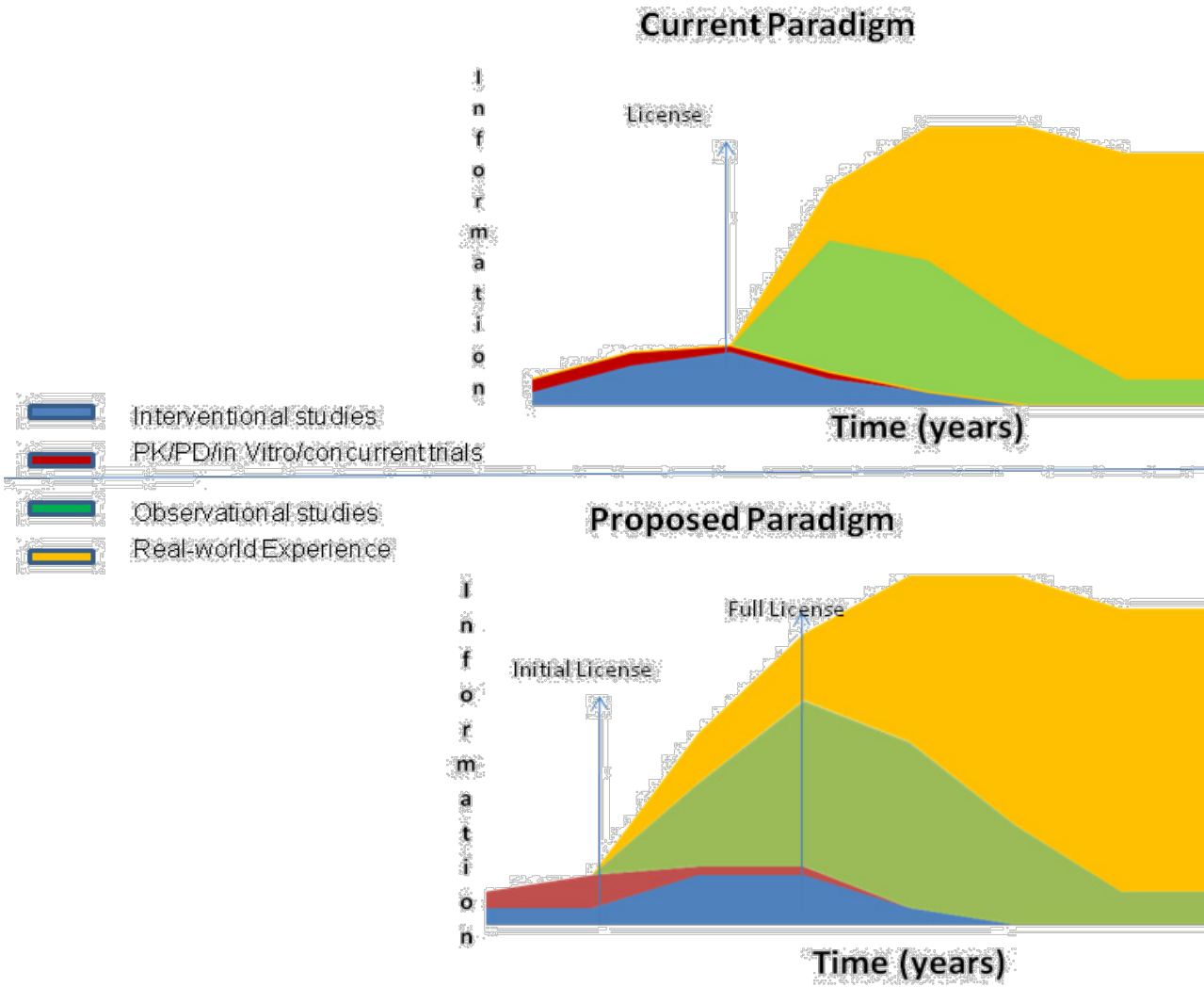
Expedited Pathway to Address Projected Resistance Patterns: Efficacy in P2, Safety Continuous

Staged approval

- Conditional approval with POC data, with limited use and promotion
- Requirement for additional data in a post-approval commitment depending on epidemiology could lead to enhanced label

Advantage

- Brings much needed medicine to patients in a timely manner
- Incentive to Discovery, Early Development
- Benefit-Risk Evolves



Alemayehu et al CID 2012

Let's Re-visit: Enriched MRSA Study in HAP/VAP Wunderink et al CID 2012

Objective: streamlined clinical trial MRSA only (innovative prior to CID supplement)

8 Inclusion Criteria (multi-component); 26 Exclusion Criteria

1225 Patients enrolled over 5.5 yrs; 3 protocol amendments; DMC changes

448 culture-positive for MRSA (mITT) ; 348 evaluable at End-of-Study (PP)

280 (63%) ventilated at baseline (mITT)

156 Centers

- 90 US (58%)
- 28 EU (18%)
- 16 Latin America (10%)
- 13 Asia (8%)
- 9 Other (6%)

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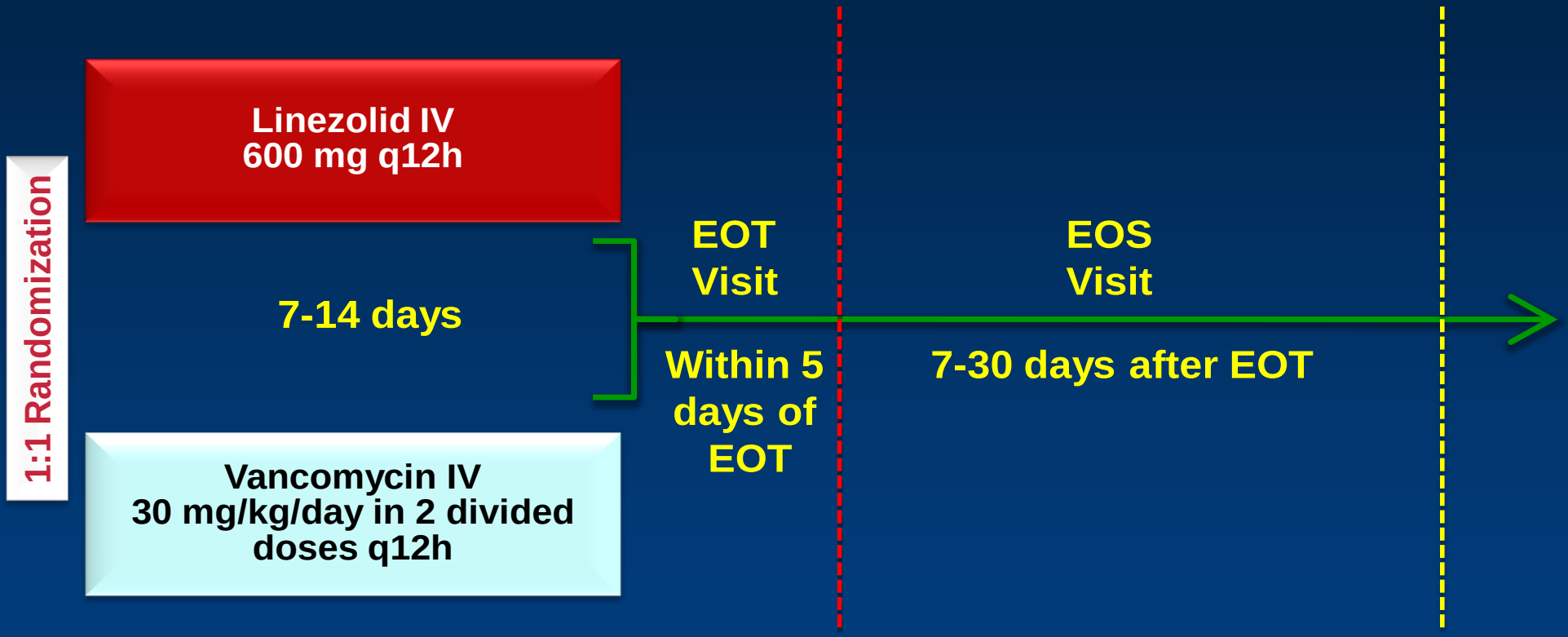
Study Design



- Vancomycin dose adjusted by unblinded pharmacist based on renal function and trough concentration
- Initial Cefepime or other Gram-negative coverage (not MRSA active) required

Key Inclusion Criteria

- Criteria must be present within 24 h of enrollment (not pre-treated)
- If pre-treated, S/S present 24 h prior to that treatment or within 72h prior to enrollment (whichever is closer to enrollment)

Two of the following:

- **Fever**
- **Hypotension**
- **Altered Mental Status**
- **Total WBCs >10,000, L shift or leukopenia**

+ positive sputum meeting criteria

OR

New onset or worsening of purulent sputum production

+ 1 of the following:

- **Fever**
- **Total WBCs > 10,000**

Key Inclusion Criteria

Hospitalized adults (≥18 yo) with clinically documented nosocomial pneumonia, defined as:

- Pneumonia with clinical onset ≥48 hours after hospitalization in an acute inpatient healthcare facility
- Pneumonia acquired in a long-term care or sub-acute/intermediate healthcare facility or in a subject who is admitted with pneumonia within 90 days of a recent hospitalization of ≥48 hours (HCAP)

To continue in study required to culture positive for MRSA

Key Exclusion Criteria

Treatment with MRSA active antibiotic for more than 48 hours prior to study

- Exception: documented treatment failure (other than linezolid or vancomycin), defined as lack of response despite at least 72 hours of treatment

Severe neutropenia (<500 cells/mm3)

MRSA resistant to either study drug

Other Conditions:

- Rapidly fatal underlying disease with estimated survival less than study duration or high likelihood of death within 72 hr
- Sustained shock > 2 hr despite fluid/ sympathomimetics
- Empyema, lung abscess
- Lung transplant or BMT

A Systematic Approach to Quality Oversight in Clinical Trials

The Integrated Quality Management Plan (IQMP) is:

- A document which prospectively describes the factors that are most important to quality and the actions that will be taken to address the risks that matter most
- A process of quality oversight whereby quality planning drives quality control which drives quality improvement

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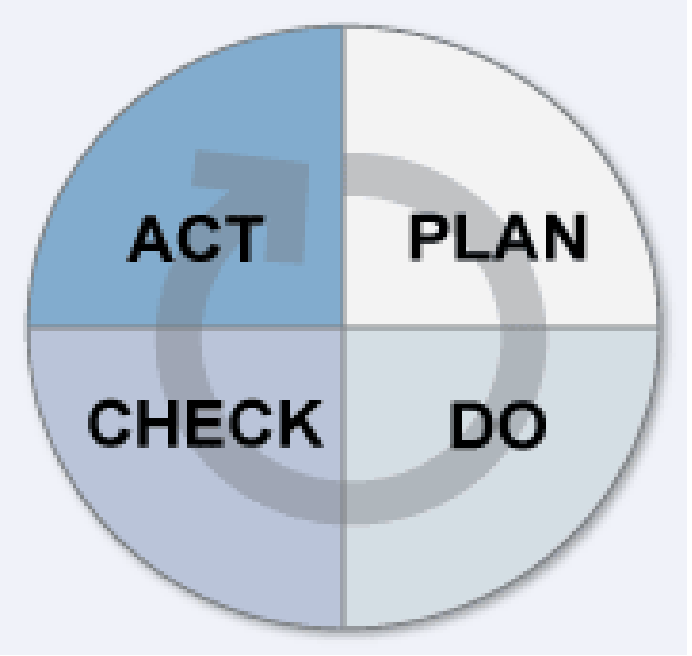
Plan-Do-Check-Act Quality Cycle



http://www.iso.org/iso/catalogue/management_standards/understand_the_basics.html

Plan

Determine quality objectives and metrics

Identify, prioritize, and mitigate risks to quality

Quality Planning

Do

Conduct the study

Check

Measure and monitor quality performance

Quality Control

Act

Respond to quality issues as identified

Quality Improvement

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Control Plan with Select CTQs and Metrics

CTQ	Measure	Target Value*	Upper Spec Limit*	Lower Spec Limit*	Minimum Measure Frequency	Respon-sible
All subjects randomized meet inclusion/exclusion criteria	Percent of subjects randomized that do not meet inclusion/exclusion criteria at the time of randomization	0%	5%	0%	Monthly	Clinical
All study procedures are completed as per the protocol	Percent of subject visits at which protocol deviations related to improper study procedures are identified	0%	5%	0%	Monthly	Clinical
Data are entered by the site into the database in a timely manner and the database is accurate and complete	Percent of subject visits meeting data entry target timelines within 4 calendar days	80%	100%	75%	Monthly	Study Mgmt

** Target values and spec limits are illustrative.*

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Protocol Quality Evaluations and Integrated Quality Management Plans

Integrating scientific integrity and parsimony for the benefit of investigators, patients and clear reporting of data

Complexity Drivers

- AE reporting is one of most burdensome tasks for investigators in Phase 3 clinical trials
- On-site monitoring
- Unnecessary eligibility criteria
- Unnecessary visit scheduling , but ICU population
- Excessive procedures: eg. labs, EKG's, but again (ICU populaiton)

Additional Mitigating Measures

Reporting needs to drive data collection rather than collect everything in case of "what if questions"

- Streamlined prognostic factor/background data collection
  - Driven by science and relevance to the research hypothesis under study
- Minimal exclusion/inclusion criteria
  - restrict criteria to those absolutely essential for scientific objectives of trial, safety of patients, and to satisfy regulatory requirements.
- Effective use of technology: EDC tools, ePROs
- Use of legacy data to fill evidentiary gap

Use of large, simple trials, when appropriate

- A large sample size, limited collection of data, little or no local site monitoring, and broad eligibility criteria.
- Hard safety endpoints vs current state of "Big Data" retrospective claims data and outcomes

Regulatory guidance and commitment critical

- Agreement on minimum data requirement for review
- Progressive development of safety database
- Balance between confirmatory RCTs and large, simple trials

2012 Guidance on Collection of Safety Data in Late Stage
www.fda.gov/downloads/Drugs/.../Guidances/UCM291158.pdf

Summary:
Protocol Level Simple Substantive Steps Now

QbD Approach to write the Tier B Phase 3 protocol and get agreement that the primary endpoint, key secondary endpoints and safety as designed are the "playing field for debate"

Agree on FDA AC Conduct Rules with Professional Moderators

Agree on Transformative QbD Safety Collection: to benefit patients, investigators and sponsors

Consider seriously the Tier C program and agree that sub-part H applies

Thank you

Some Factors Driving Operational Costs: Opportunities for Efficiency?

- First day CRO involvement
- Treatment period for each subject

- % screen failure rate
- % discontinuation
- Monitoring frequency pre-and post LSFV
- Total # SAEs
- *# Sites*
- *% Sites in each region*

- # Total CRF pages per completed patient
- # Unique tables, figures, and listings

Protocol Complexity Drives Downstream Resources

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Tufts Center for the Study of Drug Development

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Impact REPORT

ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

Growing protocol design complexity stresses investigators, volunteers

Protocol design changes challenge study conduct cycle time and performance

- The annual growth rate of unique procedures per protocol grew 6.5% between 1999 and 2005. During that same period, the total number of times unique procedures were conducted per protocol grew at a faster rate.
- To participate in clinical studies today, volunteers on average must meet a total of 49 eligibility criteria, up 58% since 2002.
- The burden to administer clinical study protocols is rising faster than the rate of growth of unique procedures or their frequency.
- Clinical trials are taking longer: between 1999-02 and 2003-06, total time from protocol design readiness to data lock rose from 460 to 780 days, or 69.6%.
- Protocol design also impacts the ability of sites to recruit and retain volunteers: enrollment rates dropped from 75% in 1999-02 to 59% in 2003-06, while retention rates declined from 69% to 48%.

Data Integrity and Study Monitoring

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Impact REPORT

ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

Study monitor workload high & varied with wide disparity by global region

Assessment sets global benchmark for CRA workload and utilization

- Clinical research associates (CRAs) worldwide devote 41% of their time at clinical trial sites, with those based in Europe spending 30% fewer hours on-site than CRAs in North America.
- Sponsor CRAs spend more time than their counterparts at contract research organizations (CROs) conducting on-site monitoring visits, monitoring trials off-site, and handling administrative tasks.
- Half (53%) of CRAs overall rate their work life as good or excellent; those based in Latin America gave the lowest ratings.
- For Phase I studies, CRAs on average conduct 3.8 investigative site visits each month.
- For Phase II-III studies, CRAs on average conduct 7.9 investigative site visits each month.
- CRAs overall have an average of 6.3 years on the job and expect to remain in their position for another 3 years, with both metrics varying widely by region.