Geographic shifts in antibacterial drug clinical trial enrollment
Implications for generalizability

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This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Drug clinical trials are increasingly globalizing

US-based investigators

1990: 96%
2007: 54%

56.9% of subjects in drug trials were enrolled from outside the US in 2008

Tufts Center for the Study of Drug Development Impact Report, 2009
Department of Health and Human Services Office of Inspector General Report, 2010
Antibacterial drug applications increasingly include non-US data

Labels for several recently approved antibacterial drugs

“The majority of the patients (99%) were from Eastern Europe; 3 patients were from the United States.”

“There were no patients enrolled within the United States.”

“The majority of sites were in Eastern Europe […] ; 3 patients were enrolled in the US.”
Speculated drivers for enrollment changes

Cost
Significant savings outside US and Western Europe

Differences in clinical practice and recruitment
Prior antibacterial drug therapy and length of hospitalization for IV drug administration
Lack of interest among investigators in some regions

Emerging markets
Expansion of sales into new regions
How is antibacterial drug trial enrollment changing?

What impact does changing enrollment have on trial generalizability?
Methods

Identified New Drug Applications (NDAs) for antibacterial drugs

• Included Phase 3 trials started after January 1, 2001, with electronic subject-level data
  • Four small trials targeting a specific organism or resistance phenotype were excluded

Geography
Regions assigned by country

Demographics
Age, sex, race, etc.

Clinical characteristics
Comorbidities, medical history, and disease severity

Microbiology
Species and resistance phenotypes

ABSSSI
Acute bacterial skin and skin structure infections

cIAI
Complicated intra-abdominal infections

CABP
Community-acquired bacterial pneumonia

cUTI
Complicated urinary tract infections
Subjects assigned to one of 7 regions
Regional assignments influenced heavily by sponsor designations
Timeline of included trials

42 Phase 3 trials identified
29,282 subjects from 57 countries

Draft Guidances

Trials initiated 2001-2009 were compared with those 2010-2017 to analyze enrollment trends
Enrollment is increasing in Eastern Europe
Except in ABSSSI trials
Enrollment is increasing in Eastern Europe
Except in ABSSSI trials

- **cUTI**
  - 2001-2009: (n=2)
  - 2010-2017: (n=6)

- **cIAI**
  - 2001-2009: (n=4)
  - 2010-2017: (n=4)

- **CABP**
  - 2001-2009: (n=4)
  - 2010-2017: (n=5)

- **ABSSSI**
  - 2001-2009: (n=5)
  - 2010-2017: (n=12)

Legend:
- **Africa**
- **Asia**
- **Australia**
- **Eastern Europe**
- **North America**
- **South America**
- **Western Europe**

Proportion of subjects (%)
Impacts on generalizability

**Demographics**
Age, sex, race, etc.

**Clinical characteristics**
Comorbidities, medical history, and disease severity

**Microbiology**
Species and resistance phenotypes

**Geography**
Shifts in enrollment toward Eastern Europe or North America

Subject-level NDA data used to investigate differences among regions
Data were pooled across entire study period, not divided by date
Eastern European subjects receive less prior antibacterial drug therapy

**p<0.01, ****p<0.0001, random effects model
North American ABSSSI subjects are disproportionately IV drug users

**p<0.01, ****p<0.0001, random effects model
Impacts on generalizability

- **Demographics**: Age, sex, race, etc.
- **Clinical characteristics**: Comorbidities and disease severity
- **Microbiology**: Species and resistance phenotypes

Subject-level NDA data used to investigate demographic differences among regions. Analyzed regional differences for cIAI, cUTI (Gram-negative aerobes) and ABSSSI (all organisms). Used FDA-recognized breakpoints to identify resistant isolates.
cIAI microbiology is similar worldwide

*K. pneumoniae* elevated in Asia

n=8 trials
Mean ± SEM
*p<0.05, **p<0.01, ***p<0.001, random effects model

**Gram-negative species** prevalence
Resistance phenotypes differ worldwide

Resistance phenotypes among Enterobacteriaceae in cUTI and cIAI trials
FDA-recognized breakpoints used to assess susceptibility
3rd-generation cephalosporins, carbapenems, and fluoroquinolones

n=8 trials for each cUTI and cIAI
Mean ± SEM
*p<0.05, **p<0.01, ***p<0.001, random effects model
Conclusions

Enrollment trends differ by indication
- cUTI, cIAI, and CABP trials increasingly enrolled from Eastern European sites
- ABSSSI trials are dominated by North American enrollment

Demographic characteristics did not differ significantly for most comparisons
- Higher BMI among North American subjects
  - Consideration in review of drug exposure data collected elsewhere

Certain clinical characteristics vary by region
- Large differences in disease severity were not detected in this analysis
- Eastern European subjects exhibited the least prior antibacterial drug therapy
  - Differences in standards of care or in enrollment efficiency
- North American ABSSSI subjects disproportionately reported IV drug use
  - Differences in infection type and microbiology

Microbiology is broadly similar among regions, with regional enrichment for some species and resistance phenotypes
- Differences could be used to guide future site selection
Demographic, clinical, and microbiological similarities lessen generalizability concerns for antibacterial drug trials.

US participation is still important, given known and unknown regional differences.
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