Regulatory aspects of balancing benefits and risks in the clinical development of antibiotics

Guest speakers: Enrica Alteri & John Alexander

Moderator: Radu Botgros

Host: Astrid Pentz-Murr (GARDP)

8 November 2022

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Global Antibiotic Research & Development Partnership

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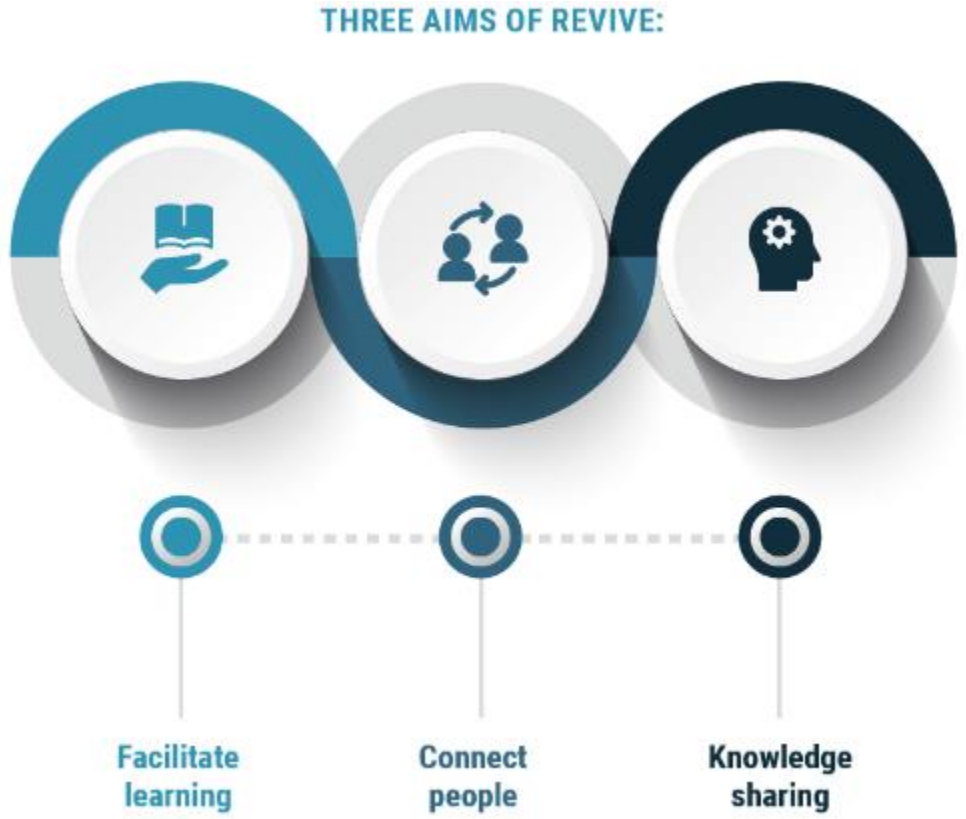

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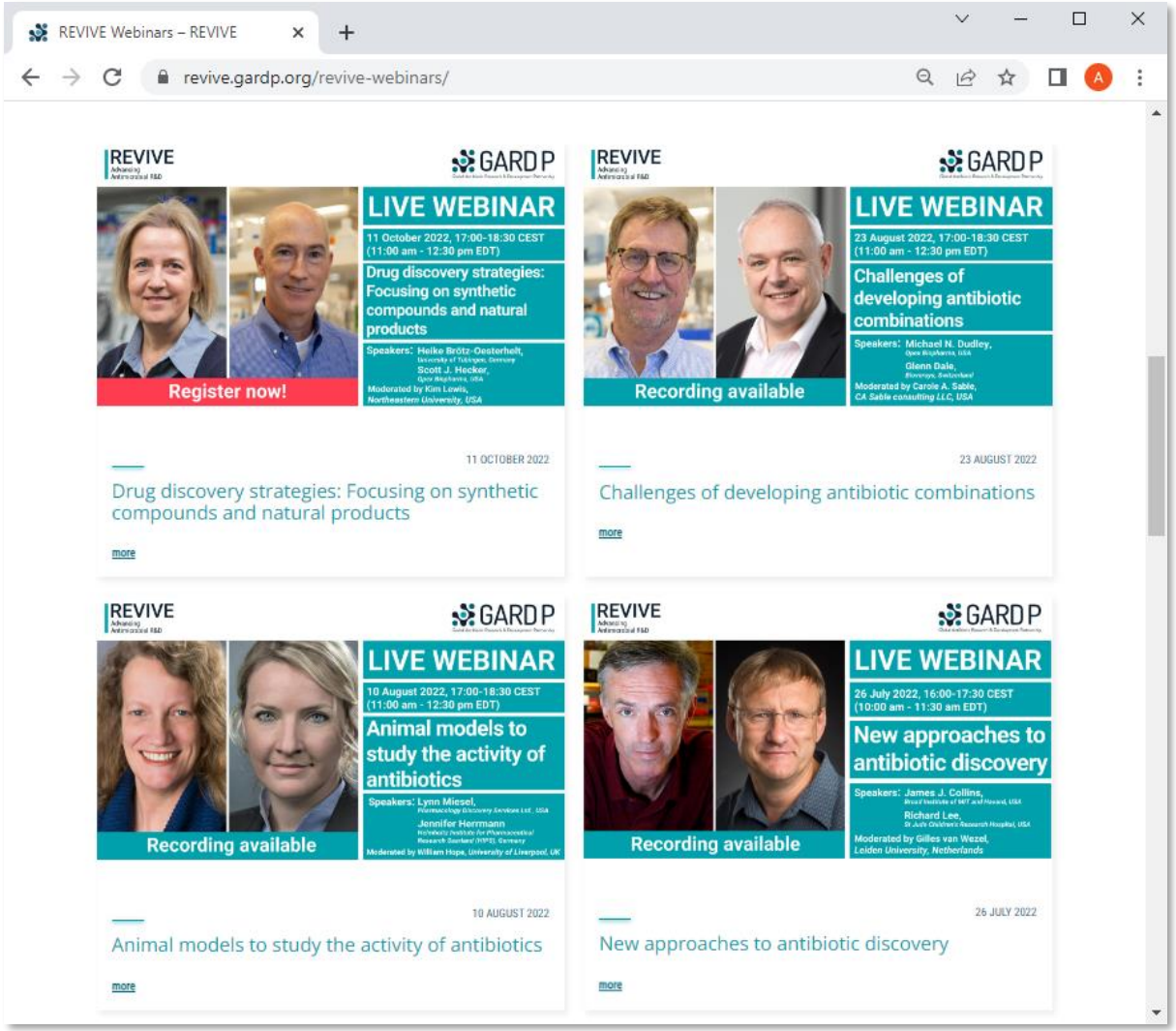

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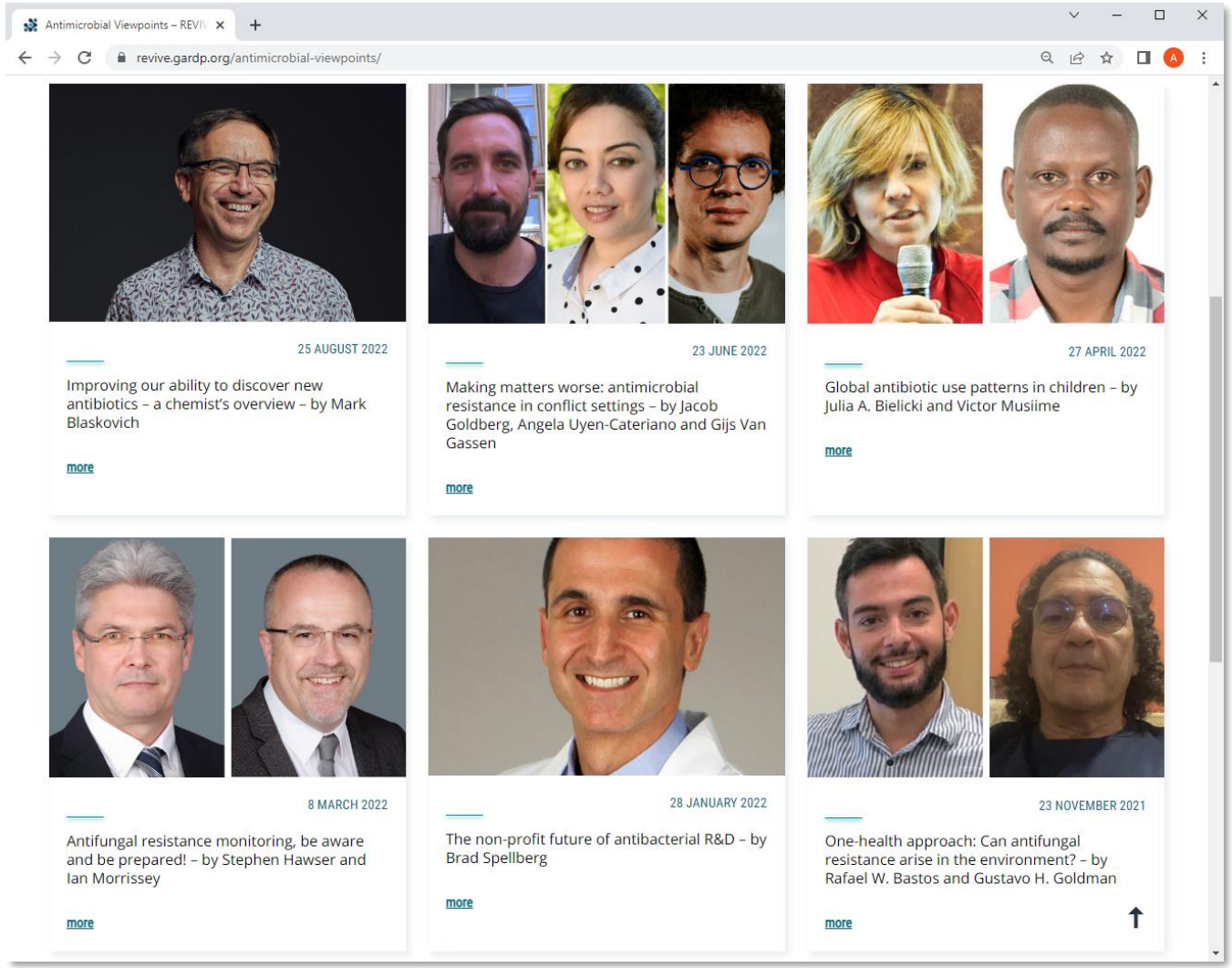

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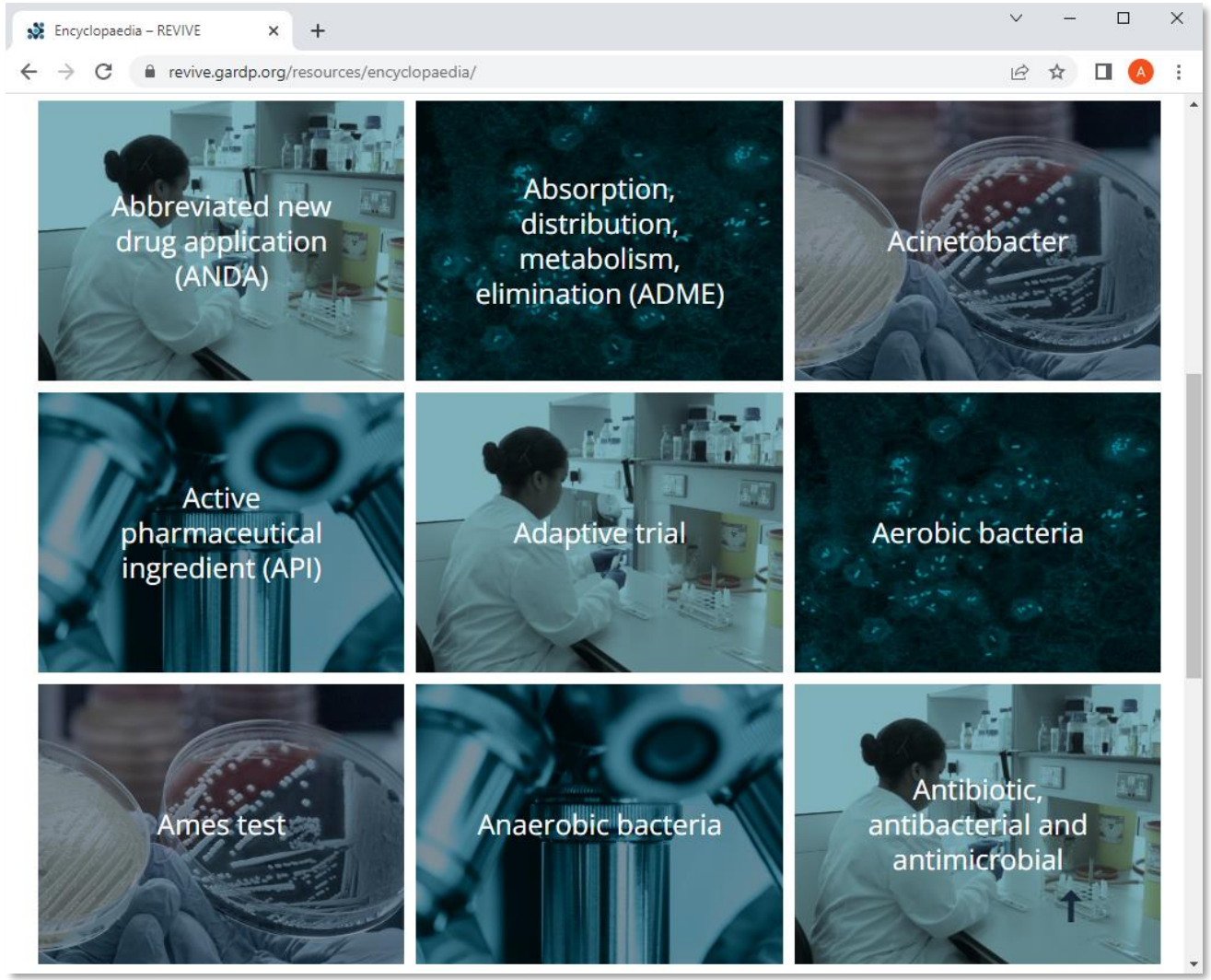

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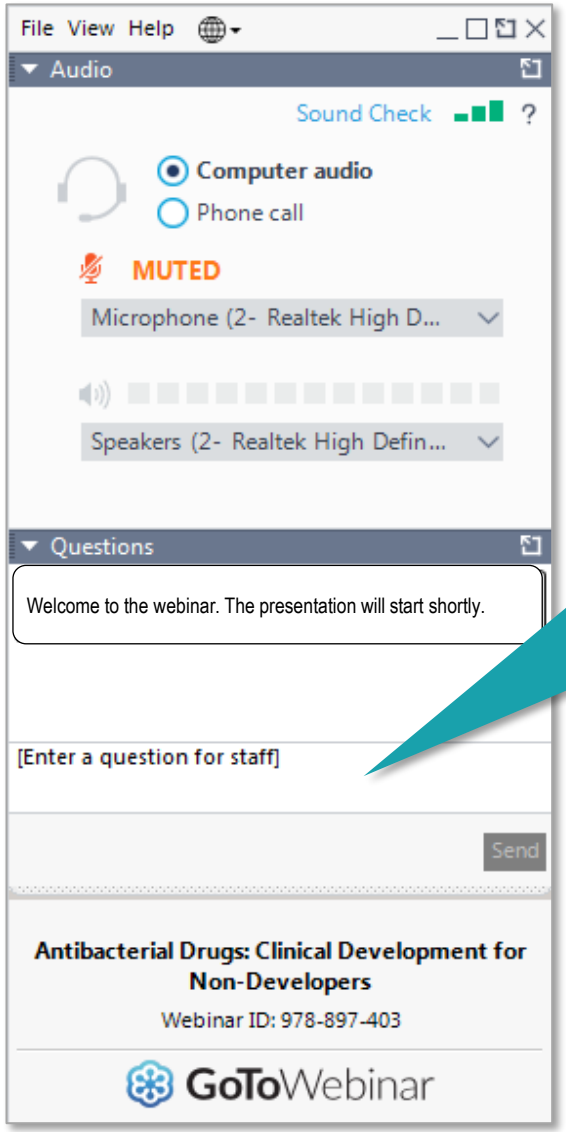

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Today’s speakers

Regulatory aspects of balancing benefits and risks in the clinical development of antibiotics

Enrica Alteri
Independent pharmaceutical professional and former Head of Division European Medicines Agency (EMA)

John Alexander
Deputy Director, Division of Pediatrics and Maternal Health
Center for Drug Evaluation and Research, US FDA (USA)

Moderator:
Radu Botgros
Senior Scientific Officer, Specialist in Infectious Diseases
Office of Health Threats and Vaccines Strategy, European Medicines Agency (The Netherlands)

Radu Botgros

Radu Botgros is an infectious diseases specialist that holds the position of Senior Scientific Officer for the Office of Health Threats and Vaccines Strategy at the European Medicines Agency.

He worked as an ID clinician for 10 years before joining the Agency in 2009 as Scientific Administrator in the Paediatric team. From there he moved to the Anti-infectives and Vaccines team where he worked with the efficacy and safety-related pre- and post-authorization aspects of centralized marketing authorization applications for the treatment and prevention of infectious diseases. Since March 2020 he is a member of the Health Threats and Vaccines Strategy team. Radu’s main interests are with the development of antibacterial, antifungal and antiviral medicines and with public health, with a special focus on the fight against AMR.

Enrica Alteri

Enrica Alteri spent 25 years in the pharmaceutical industry, where she was involved in major projects that yielded important drugs such as Gleevec for myeloid leukaemia, Coartem for malaria and Reyataz for HIV-AIDS, after completing her medical studies in Rome and a postdoctoral fellowship at the National Cancer Institute in Bethesda (USA). In 2012 she joined the European Medicines Agency (EMA), where she was Head of Human Medicines R&D support Division, and member of the Executive Board. In these roles, Enrica was part of many high impact EMA's initiatives.

Enrica is currently a member of the Scientific Committee and faculty of the master course in Drug R&D of the University of Geneva, and master courses in R&D at the Luiss University and Universita' Cattolica in Rome. Recently she has been appointed Core Member of the Unitaid Proposal Review Team. In addition, Enrica is a member of CIOMS working group Real World Data and Education.

Regulatory aspects of balancing benefits and risks in the development of antibiotics: Overview

REVIVE Webinar 8 November 2022

Enrica Alteri, MD

Former Head
Human R&D Support Division / European Medicines Agency

Disclaimer

This talk contains exclusively my personal thoughts, it should in no way be seen as expressing the views or positions of my former employer, the European Medicines Agency

Themes

- Some background
- The regulatory environment
- Recent guidance
- Benefit/Risk (B/R) balance for antibiotics: an individual choice?
- The road ahead

Some background

- AMR a major threat
- R&D lagging
- Complexity : animal/human/individual country practices
- Data availability: utilisation, indications

The regulatory environment

- Recognise sphere of influence of the various players
- Targeting a bug or a disease?
- Harmonisation efforts ongoing

Recent guidance

- A new EMA Guideline will come into effect on December 2022.
- Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections

- https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf

- Parallel development of the paediatric addendum

Benefit/Risk of antibiotics: an individual choice?

- During R&D, the benefits of a products are studied, risks are identified and managed
- The individual patient is the target of therapeutic intervention: the B/R balance is identified in relationship to the patient
- For antibiotic, the issue is more complex

The road ahead

- Continue the effort on all fronts – the concept of One Health
- Approaches other than antibiotics
- Work on the details without losing sight of the big picture

Thank you!

Any Questions?

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John Alexander

John Alexander is currently Deputy Director of the Division of Pediatric and Maternal Health in the Center for Drug Evaluation and Research at FDA. John is a pediatrician who joined the US Food and Drug Administration in 1995 as part of a joint fellowship in pediatric infectious diseases with FDA and Children's National Medical Center. After completion of his fellowship, he became a full-time medical officer, and subsequently a team leader, in the Division of Anti-Infective Products. He has worked in the review of antibiotic drugs and pediatric drug development for more than 20 years.

Safety Considerations in Pediatric Antibacterial Drug Development

John Alexander, MD, MPH
Deputy Director, Division of Pediatrics
and Maternal Health, CDER, FDA
November 8, 2022

Disclaimer

- This presentation reflects my views and should not be construed to represent FDA's views or policies.

- I have no financial conflicts of interest related to this presentation.

Outline

- Pediatric drug development framework in US
- Adult antibacterial drug development
- Pediatric extrapolation for antibacterials
- Pediatric antibacterial drug development

Pediatric Drug Development Framework in US

Pediatric Drug Development
General Principles

- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

From FDA guidance to industry titled *E11 - Clinical Investigation of Medicinal Products in the Pediatric Population,* December 2000

US Pediatric Legislation

- Pediatric Research Equity Act (PREA)
  - Requires companies under certain circumstances to assess safety and effectiveness of new drugs/biologics in pediatric patients
- Best Pharmaceuticals for Children Act (BPCA)
  - Provides a financial incentive to companies to conduct pediatric studies

PREA Requirements

- PREA gave FDA authority to require a pediatric assessment under certain circumstances
  - Data gathered from pediatric studies using appropriate formulations to assess safety and efficacy and to support dosing and administration of a drug or biological product in all relevant pediatric subpopulations for same indication(s) being sought in adults – unless requirement is waived or deferred
- FDA may also require companies to develop age-appropriate formulation to conduct required studies but does not require companies to market the formulation
- PREA provides specific criteria for when study requirements could be waived
- PREA does not apply to products granted orphan designation, except for molecular targets in oncology
- Initial Pediatric Study Plan (iPSP) allows earlier communication on pediatric product development (end-of-phase 2)

Adult Antibacterial Drug Development

Adult Antibacterial Drug Development

- Generally for antibacterials, will have adult data
  - Pediatric-specific antibacterial development is rare
- Few indications (e.g., acute otitis media) where efficacy is established in pediatric patients

Consider aspects of adult program that support pediatric development…

Adult Antibacterial Drug Development

- Drug product (active ingredient and excipients)
- Nonclinical toxicology studies
- Animal models of infection
- Adult phase 1/phase 2
  - Initial Safety
  - ADME
- Adult phase 3 trials
  - Indications being studied

Pediatric Extrapolation for Antibacterials

Pediatric Extrapolation for Antibacterials

- Two factors: similarity of disease and expected response to treatment
- Antibacterial effect mainly based on direct effect on the pathogen
  - Independent of adult or pediatric host

- Extrapolation of safety – ICH E11A draft guidance on pediatric extrapolation
- Focus of pediatric trials is generally on safety and PK

Pediatric Antibacterial Drug Development

Pediatric Population

- Pediatric population to be included in studies typically is based on epidemiology of the infection(s) being studied.
  - Can be complicated when adult studies for some indications are planned as supplements to the original application
- Adolescents should be considered for inclusion in adult trials, in certain circumstances
  - Prospect of direct benefit and risk/benefit considerations, as well as practical aspects of their inclusion
  - Typically receive same fixed dose as adults
  - Some confirmation of similar exposure with sparse PK may be helpful
  - What safety evaluation is planned in this subgroup?
  - May need to be ready to conduct additional studies in this age group, if there's low adolescent enrollment

Pediatric Studies

- Single-dose PK studies done, when needed
  - Consider ADME, PK modeling
  - Limited safety data
- Pediatric studies should be designed around evaluation of safety of the product given at the dose and duration intended for clinical use
  - Exposure matching to effective dose in adults
  - Staggered enrollment by age groups often done, not always needed

Pediatric Studies

- Inclusion of neonatal population
  - Determination of dosing regimen for term and preterm neonates
  - Careful attention to excipients
- Safety concerns to be evaluated?
  - Safety monitoring and laboratory cutoffs should be age-appropriate

Referenced Guidances

- Development of Anti-Infective Drug Products for the Pediatric Population (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-anti-infective-drug-products-pediatric-population)
- E11 Clinical Investigation of Medicinal Products in the Pediatric Population (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population)
- E11(R1) Addendum (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population)
- Draft Guidance: Pediatric Extrapolation ICH E11A
- General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-neonatal-studies-drugs-and-biological-products-guidance)
- Draft Guidance: Ethical Considerations for Clinical Investigations of Medical Products Involving Children (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children)


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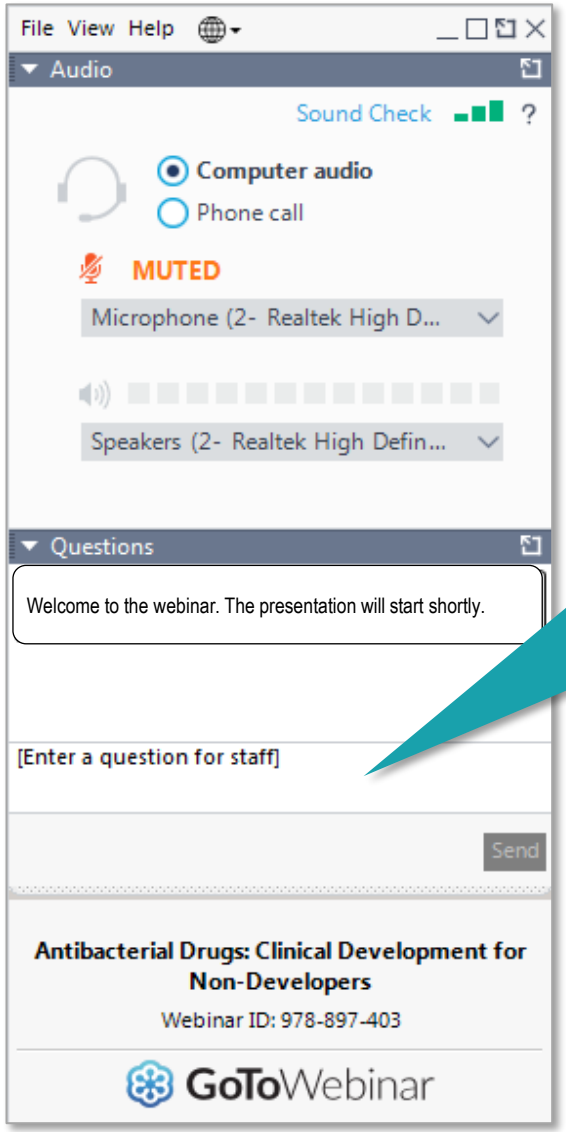

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Moderator:

- Neeloffer Mookherjee, University of Manitoba

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