The Pharmaceutical Industry and Clinical Trials: What's in it for Clinicians?

Stephen D. Shafran, MD, FRCPC, FACP, FIDSA
Professor, Division of Infectious Diseases
Department of Medicine
University of Alberta

Learning Objectives

- Understand the process for drug development in humans
- Understand that human drug development can only be done via partnerships between Pharma and clinicians and that these partnerships can benefit both parties when studies are well designed to answer clinically relevant questions
- Understand the gray zone between the scientific and marketing mandates of Pharma

Disclosure Statement

In my career, I have received research funding for clinical trials from:

- AbbVie Laboratories
- Boehringer Ingelheim
- Bristol Myers Squibb
- Burroughs Welcome (now part of GSK)
- Fisons Pharmaceuticals
- Gilead Sciences
- Glaxo SmithKline
- Janssen
- Merck
- Pfizer
- Pharmacia
- Roche
- Sanofi Aventis
- Schering (now part of Merck)
- SmithKline Beecham (now part of GSK)
- Vertex
- ViroPharma (now a part of Shire)
- Wyeth

About me- part 1

- I have practiced as an academic adult ID physician since 1986
- I consider myself to be a “clinical trialist”
- I was exposed to antiviral clinical trials as an ID Fellow (1983-1986)
  - NIAID study of IV acyclovir vs vidarabine in HSV encephalitis (brain Bx req’d; PCR not yet invented)
- I started being an independent clinical trialist in 1987, initially focusing on studies of anti-HSV therapies

About me- part 2

- I have conducted clinical trials of:
  - Antivirals
    - HSV (oral and topical)
    - VZV
    - HIV
    - HBV
    - HCV
  - Antifungals
    - Candida
    - Aspergillus
  - Antibacterials
  - Anti-protozoals (malaria)
  - Viral vaccines in adults (HBV, influenza, qHPV)

Anti-infective drugs I have evaluated in clinical trials

- Bictegravir/FTC/TAF
- Boceprevir
- Cefotaxime
- Cefpirome
- Ceftriaxone
- Cidofovir gel
- Ciprofloxacin
- Clofazimine
- Daclatasvir
- Danoprevir
- Docosanol cream
- Elbasvir/grazoprevir
- Entecavir
- Ethambutol
- Faldaprevir
- Famciclovir
- Filibuvir
- Fluconazole
- Glecaprevir/pibrentasvir
- Lomefloxacin
- Lopinavir/ritonavir
- Mericitabine
- Parataprevir/ombitasvir/ritonavir + dasabuvir + ribavirin
- Piperacillin-tazobactam
- Rifabutin
- Rifampin
- Rilpivirine/FTC/TAF
- Sofosbuvir + ribavirin
- Sofosbuvir/ledipasvir + ribavirin
- Sofosbuvir/velpatasvir
- Sofosbuvir/velpatasvir/voxilaprevir
- Tegobuvir
- Teicoplanin
- Telaprevir
- Tenofovir alafenamide (TAF)
- Tigecycline
- Tipranavir
- Undecylinic acid
- Valacyclovir
- Vedroprevir
- Voriconazole

Goals of Pharma

- Develop and market drugs, biologicals, vaccines and devices

- Maximize profits (profit is not a “dirty” word)
  - Develop effective and safe drugs
    - the better the drug, the greater potential for profit
  - Promote use of their products
  - Defend patents

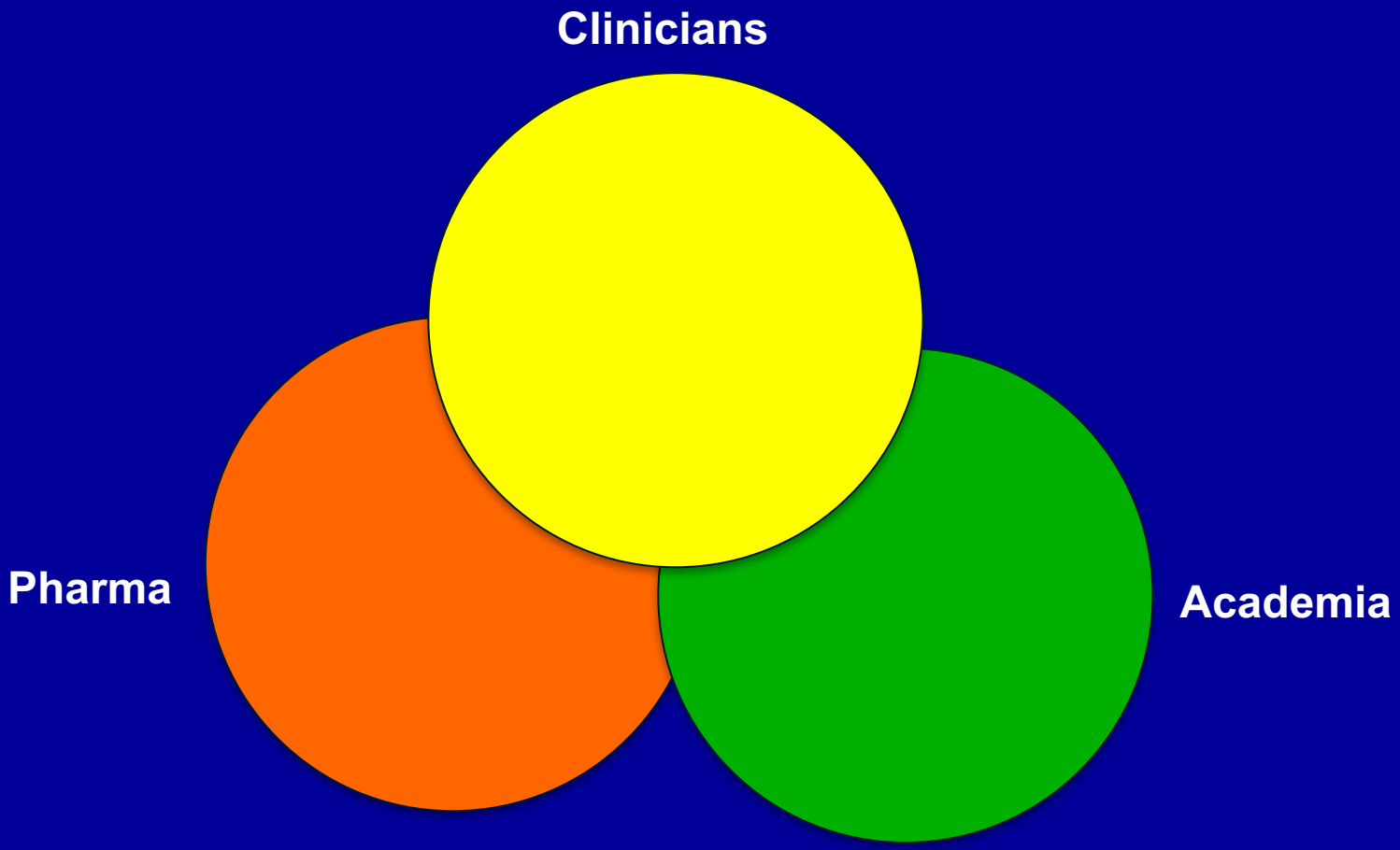
Goals of Clinicians

- Best medical care for patients
- Least hassle for the clinician
- So for drug therapy, clinicians wish for:
  - Best efficacy
  - Minimal adverse effects
  - Minimal drug-drug interactions
  - Least clinical and lab monitoring necessary

Goals of Healthcare Academia

- Improve prevention, diagnosis and treatment of illness
- Research funding, abstracts and publications
- Invited lectures
- Promotion, tenure and peer recognition

Overlap of Clinicians, Academia and Pharma



Overlap of Clinicians, Academia and Pharma

When an investigational therapy in a clinical trial offers:

- High efficacy for the patient
- Minimal toxicity for the patient
- Funding to the researcher/institution
- Abstracts and publications for the researcher
- Peer recognition for the researcher
- Licensure for Pharma → sales and profit

Win-Win-Win

Human Drug Development: Phases

Pre-clinical

- In vitro
- Animal safety and pharmacology
  - At least 3 mammals, at least one non-rodent
- Animal efficacy (if there is an animal model)

Clinical

- Phase 1- pharmacology & safety, including DDI studies
- Phase 2- initial efficacy and dose finding
- Phase 3- efficacy in larger numbers ("registrational" studies)

Human Drug Development: Clinical Phases

- Phase 1: requires specialized units where participants can be kept for 24h, sometimes longer
  - Most phase 1 sites do studies for a wide variety of drugs are are not experts in specific diseases
- Phase 2 and 3: requires clinics where suitable patients can be found ***and*** there is expertise in conducting clinical trials

Human Drug Development

- Extremely costly ($200,000 to $500,000 USD)
- Many more failures than successes
- >90% funded by Pharma
- Pre-clinical done almost completely in Pharma
- Pre-clinical requires extensive expertise:
  - Medicinal chemistry
  - Formulation
  - Pharmacology
  - Biochemistry: development of assays for drugs and metabolites and interacting drugs
  - Mutagenic assays
  - Animal care
  - Veterinary pathology

Human Drug Development: Pharma and Clinician Partnership

- Pharma can do all the preclinical work and choose to publish or not
- Pharma cannot do the human clinical work; Pharma must partner with clinicians
- Pharma used to partner only with academia, but increasingly uses a mixture of academic and non-academic sites
  - Non academic sites are often less costly and more efficient
  - Pharma wants some academic sites for KOLs

Pharma-Clinician Partnership for Clinical Trials: What's in it for Pharma?

- Pharma has no access to patients without clinicians
- A relationship with clinician-investigators can lead to more successful marketing of those products which come to market after the clinical trials are completed
  - Clinician-investigators are already familiar with the drug and may have a more favorable impression

Pharma-Clinician Partnership for Clinical Trials: What's in it for Clinicians?

- Provides their patients with earlier access to new therapies
  - esp when licensed therapies don't exist or are of poor efficacy and/or high toxicity
- Funds investigators' research programs
- Potential for abstracts and publications, including high impact ones
  - Publications help promotion and tenure
- Potential for recognition as a KOL and for invited lectures

A COMPARISON OF TWO REGIMENS FOR THE TREATMENT OF *MYCOBACTERIUM AVIUM* COMPLEX BACTEREMIA IN AIDS: RIFABUTIN, ETHAMBUTOL, AND CLARITHROMYCIN VERSUS RIFAMPIN, ETHAMBUTOL, CLOFAZIMINE, AND CIPROFLOXACIN

STEPHEN D. SHAFRAN, M.D., JOEL SINGER, PH.D., DONALD P. ZAROWNY, M.D., PETER PHILLIPS, M.D., IRVING SALIT, M.D., SHARON L. WALMSLEY, M.D., IGNATIUS W. FONG, M.B., M. JOHN GILL, M.B., CH.B., ANITA R. RACHLIS, M.D., RICHARD G. LALONDE, M.D., MARY M. FANNING, M.D., PH.D., AND CHRISTOS M. TSOUKAS, M.D., FOR THE CANADIAN HIV TRIALS NETWORK PROTOCOL 010 STUDY GROUP*

N Engl J Med 1996; 335:377-83.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Peginterferon Alfa-2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3

Mitchell L. Shiffman, M.D., Fredy Suter, M.D., Bruce R. Bacon, M.D., David Nelson, M.D., Hugh Harley, M.B., B.S., Ricard Solá, M.D., Stephen D. Shafran, M.D., Karl Barange, M.D., Amy Lin, M.S., Ash Soman, M.B., B.S., and Stefan Zeuzem, M.D., for the ACCELERATE Investigators*

N Engl J Med 2007; 357:124-34.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

J.J. Feld, I.M. Jacobson, C. Hézode, T. Asselah, P.J. Ruane, N. Gruener, A. Abergel, A. Mangia, C.-L. Lai, H.L.Y. Chan, F. Mazzotta, C. Moreno, E. Yoshida, S.D. Shafran, W.J. Towner, T.T. Tran, J. McNally, A. Osinusi, E. Svarovskaia, Y. Zhu, D.M. Brainard, J.G. McHutchison, K. Agarwal, and S. Zeuzem, for the ASTRAL-1 Investigators*

N Engl J Med 2015; 373:2599-607.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

N Engl J Med 2011; 364:422-631.

Advantages to Clinicians of Conducting Pharma Funded Clinical Trials

- Early access to promising therapies
- Research funding
- Research abstracts and publications
  - Best opportunity for publication in high impact journals
  - Many possibilities for substudies/subanalyses/multiple publications
- Lecture opportunities

Fidaxomicin Attains High Fecal Concentrations With Minimal Plasma Concentrations Following Oral Administration in Patients With *Clostridium difficile* Infection

Pamela Sears,[1] Derrick W. Crook,[2,3] Thomas J. Louie,[4,5] Mark A. Miller,[6] and Karl Weiss[7]

Treatment of First Recurrence of *Clostridium difficile* Infection: Fidaxomicin Versus Vancomycin

Oliver A. Cornely,[1] Mark A. Miller,[2] Thomas J. Louie,[3,4] Derrick W. Crook,[5,6] and Sherwood L. Gorbach[7,8]

Fidaxomicin Preserves the Intestinal Microbiome During and After Treatment of *Clostridium difficile* Infection (CDI) and Reduces Both Toxin Reexpression and Recurrence of CDI

Thomas J. Louie,[1,2,3] Kris Cannon,[2] Brendan Byrne,[1] Judy Emery,[1] Linda Ward,[3] Melissa Eyben,[3] and Walter Krulicki[3]

[1]Department of Medicine, and [2]Department of Microbiology-Immunology and Infectious Diseases, University of Calgary, and [3]Infection Control Program, Calgary Zone, Alberta Health Services, Canada

Fidaxomicin Versus Vancomycin for *Clostridium difficile* Infection: Meta-analysis of Pivotal Randomized Controlled Trials

Derrick W. Crook,[1,2] A. Sarah Walker,[1,2] Yin Kean,[3] Karl Weiss,[4] Oliver A. Cornely,[5] Mark A. Miller,[6] Roberto Esposito,[7] Thomas J. Louie,[8,9] Nicole E. Stoesser,[1,2] Bernadette C. Young,[1,2] Brian J. Angus,[1] Sherwood L. Gorbach,[3,10] and Timothy E. A. Peto[1,2] for the Study 003/004 Teams

Efficacy of Fidaxomicin Versus Vancomycin as Therapy for *Clostridium difficile* Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections

Kathleen M. Mullane,[1] Mark A. Miller,[2] Karl Weiss,[3] Arnold Lentnek,[4] Yoav Golan,[5] Pamela S. Sears,[6] Youe-Kong Shue,[6] Thomas J. Louie,[7] and Sherwood L. Gorbach[5,6]

Disadvantages to Clinicians of Conducting Pharma Funded Clinical Trials

- It takes way more time that most realize
  - Investigator meetings
  - On site initiation meetings
  - Ongoing study visits
  - Lab report sign-offs
  - Adverse event assessment
  - GCP certification/maintenance
- Must be done strictly per protocol and to GCP standards
- Need to keep finding funding to support research staff
  - Generally need to conduct “unimportant” me-too clinical trials to “pay the bills”

Practical Considerations re Conducting Pharma Sponsored Clinical Trials

- It's hard to break in
- It's more work than you think
- You are always wondering where your next dollar is coming from to pay your research staff
- But sometimes it's magical
  - "Game changing" therapy (HIV and HCV)
  - Curing the incurable (decompensated HCV cirrhotics and a growing list of cancers)
  - Near elimination of disease with vaccines

Concluding Thoughts 1

- We have made a societal decision that drug development is to be done by the for-profit private sector
- The consequence of this decision is that drug development is heavily influenced by the potential for profit
  - Diseases that are both common AND incurable are most profitable
    - Leads to many “me-too” therapies and not enough “breakthrough” therapies
  - Uncommon diseases are generally not profitable
  - Little incentive to develop new drugs in therapeutic areas where there are effective generic drugs

Concluding Thoughts 2

- Pharma can't do human studies in house; Pharma need clinicians to partner with
- Clinicians can become skilled clinical trialists, but it takes time and effort
- There are rewards for clinicians and their patients in conducting clinical trials, but there are hassles too
- We **all** benefit from Pharma sponsored clinical trials, even if we never participate, because almost all clinical trials that change practice are funded by Pharma

CLINICAL TRIALS AWARENESS WEEK

Clinical trials are important to health research. Trials are conducted with patients and healthy volunteers to answer important questions such as "Does this treatment work?" There are a number of ways YOU can celebrate Clinical Trials Awareness Week!
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