M E.M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

5127 '01 NOV 30 P1:52

Date: November 21, 2001

To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: Bioequivalence Issues

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

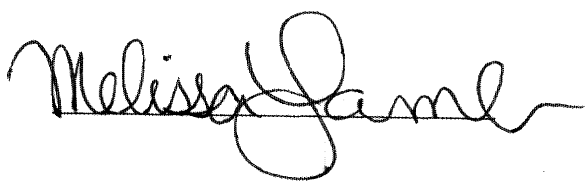
Title of Presentation: Bioequivalence Issues

Presented for: GphA Technical Committee Fall Workshop

Date Presented: October 29, 2001

Presented by: Dale P. Conner
Director
Division of Bioequivalence, OGD

Number of Pages: 14



Attachment

90S-0308

M720

Bioequivalence Issues

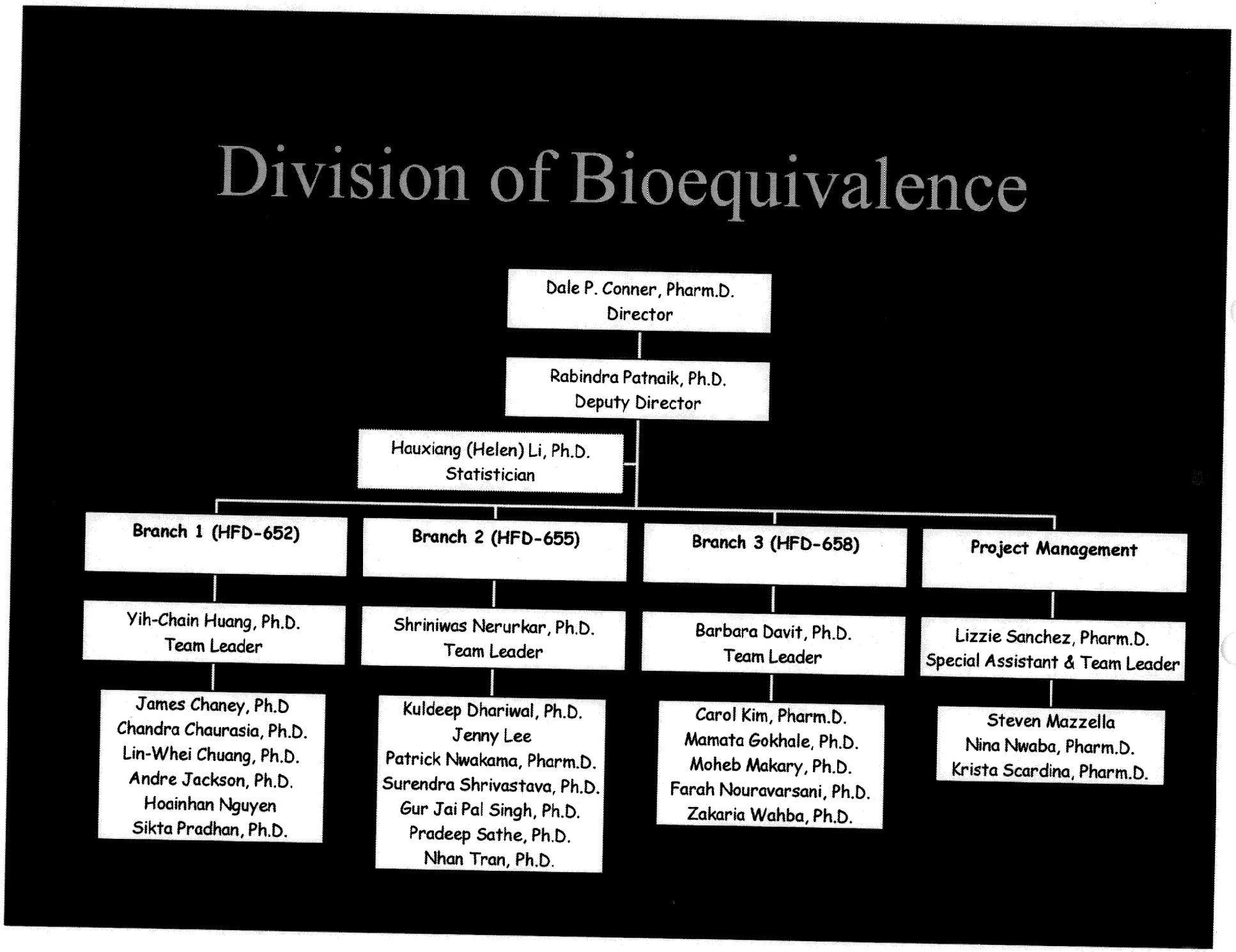
GPhA Technical Committee Fall Workshop

Dale P. Conner
Division of Bioequivalence, OGD

Introduction

- Structure of Division of Bioequivalence
- Various BE Issues/Questions

Division of Bioequivalence



Replicate Design vs. Two-Way Crossover

- General BA/BE guidance recommends replicate design for MR products
- Some sponsors are not conducting replicate designs for these products
- Alternative designs to those specified in the guidance should be scientifically justified in the application

Reserve Sample Retention

- 21 CFR 320.63 and 21 CFR 320.38
- Continues to be a problem
- Problems frequent in bioequivalence studies with clinical end-points
- Clinical investigator should choose test article samples for retention
- DSI currently drafting a guidance on this topic

SUPAC: Comparisons for In Vivo vs. In Vitro Studies

- "If a BE study is required (sic) to implement a SUPAC change, is the comparative dissolution requirement (1) test vs. reference or (2) pre-change vs. post-change?"

Food-Effect BE Studies

- New draft guidance will be released for comment
- Currently
  - If a food effect (even a negative one) on bioavailability is mentioned in the labeling a fed BE study should be submitted
  - If the labeling instructions say to ONLY take on an empty stomach then a fed BE study is not necessary

Food-Effect BE Studies

- Currently
  - Two-way crossover studies
  - Point estimates should fall within 80 - 125%
  - No waivers of fed-BE studies for BCS Class 1 drugs (yet)

General Population vs. Normal Healthy Young Males

- General BA/BE guidance recommends subjects from the "general population"
- This is essential for the IBE approach and strongly recommended for all other studies
- General population: age, race, sex, stable medical conditions
- If you do not recruit subjects from the "general population" then provide justification in your application

Date of Implementation of Guidances

- Date may be stated in the guidance
- If not stated it is usually on the date of issuance of the final copy
- If you have a pending deficiency and a new guidance seems to say that this is no longer a deficiency -- consult the appropriate review division

Possible Changes in Guidances

- Five-day grace period for upward waivers (BA/BE)
- IBE will be discussed at upcoming advisory committee meeting in November (BA/BE)
- Dermatopharmacokinetics (DPK) will be discussed at the advisory committee in November

Biopharmaceutics Classification System (BCS)

- Few ANDA submissions
- Almost none contain permeability data performed by sponsors
- Literature data?

"Failed" Studies

- Agency is requesting submission of "failed" or additional studies
- Studies on the "final" formulation
- These studies to be submitted as complete summaries
- Clarification of regulations is planned
- Guidance is also planned after regulation changes are finalized

Pharmacokinetic Reassays

- Reassay of samples for "pharmacokinetic" reasons
- This is discouraged, but if you do it
- Objective a priori criteria should be stated in SOP
- Provide a complete before and after data analysis

In Vitro Dissolution

- Provide laboratory site information
- DSI inspections are planned