Bioequivalence Update

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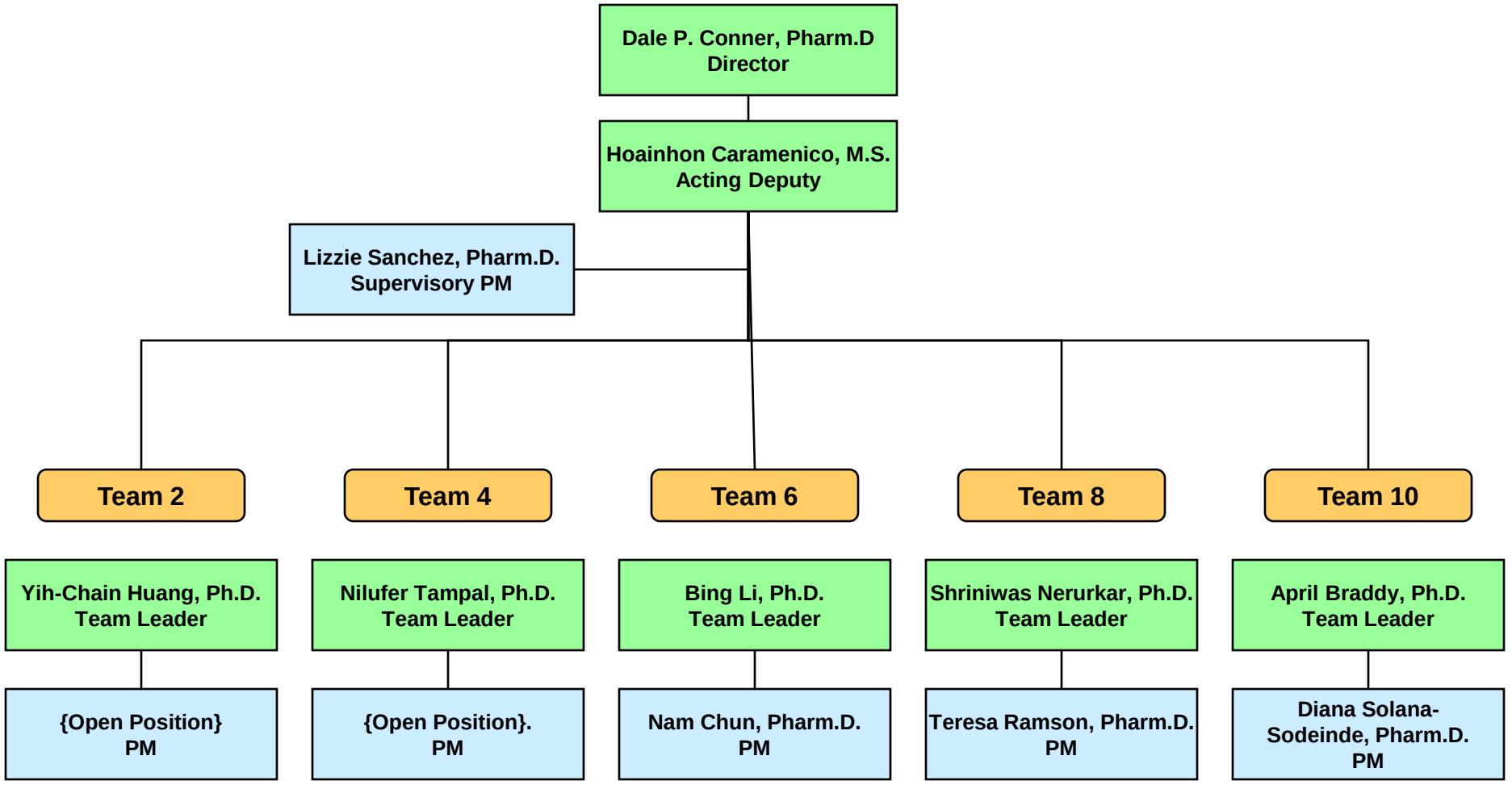
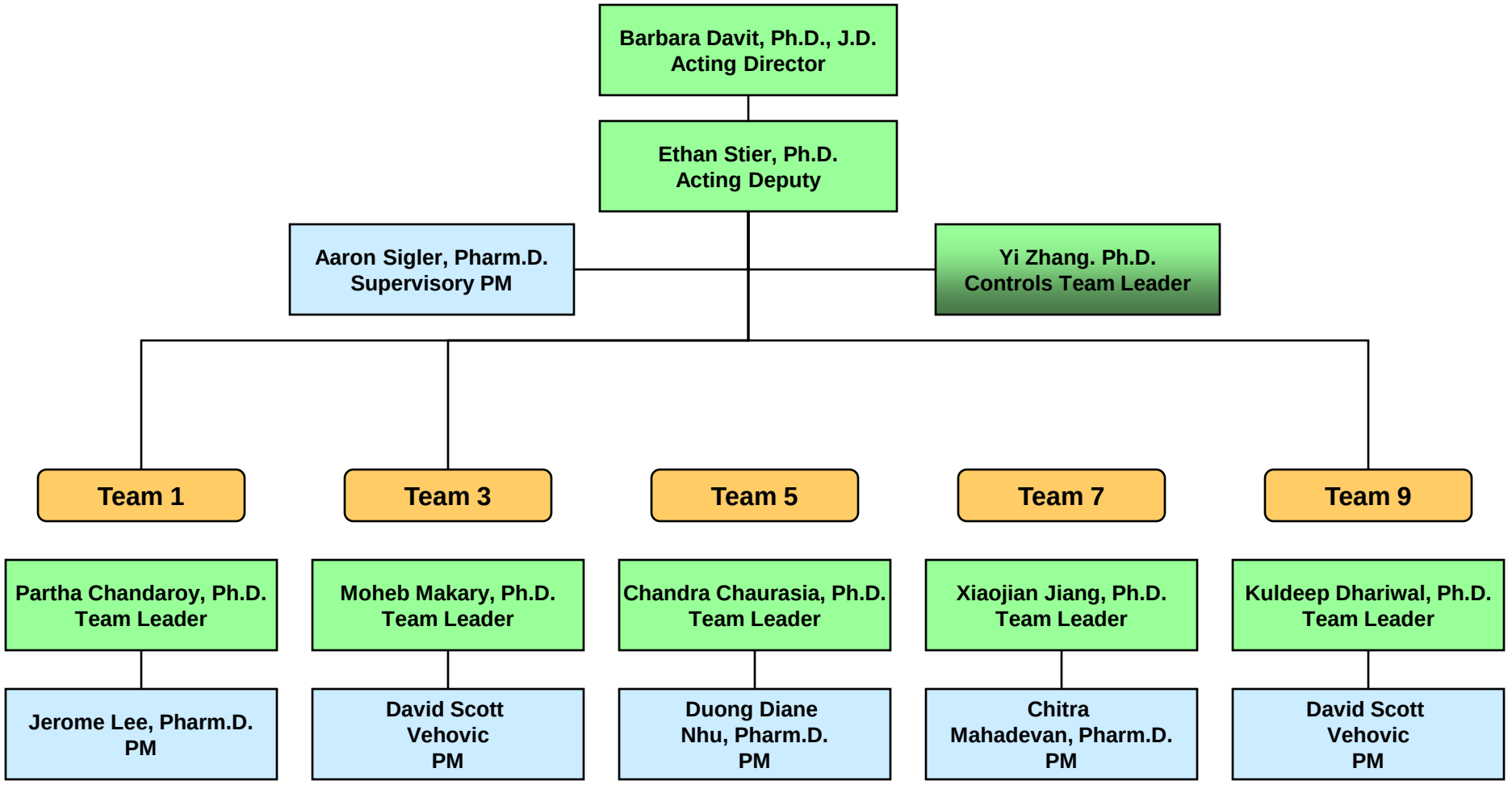
Overview

- Division of Bioequivalence staffing
- Recurring problems with submissions
- BE Question – How to determine what kind of study to do for cancer chemotherapy drugs

Division of Bioequivalence 1, OGD



Division of Bioequivalence 2, OGD



Recurring problems with BE submissions

- Electronic data tables wrong or incomplete
- Frozen storage stability < time between study completion and sample analysis
- Potency and content uniformity data not included in BE section
- “PK repeats”
- Bioanalytical SOPs not submitted
- Poorly-organized BE submission
- Electronic summary tables prepared incorrectly

Organization of ANDA

- BE reviewers take longer to review poorly organized submissions
- We ask companies to submit in CTD format (or eCTD)
  - Module 2 – clinical summaries
  - Module 5 – clinical study reports
- Electronic submission facilitates quick review

Problems with electronic tables

- Not filled out completely
  - Instead of data, information about the relevant volume and page number inserted
  - Not all strengths listed in formulation tables
  - Missing information
- Not prepared properly
  - File created by scanning tables rather than by creating a PDF file

Problems with Electronic Datasets

- Files missing
- Wrong files submitted
- Draft/noncurrent files submitted
- Blank files submitted
- Wrong format/arrangement of data

BE Question
BE Studies for Anticancer Drugs

- Most anticancer drugs are not safe to be administered to normal healthy volunteers
- What thought process/procedure is used to determine
  - Is the drug too dangerous to give to normal subjects?
  - If patients must be used?

BE Question
BE Studies for Anticancer Drugs

- BE Studies in Patients
  - Should not change patients' normal therapy
  - Need to be flexible about the dose (but not dosage strength) used for each patient subject in the study
  - Steady-state studies are sometimes necessary

BE Studies for Anticancer Drugs

- Information needed to design BE study
  - PK information on drug (especially elimination half-life)
  - Normal range of doses and regimen used in patients to be studied
  - Other constraints
    - Amount of blood that can be collected
    - Stability of the patients' medical condition
    - Stability of dosage regimen

BE Studies for Anticancer Drugs

- Example 1
  - Dosage range: 100-600 mg
  - Dosage units: 100 and 200 mg (proportionally similar)
  - Elimination half-life: 2 hr
  - Regimen: QD for 5 days, 25 days until next course
  - Possible study design:
    - Two-way crossover, first 2 days of treatment
    - Essentially a two-way crossover, single-dose study
    - Use doses made up of one dosage strength for study

BE Studies for Anticancer Drugs

- Example 2
  - Dosage range: 50-500 mg
  - Dosage units: 50,100 and 250 mg (proportionally similar)
  - Elimination half-life: 20 hr
  - Regimen: QD x 7 days repeat each month
  - Possible study design:
    - Two-way crossover sampled at day 7 on two separate months
    - A two-way crossover, steady-state study
    - Use doses made up of one dosage strength for study
    - Alternate design: Parallel steady-state