# A regulators experience of non-clinical statistical interactions with industry

Meiyu Shen
Center for Drug Evaluation and Research,
U.S. Food and Drug Administration

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

# Outline

- Review meetings
- Information requests
- Guidance development
- Workgroups
- Statistics workshops
- CMC meetings
- Statistics conferences
- USP statistical expert group
- Publication topics
- Case studies

# Review meetings during review cycles

- Face-to-face meetings for Investigation New Drug applications (INDs), Biological License Applications (BLAs), New Drug Applications (NDAs)
  - FDA preliminary comments prior to the meetings
    - Each discipline team at FDA addresses all questions carefully
      - Internal meetings to discuss the agency's responses
  - Meeting discussion
    - Industry statisticians will discuss the study designs and statistical methods with regulatory statisticians
  - Post meeting comments
    - FDA adds comments for the questions and issues raised during the meeting or asked shortly prior to the meeting

# Information requests during review cycles

- FDA issues the Information requests for asking the sponsor
  - To address some relevant scientific and statistical questions
  - To Provide more evidence to support the sponsor’s position
- Sponsors provide the responses to address regulator's concerns

# Guidance development

- The FDA guidance on stability study and shelf-life determination
- The draft guidance on Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity
  - Published in 09/2017
  - Industry can provide comments now
- The draft guidance on Assay Development for Immunogenicity Testing of Therapeutic Proteins
  - Published in 2016
  - Industry provided comments
  - FDA is addressing the public comments for the final guidance's publication

# FDA and industry working group

- IPAC-RS DDU team and FDA DDU working group
  - IPAC-RS: International Pharmaceutical Aerosol Consortium on Regulation & Science

# Statistics workshops jointly organized by industry and FDA

- ASA regulatory/Industry (former FDA/Industry) statistics workshop
  - ASA and FDA
  - 3 designated CMC sessions to discuss statistical issues and challenges related to CMC areas
- Statistical and Data Management Approaches for Biotechnology Drug Development
  - IABS and FDA
- DIA/FDA statistics forum
  - DIA and FDA
- FDA/Duke statistical Symposium
  - Duke, Industry and FDA
- Nonclinical biostatistics conference, held in east coast every other year

# CMC workshops jointly organized by industry and FDA

- CMC visitation days
  - A group of industry statisticians from multiple pharmaceutical companies came to FDA for a whole day face-to-face meeting with CMC reviewers and statistics reviewers
- AAPS CMC statistics Focus Group Joint F2F meeting
- CASSS CMC Strategy Forum
- Bioassays: Scientific Approaches and Regulatory Strategies

# Statistics conferences

- Midwest Biopharmaceutical statistics workshop
- Joint Statistical Meeting
- Applied Statistics Symposium sponsored by International Chinses Statistical Association (ICSA)
- Easter North American Association meeting
- Biopharmaceutical Applied Statistics Symposium

# USP statistical expert group

- We participate in USP statistical expert group
  - Bioassay
  - Uniformity of dosage units
  - dissolution

# Journal list for publications

- We published the statistics methods at
  - Journal of Biopharmaceutical Statistics
  - Pharmaceutical statistics
  - Therapeutic Innovation & Regulatory Science
  - Pharmaceutical Research
  - United States Pharmacopeia forum
  - Journal of Pharmaceutical Sciences
  - Others

# Publication topics covered

I. Analytical similarity
   a. Tier 1 equivalence test and margin determination
   b. Tier 2 quality range determination
   c. Adjustment for sample size imbalance
   d. Sample size determination
   e. Alternative equivalence tests for tier 1 CQAs

II. Dose content uniformity
   a. USP multiple stage sampling acceptance rule
   b. Tolerance interval and type I error spending for the 3 stages
   c. Median to large sample size rules

III. Delivery dose uniformity

IV. Stability and shelf life determination

# Publication topics covered

V. Dissolution profile equivalence

VI. Quality specification

VII. Particle size distribution equivalence

VII. Assay cut point determination

VIII. Method transfer assessment

IX. PK Bioequivalence for sparse sampling

# CASE I: ANALYTICAL SIMILARITY

# Tiered approach

- Positive interaction between industry statisticians and regulatory statisticians for many years inspired the FDA statisticians proposing a Tiered approach
  - a pragmatic approach for evaluating analytical similarity of many quality attributes
    - Most of them are correlated

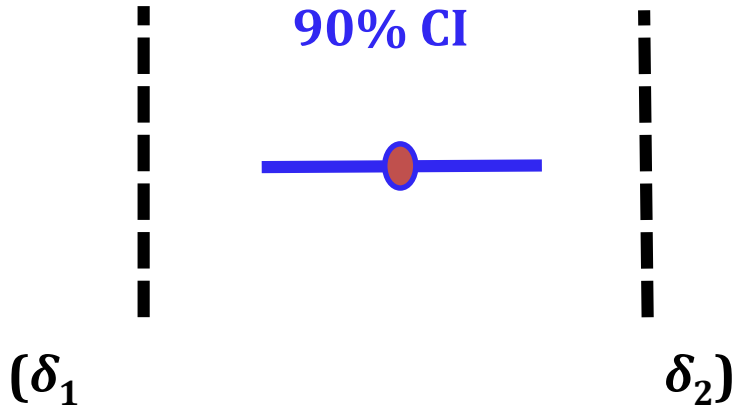
# Tier 1 equivalence test

- Bottle neck:
  - Limited number of batches available during premarket
- Solution:
  - An equivalence design with a margin proportion to reference variability for comparing the biosimilar product to the reference product with a limited number of available batches

# Tier 1 equivalence test (continued)

- Usually 2 -3 critical QAs are assigned to Tier 1 (for example, Bioactivity and Content)
- Tier 1 has the most rigorous statistical method in all tiers;
- Equivalence Margin = $(-1.5\sigma_C - \Delta\ ,\ 1.5\sigma_C + \Delta)$:

$$H_0 : \mu_B - \mu_R \le \delta_1 \quad \text{or} \quad \mu_B - \mu_R > \delta_2$$
$$H_a : \delta_1 < \mu_B - \mu_R < \delta_2$$



# Tier 1 equivalence test (continued)

- Positive interaction between industry statisticians and regulatory statisticians motivated the agency to improve newly proposed equivalence test
  - At application meetings and public conferences
    - Industry statisticians and regulatory statisticians discussed
      - issues of correlated lots from the same drug substance lot
      - issues of splitting the reference lots into variability estimation and hypothesis test
      - Others
  - Both industry statisticians and regulatory statisticians published many statistical manuscripts to address these issues using better statistical analyses

# Tier 2: Quality Range Analysis

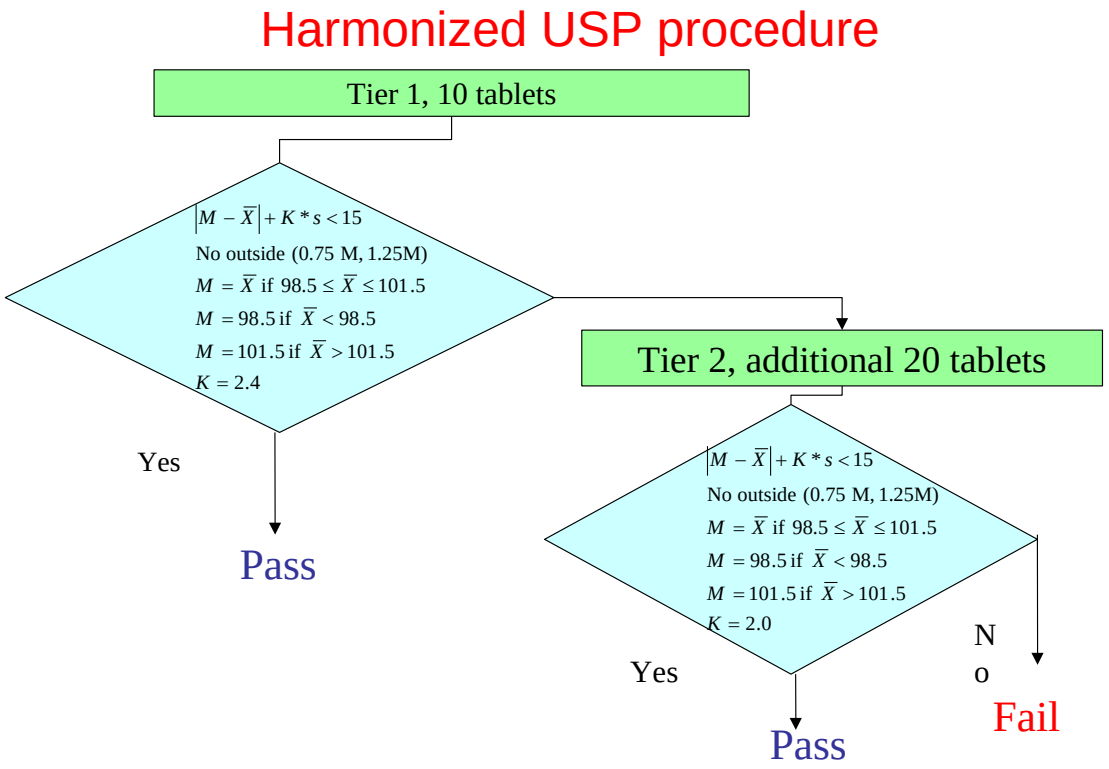
- Quality Range = Mean ± X SD
  - Mean and SD of quality attribute data from the comparator measured by applicant
  - Multiplier (*X*) should be scientifically justified, e.g., X=3
- Comparison of test and reference support a finding of high similarity if
  - High proportion (e.g., 90%) of observed batch values of the test fall within the quality range derived from the comparator

- **Quality range of comparator**
- **Batch values of test**

# CASE II: UNIFORMITY OF DOSAGE UNITS

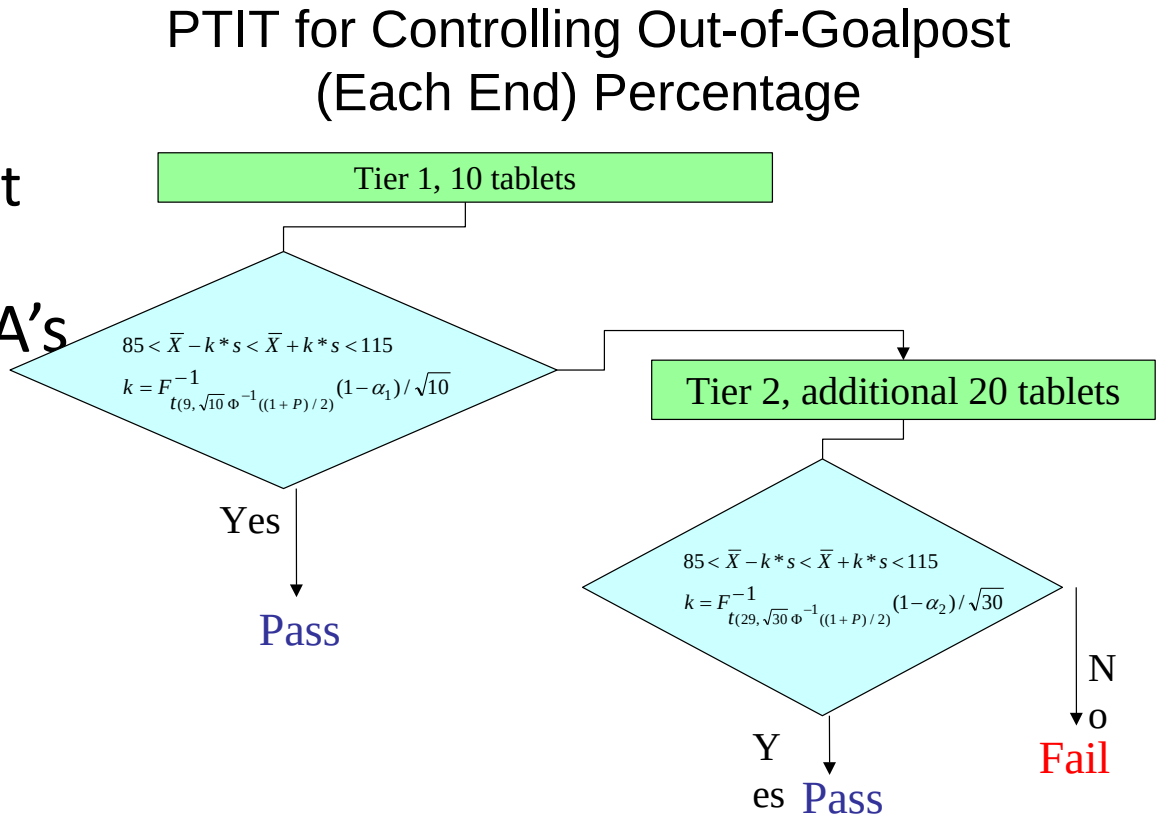
# Uniformity of Dosage Units

- 2004
  - FDA evaluated
    - USP <905>: USPXXIV
    - Japan Pharmacopoeia JPXIV
    - Europe Pharmacopoeia III testing procedure
    - Harmonized USP UDU procedure



# UDU: PTIT proposed by FDA

- 2005 JSM oral and proceeding
  - The FDA's version on content uniformity test presented
- 2007 JBS published FDA's proposal
  - A Tolerance Interval Based Two-Stage Sequential Quality Assurance Test on Content Uniformity of Drug



# UDU and large n dose content uniformity test

- In 2005, Development of a content uniformity test suitable for large sample sizes
  - PhRMA CMC Statistics Expert Team
  - PhRMA PAT Expert Team
  - PhRMA GMP Steering Committee
- In 2005, FDA statisticians participated the meetings between Office of Pharmaceutical science (OPS) of CDER, FDA and PhRMA
- Statisticians of PhRMA presented their approach in many statistical conferences which FDA statisticians attended
- A few statistical papers on large n UDU test were published soon after

# FDA's publications on UDU and large n dose content uniformity test

- 2011, Pharmacopeia forum
  - Bias Of The United States Pharmacopeia Harmonized Test For Dose Content Uniformity,
- 2014, Therapeutic Innovation & Regulatory Science
  - FDA statisticians proposed large n test for Dose Content Uniformity,
- 2015 JBS
  - Using Tolerance Intervals for Assessment of Pharmaceutical Quality

# CASE III: DELIVERED DOSE UNIFORMITY (DDU)

# DDU: Historical Summary*

- Pre-1998; Walter Hauck, as SGE, presents the kernel of PTIT for delivered dose uniformity testing to FDA
- Hauck's original tenets:
  - Agency sets goalposts
  - Agency sets coverage within goalposts
  - Applicant determines sample size to meet Agency requirements
- Fits well with our current initiatives:
  - QbD and demonstration of product and process knowledge
  - Science and risk-based specification of drug product
- 1998, Inhalation Drug Product Workshop (about 600 attendees)
- 1998 draft guidance for DDU
- IPAC-RS evolved from these discussions
- 11/2001, IPAC-RS presented a report in response to Dr. Hauck's presentations

* Credit to Dr. Lostritto, 2005 AC presentation

# DDU: Historical Summary*

- Infrequent updates follow over the next few years from IPAC-RS in response to discussions with the Agency
- Since 2001, FDA's position has been that data should be provided to support any proposed PTIT criteria from approved drug products in the United States or from those which are, "close" to approval in the U.S. (e.g., NDA in review or IND in late Phase-3)
- During this period, various approaches to PTIT were discussed
- 2003-2004, CDER forms a working group with Bob O' Neil, Moheb Nasr, Badrul Chowdhury and Lawrence Yu
- 2004 – 2005: An IPAC-RS and FDA Technical Subgroup is formed with Bo Olsson, Dennis Sandell, Rik Lostritto, Guirag Poochikian, Yi Tsong, and Meiyu Shen to provide evaluations and recommendations

* Credit to Dr. Lostritto, 2005 AC presentation

# IPAC-RS and FDA: General Agreements*

- PTIT is a good scientific and risk based approach to setting DDU specifications
- Elimination of the zero tolerance criteria is appropriate in this context
- Distribution of alpha between Tiers I and II:
  - 1-alpha is the confidence level (e.g., 95%) that an accepted batch fulfills the limiting quality criteria
  - Alpha is conserved for the overall test but may be distributed between Tiers I and II in a number of ways

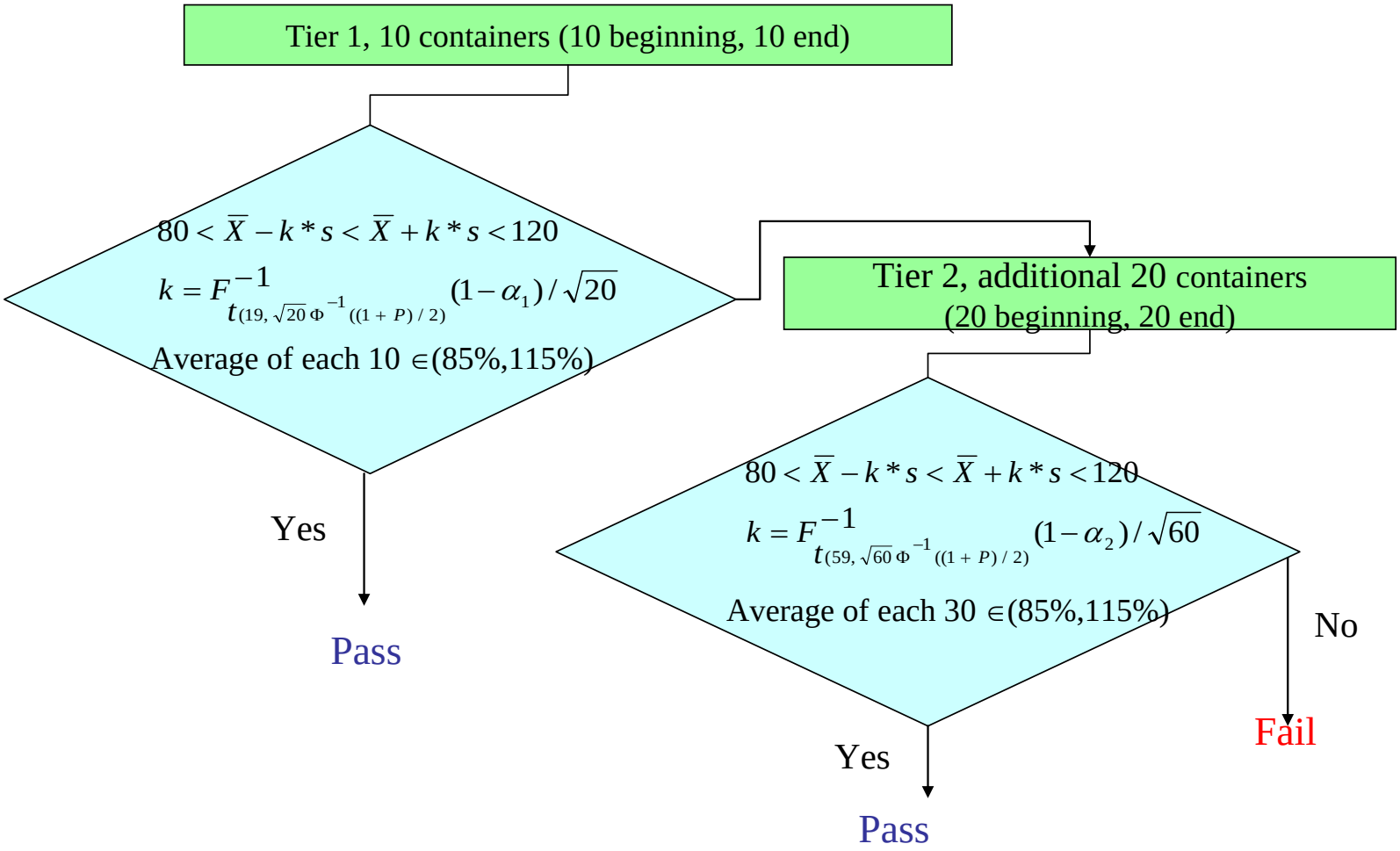
* Credit to Dr. Lostritto, 2005 AC presentation

# IPAC-RS and FDA: General Agreements*

- Goalposts: 80-120% of label claim
- Treatment of upper and lower "tails" outside goalposts. Pool or separate?
  - Pooling of tails was rejected as inappropriate
  - Separating the tails was accepted because safety and efficacy risks are better illuminated and appropriately accounted for within any given set of goalposts, coverage, n, etc.
- The Agency is appreciative for the collaboration with IPAC-RS throughout the process
  - All parties came to a better understanding of respective positions
  - These agreements are significant and took a substantial time to reach
- The Development and Description of the FDA's current position follows…

* Credit to Dr. Lostritto, 2005 AC presentation

# PTIT for Controlling Out-of-Goalpost (Each End) Percentage



The first step is to calculate K values using the PTIT model described herein (80%-120 Goalposts, 2 tiers with Pocock distribution of alpha). These values are the used in evaluating various options for coverage (as % within goalposts)*.

**Table 1. K Values** Used for PTIT Calculations
n = sample size

| % **coverage** | n=10 Tier-I | n=30 Tier-II | n=20 Tier-I | n=60 Tier-II | n=30 Tier-I | n=90 Tier-II |
|---|---|---|---|---|---|---|
| | **K 10** | **K 30** | **K 20** | **K 60** | **K 30** | **K 90** |
| 82.5 | 2.82 | 1.94 | 2.20 | 1.74 | 2.00 | 1.66 |
| 85.0 | 2.96 | 2.04 | 2.32 | 1.83 | 2.11 | 1.75 |
| **87.5** | **3.12** | **2.16** | **2.45** | **1.94** | **2.23** | **1.86** |
| 90.0 | 3.31 | 2.30 | 2.60 | 2.07 | 2.37 | 1.98 |

* Credit to Dr. Lostritto, 2005 AC presentation

# DDU: Post-AC's interaction

- 2006 FDA's oral presentation and proceeding at JSM
  - Parametric Two-Tier Sequential Quality Assurance Test Of Delivery Dose Uniformity Of Multiple-Dose Inhaler And Dry Powder Inhaler Drug Products,
- 2008, FDA's publication at Journal of Biopharmaceutical Statistics
  - Parametric two-tier sequential quality assurance test of delivery dose uniformity of multiple-dose inhaler and dry powder inhaler drug products.
    - Tsong, Y, Shen, M, Lostritto, RT, and Poochikian, GK (2008).
- 2009, Industry's comments on FDA's publication at AAPS PharmSciTech
  - "A two one-sided parametric tolerance interval test for control of delivered dose uniformity.
    - Part 1—characterization of FDA proposed test.",
    - Part 2—Effect of Changing Parameters
      - Novick S., Christopher D., Dey M., Lyapustina S., Golden M., Leiner S., Wyka B., Delzeit HJ, Novak C., Larner G
- 2015, FDA's publication at JBS
  - Quality Assurance Test Of Delivery Dose Uniformity Of Multiple dose Inhaler And Dry Powder Inhaler Drug Products
    - Tsong, Dong, M. Shen, R. Lostritto,

# Acknowledgement


- Dr. Yi Tsong, CDER/OB
- Dr. Richard Lostritto, CDER/OPQ