Did We Consider The World Around Us
Clinical vs Preclinical

MSD

INVENTING FOR LIFE

20 May 2019

Eric J. Woolf

Disclaimer

This presentation does not necessarily represent the explicit views of EBF. Rather, it is the intent of the author to try to raise concerns generally expressed on the topic by the global bioanalytical community since the release of the M10 draft

Key Aspects to Consider

- Scope of M10
- Population Diversity (or lack thereof)
- Matrices

M10 Scope

This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions. The guideline is applicable to the validation of bioanalytical methods used to measure concentrations of chemical and biological drug(s) and their metabolite(s) in biological samples (e.g., blood, plasma, serum, other body fluids or tissues) obtained in *pivotal nonclinical TK/PK studies* that are used to make regulatory decisions and *all phases of clinical trials* in regulatory submissions. Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary. The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.

Scope – Clinical

- Scope is clear and relatively unambiguous, albeit broad
  - All phases of development
  - No differentiation with respect to driving regulatory decisions
- Could narrowing the clinical scope be considered?
  - Consider study objectives
    - Restrict full validation to studies whose **primary** objectives are PK related and/or label content driving
      - Bioequivalence
      - Definitive PK
      - Drug-drug interactions
- Need for “fully” validated assays for metabolites and multiple matrices still an area of uncertainty

Scope - Nonclinical

- General agreement that scope is ambiguous
  - What are “pivotal nonclinical PK/TK studies”?
    - Nonclinical TK studies
      - Typically run in safety assessment/toxicology departments
      - Generally conducted under the GLPs.
      - Bioanalysis historically conducted using “fully” validated methods – at least for primary matrix
    - Nonclinical PK studies
      - Typically run in DMPK departments
      - Not within scope of GLPs
      - Historically “fit for purpose” validation applied to BA methods

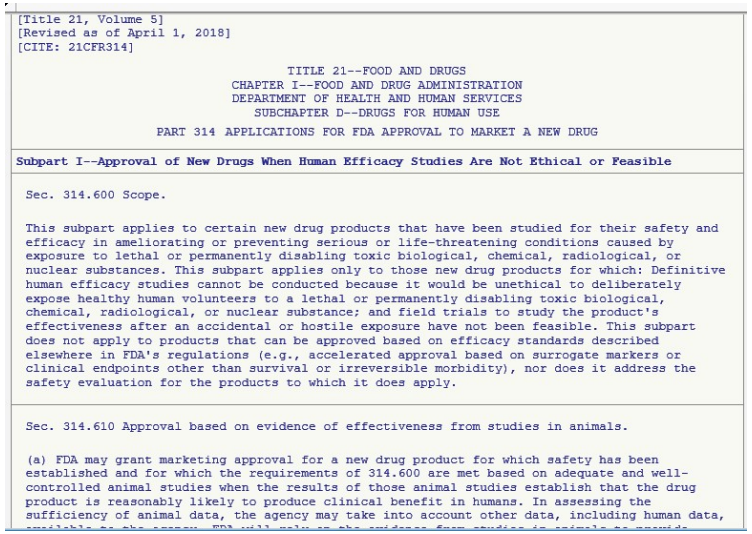
Nonclinical PK Studies

- Recent submission contained 23 nonclinical “PK Studies”
  - Multiple study type buckets
    - Several to characterize PK in safety assessment species
      - Drive TK study conduct
    - Several formulation assessments
      - Goal was to identify optimal formulation to be used in TK studies
    - Studies with radiolabeled drug
      - Characterize metabolism in safety species
    - In vitro studies
      - Potentially guide clinical metabolism/DDI studies

Are Any of these Studies Pivotal with Respect to PK?

What is a Pivotal Nonclinical PK Study

- The results from practically all nonclinical PK studies are superseded by data from other studies
  - GLP TK studies are the source for definitive PK data from safety assessment species
  - Human DDI studies generally are available to confirm observations from in-vitro metabolism studies
- Pivotal nonclinical PK studies should be restricted to those studies that are surrogate for clinical studies that are normally conducted during development programs, but cannot, for a given therapeutic, be conducted
  - Best example is “animal rule” studies



[Title 21, Volume 5]
[Revised as of April 1, 2018]
[CITE: 21CFR314]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 314 APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

Subpart I--Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

Sec. 314.600 Scope.

This subpart applies to certain new drug products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances. This subpart applies only to those new drug products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible. This subpart does not apply to products that can be approved based on efficacy standards described elsewhere in FDA's regulations (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation for the products to which it does apply.

Sec. 314.610 Approval based on evidence of effectiveness from studies in animals.

(a) FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of 314.600 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data,

The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

Potential Scope Narrowing and Clarification

This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions. The guideline is applicable to the validation of bioanalytical methods used to measure concentrations of chemical and biological drug(s) and their metabolite(s) in biological samples (e.g., blood, plasma, serum, other body fluids or tissues) obtained in *nonclinical TK studies falling under the scope of the GLPs that are used to make regulatory decisions, nonclinical PK studies that are conducted as surrogates for clinical studies, and all phases of clinical trials in regulatory submissions for which a primary objective of the study is to assess, compare or characterize drug exposure.* Full method validation is expected for the primary matrix(ces) intended to support regulatory submissions. Additional matrices should be partially validated as necessary. The analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents.

Study Populations

- Clinical
  - Potential for highly diverse populations
    - Ethnicity, age, diet, sex, etc.
- Nonclinical
  - Nonclinical
    - Generally homogeneous populations
      - Purpose bred
      - Consistent diet and age

Should the Homogeneity of Nonclinical Populations be Considered to Reduce the Number of Assessments Needed for “Full” Nonclinical Validations

Population Driven Assessments

- Selectivity
  - Selectivity is evaluated using blank samples (matrix samples processed without addition of an analyte or IS) obtained from *at least 6 individual sources/lots* (non-haemolysed and non-lipaemic)
- Matrix Effects
  - During method validation it is necessary to evaluate the matrix effect between different independent sources/lots. The matrix effect should be evaluated by analysing at least 3 replicates of low and high QCs, each prepared using matrix from at least *6 different sources/lots*.

Recommendation

The number of individual matrix sources required for selectivity and matrix effect assessment should take into account the diversity of the study population. An assessment in a single lot may be satisfactory for a study in a non-diverse nonclinical population

Nonclinical vs Clinical Matrices

- Nonclinical
  - Wide variety of matrices possible
    - Liquid: blood, plasma, urine
    - Tissues: whole organs, biopsies
    - Solid: Feces
  - Clinical
    - Matrix availability more limited
      - Whole organs not available
  - Concerns
    - Is it possible to “fully” validate an assay for a non-liquid matrix?
      - Standards and QCs typically prepared in homogenates
    - Are non-liquid matrices ever considered a “primary” matrix with respect to PK characterization

Recommendation: Restrict “Full” Validation to Primary Liquid Matrices

Primary Matrix(ces)

- Full Validation in Multiple Matrices – Does primary = one?
  - Needs to be considered on a case by case basis
  - Objective of study is a critical point to take into consideration
  - Consider a drug highly excreted unchanged in human urine
    - Data from urine may be complimentary to that of plasma with respect to the interpretation of PK in special populations (e.g. renal impairment) or in the case of drug-drug interactions
      - In such a case, a “fully” validated clinical urine assay to support such studies is likely appropriate
      - Is a fully validated urine assay needed to support FIH for such compounds
        - Likely not, as primary objective of such studies is safety and tolerability - “fit for purpose” assay should be available
  - What about non clinical
    - Urine data available from metabolism profiling generally reduces the need for fully validated urine assays
    - Consider study objectives
      - A study designed to understand renal tox thought to be caused by parent may necessitate full validation for urine
      - Full validation of assays for milk may be appropriate for repro tox studies.
  - Primary matrix may change from study to study and studies may have multiple primary matrices

Conclusions

- Current M10 scope seems overly broad and, with respect to nonclinical applications, somewhat ambiguous
  - Recommend
    - Restrict clinical scope to studies whose primary objectives are PK related and/or label content driving
    - Tying TK application to studies to which GLP applies
    - Clarifying nonclinical PK application to those studies done as surrogate for clinical studies
- Current M10 validation assessment fail to recognize differences with respect to diversity between clinical and nonclinical study population
  - Recommend
    - Considering population diversity when determining number of matrix sources in selectivity and matrix effect assessments
- Current M10 draft potentially places both solid (tissues) and liquid matrices in scope
  - Recommend
    - Restricting to liquid matrices
- Recognition needed that “primary” matrix may change from study to study
  - Multiple “primary” matrices may exist in some studies and across development programs

THANK YOU