Overview of USFDA Drug Regulatory Requirements Pharmaceutical Quality and Facility Inspections (GMP)

Session I

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Quality – One Side of Chemistry, Manufacturing & Controls (CMC)

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Salamandra, LLC

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- Small consulting company based in the US (1996 to date)
- Offers technical & strategic assistance to the pharmaceutical industry
- Clients are US and non-US companies
- Professional staff mostly former FDA scientists (clinical, pharmacology, toxicology, quality, regulatory experts, and submission experts)
  - Mona Zarifa, Ph.D: Head of Quality (CMC) Team (2003 to date; previously 10 years at FDA)
  - More information about Salamandra is on our site, www.salamandra.net. Please visit!

Topics of Discussion

- What is quality?
- What are the attributes evaluated for quality?
- How to ensure quality of a product?
- How to report quality information?
- ICH Guidelines pertaining to quality information

Quality:
One of the Two Sides of CMC

What is Quality?

- ICH Q6A definition of Quality:
  - Suitability of a drug substance (API) or finished drug product (DP) for its intended use

Specific Attributes Evaluated for Quality

- Composition: Active and inactive Ingredients
- Manufacturing and Packaging
- Product Development Studies
- Controls
- Impurities
- Stability

Characterization of the Active Pharmaceutical Ingredient (API)

- Elucidation of chemical structure (elemental and spectroscopic)
- Chemical identification of potential related substances
- Particle size distribution
- Solubility in different pH media
- Compatibility with formulation's inactive ingredients
- Solid state properties (if API for tablets, capsules, semi-solids, suspensions)
- Establish a retest period (stability plan based on ICH Q1A)

Essential Specifications for the API

- Identity: Infra-red (IR) test, or two non-specific tests that are of a different technique; salt identification
  - For an abbreviated new drug application (ANDA), if a USP monograph exists, the "Identity" specification should be exactly the same as USP (including the crystal form). If there is no USP monograph, you can differ in physical forms.
- Impurities/degradants, residual solvents (primarily based on batch results, manufacturing capability) need to comply with ICH limits
  - USP is only a minimum acceptable standard, FDA may be stricter in this regard
- General USP <tests>
  - Specifications established for the relevant USP test parameters (heavy metals, sulfated ash, moisture content, *etc*)

API Properties are Not Essential in Specification Sheet of the API

- Do not add general physicochemical properties – these are addressed in your characterization report

Attributes Evaluated for Drug Product Quality

- Contains suitable API content (assay)
- Contains acceptable amounts of impurities/degradants
- Free of toxic inactive ingredients or contaminants
- Reproducible from batch to batch in terms of all characteristics affecting its intended medical use
- Accurately and clearly described in labeling (on container and package insert)
- At the time of submission, maintains the above standards for
  - 6 months under accelerated conditions (ANDA)
  - 12 months under long-term and 6 months under accelerated conditions (NDA)

Ensuring Quality

- Pharmaceutical development
  - Set acceptance criteria for the API based on regulations (accept from supplier with COA, retest fully or only for identity?)
  - Demonstrate the compatibility between the API and the selected excipients
  - Set acceptance criteria for the excipients within limits approved by FDA in other marketed products of the same dosage form (II Guide Database)
  - Set specifications for the DP based on manufacturing capability and batch conformance history and compliance with the regulations
  - Demonstrate suitability & compatibility of your packaging
  - Have a stability protocol (ICH Q1-type) to implement for demonstrating quality of product throughout the intended shelf life
- Validation
  - Process and analytical methods validation

Ensuring Quality

- Batch-to-batch consistency
  - Ensure consistency between at least 3 representative batches of the API and DP

Alternatively,

  - Demonstrate Quality by Design (Qbd)
    - A chemo-metric approach detailed in ICH Q8
    - Qbd approach is not widely used; it is attempted only by big pharmaceutical firms that can absorb and justify the expenses over a long time span
    - Qbd is out of scope of this talk, but if you are interested, you can consult http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073507.pdf

Reporting Quality Information to the FDA

- *The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: ICH M4Q(R1)*
  - Module 2 – Common Technical Document Summaries
    - Module 2.3 Quality Overall Summary (QOS)
  - Module 3 – Quality
    - Module 3.1 Table of Contents
    - Module 3.2 Body of Data [includes Drug Substance, Drug Product and Regional Information (country-specific information; *e.g.*, executed batch record for US)]
    - Module 3.3 Literature References

Link to ICH MQ4(R1): http://www.gmp-compliance.org/guidemgr/files/MEDIA556.PDF

Reporting Quality Information to the FDA

Marketing Application (Dossier) filed with the Center of Drug Evaluation & Research (CDER)

- ANDA – generic drug intended to be bioequivalent to innovator drug of same medical claim
  - ANDA (21 CFR 314.94): Focus is on demonstrating quality in comparison to innovator's product
  - Follow FDA's ***Question Based QOS Template*** for ensure "acceptance to file"
- Reformulation NDA – intended to differ in medical claim (*e.g.*, in indication, salt form, dosage form, strength, etc):
  - NDA (21 CFR 314.50): Focus is on demonstrating quality of your own product, not necessarily in relation to the innovator's product
  - Follow QOS in Module 2 as in ICH electronic Common Technical Dossier (eCTD)

ANDA *versus* Reformulation NDA

	ANDA	NDA
Food, Drug and Cosmetic (FD &C) Act	**505(j)**	**505(b)(2)**
Intent	"Duplicate" of approved drugs without need for evidence of effectiveness and safety	Approval of applications other than those for duplicate products and permits reliance for such approvals on literature or an Agency finding of safety and/or effectiveness
Examples	Drug products that are the same as a listed drug. "Same as" means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use. *– 21CFR314.92*	Formulation: different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies to a 505(j) application *– Draft Guidance*

ANDA *versus* Reformulation NDA

Caveats addressed in FDA's Guidances – remember:

ANDA

- Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the act and the proposed product must be shown to be bioequivalent to the reference listed drug.

NDA

- Applications for proposed drug products where the rate and/or extent of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug "may require additional clinical studies" and this "should be reflected in the labeling."
- A 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence.

Reporting to FDA *versus* EU

	FDA	EU
Venues to reduce clinical requirements?	Yes FD& C Act Generic (ANDA) 505(j) FD & C Act NDA 505(b)(2)	Yes Generic MAA Hybrid MAA (Article 10, Directive 2001/83/EC
Generic definition	Based on WHO definition: generic medicines are those where the original patent has expired and which may now be introduced by other than the innovator patent-holding company	Same as FDA (WHO definition)
BE requirement for generic drug	Same API, dosage form, indication as for innovator's product, is pharmaceutically equivalent, and has a similar rate and extent of availability after administration in the same molar dose	Same as FDA

Reporting to FDA *versus* EU

	FDA	EU
BE similarity: to what degree?	80 – 125% of the area under the concentration time curve (AUC) or Cmax at a 90% confidence interval (C.I.)	Same as FDA except for drugs with narrow therapeutic indices (NTIDs; see row below)
BE similarity for NTIDs	•No, tighter range than for other drugs. •FDA created a list of 26 NTIDs in 1988; the list is published as part of the Orange Book and these drugs are often flagged in this database as difficult to match for therapeutic equivalence http://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm	•Have tighter similarity range: 90 – 111% •These drugs are assessed differently on a case-by-case basis depending on clinical considerations of their dose- or concentration variability •No NTIDs list exists

Reporting to FDA *versus* EU

	FDA	EU
505(b)(2)/hybrid MAA	•Can use non-proprietary data in support of the application (*e.g.* from published literature) in any part of the 505(b)(2) application	•May not use non-proprietary data •Requires tailored studies on the drug regarding differences from the innovator's product

Post Approval Reporting

- CMC Supplements 21 CFR 314.70 and 21 CFR 314.71
- Annual Report 21 CFR 314.81(b)(2)
- Development Safety Update Report (DSUR; ICH QE2F)
  - Can replace the Annual Report for sponsors with common applications of the same drug in the US and EU countries
  - Field Alert 21 CFR 314.81(b)(1)

Quality and Reporting Responsibilities

- The FDA holds the sponsor of an ANDA or NDA responsible for all quality and reporting requirements
  - Ascertaining CMC source reports from manufacturers and suppliers and making those documents available for submission in ANDA or NDA applications
  - Obtaining all required certifications/statements (*e.g.,* BSE and residual solvents statements, CFR compliance statements for colorants and ingredients generally recognized as safe (GRAS), etc) from manufacturers and suppliers
- Note:
  - A drug master file (DMF) is only reviewed in conjunction with an NDA or ANDA with a letter of authorization (LOA) to the Agency
  - The registered manufacturer's only responsibility to FDA is that of maintaining registration and good manufacturing practice (GMP)

What is the USP?

- The United States Pharmacopeia (USP)
  - Official public standards-setting authority in the US for all prescription and over-the-counter medicines, health care products, and materials that come in contact with food
    - Non-governmental, not-for-profit

The Role of USP in FDA Quality Regulations

- Establishes standards for inactive ingredients for drugs and food
- Develops and publishes reference standards enforceable by the FDA
- Contains general chapters for testing procedures enforceable by the FDA
- Contains monographs for APIs and FDA approved drug products
  - Existing API monograph is to be followed exactly in case of ANDA
  - For API in NDA and for all drug products, USP monographs are only minimum requirements for approval (FDA can ask for more)
- Contains harmonized testing procedures
- FDA may accept other non-US Pharmacopeial standards if proven equivalent

ICH Quality Guidelines Adopted by the FDA

- Q1A (new dosage forms): Stability Testing
- Q1B: Photostability Testing
- Q1D: Bracketing and Matrixing Designs
- Q1E: Evaluation of Stability Data
- Q2A, Q2B: Validation of Analytical Procedures
- Q3A: Impurities – In New Drug Substances
- Q3B: Impurities – In New Drug Products
- Q3C: Impurities – Residual Solvents
- Q4B: Harmonization of Selected Compendial Methods
- Q6A: Specifications: Small Molecules – Drug Substances & products
- Q7A: GMP for API
- Q8, Q9, Q10: Pharmaceutical Development & Quality Systems

Scope of ICH Quality Guidelines

- Suggested guidance to industry, not regulations
- Q3A, Q3B, Q6A: Not applicable to herbal drugs, biologicals, peptides, oligonucleotides
    - For example, herbal products should be free of contaminants and adulteration and synthetic impurities are not relevant in this case
- Q3A, Q3B, Q6A: API and Drug Product in reformulations meet these recommendations by default
    - These substances and products cannot exceed innovator limits without additional toxicological or clinical studies supporting limits above what exists for the approved drug
- Specifications (Q6A) and Impurity limits (Q3A, Q3B) are meant to confirm the quality of the drug to ensure safety and efficacy, and not replace full characterization during development (covered by Q8, Q9 and Q10)

Impact of Quality on Other Disciplines

- Toxicology
  - Presence of impurities/degradants to be confirmed to support toxicological qualification
  - Inactive ingredient compositions/allowable levels to be verified in in order to support toxicological qualification
- Biopharmaceutical
  - *In vitro* dissolution profiles support or replace *in vivo* bioequivalence determinations for oral dosage forms

Impact of Quality on Other Disciplines

- Clinical
  - Clinical findings are of no relevance if no one knows what caused them – hence the importance of identity, assay, and the rest of the specifications
  - Physicochemical properties like pH solubility, PK_a, Partition Coefficient (Octanol/Water) are important indicators for *in vivo* behavior of drug
  - Dose content uniformity impacts variability of response
  - Container closure delivery mechanisms (ointment tubes, spray pumps, etc.) determine dose to be administered and impact the accuracy of dosing

Impact of Quality on Reformulation Approval

- Quality information required on the drug label (package insert and container label) for approval:
  - Accurate description and composition of the drug
  - Accurate presentation of the drug product
  - Storage conditions of the drug product
  - Shelf life
- Reformulations will not be granted approval unless they meet the same quality standards of the approved innovator drug

Quality – C’est Fait!

Merci à Tous!