

ANDA PROCESS

Generic Drug - ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence

MANUFACTURING, CONTROLS (CMC)

Objective is to characterize Drug Substance (DS) and Drug Product (DP) to establish and control important quality, safety, and efficacy of the product:

- Components and composition
- API, Excipients controls
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Specifications and tests
- Packaging
- Stability

COMPONENT AND COMPOSITION

- ❑ Describe function, and qualitative and quantitative formulation of DP
- ❑ List all components regardless of whether or not they appear in the finished product (gases, solvents, water, ink etc). If they do not appear in the finished product, make a footnote “removed during processing)
- ❑ Reference to quality standards (USP/NF)
- ❑ Amount: per unit, and production batch

DRUG SUBSTANCE

- ❑ CMC information about drug substances can be incorporated in the ANDA or make reference to Drug Master File (DMF) of the manufacturer of DS
- ❑ A letter of authorization from the DS manufacture should be included in the ANDA
- ❑ They are reviewed for adequacy by FDA. DMF's are not approved

DRUG SUBSTANCE

Provide:

- ❑ DS Manufacturer's Certificate of Analysis (COA)
- ❑ Organic Volatile Impurities (OVI) statement
- ❑ Applicants specifications and test results (COA)
- ❑ Information on reference standard/s (RS)
 - ❑ Primary RS, Secondary RS
 - ❑ Source
 - ❑ Qualification
- ❑ Retest schedule

SPECIFICATIONS

- A Specification is defined as a list of test, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described (ICH Q6A)
- Specifications are part of strategy to ensure product quality and consistency
 - Universal tests (description, ID, Assay, impurities)
 - Specific tests (pH, particle size, polymorphic forms, chirality etc)

EXCIPIENTS

- Provide specification and test results for all excipients
 - Compendial: Test per monograph (USP/NF)
 - Non compendial: DMF and supporting data
- Human or animal origin: source, origin
- DS and excipients compatibility data by stability

MANUFACTURING AND CONTROLS

- ❑ Name & address of manufacturing, testing facility/ies (to facilitate pre-approval inspections)
- ❑ Detailed description of manufacturing process
- ❑ Flow diagram (from weighting to FP release; identify critical steps)
- ❑ Blank batch (Master Manufacturing Card) and packaging record for production batch

MANUFACTURING AND CONTROLS

- ❑ Executed batch records for submission or Biobatch
- ❑ Process controls (operational parameters, tests etc carried out for assurance for reproducibility of FP. The acceptance criteria may be numerical ranges or limits)
- ❑ Reprocessing (approved process) and Reworking (process not described in the application)

DRUG PRODUCT CONTROL

- ❑ Specifications
- ❑ CGMP
- ❑ COA (Batch #, strength, size, date of manufacture, site of manufacture, etc)
- ❑ Justification for the proposed specifications

ANALYTICAL PROCEDURES

- Analytical Procedures should be described in the submission
- Analytical Procedures should be validated. Validation of Analytical Procedures is described in USP, ICH Q2A and CDER Guidance and should demonstrate that the method is suitable for the intended use

CONTAINER CLOSURE

- Description
- Primary packaging
 - Material of construction of each packaging component
 - Specifications, COAs, DMF authorization letter
- Functional secondary packaging
- Same information as above
- Non functional secondary packaging
 - Brief description

DRUG PRODUCT STABILITY

- Stability Protocol, Specifications, and Commitment
- Stability data:
 - Accelerated – 1, 2, 3 months at 40°C, 75% RH
 - Long-Term – 3, 6, 9, 12, 18, 24 months at 25°C, 60% RH
- Stress studies or stability indicating method.
- Tentative 24 Months expiration is granted, if no significant degradation under accelerated storage.

DRUG PRODUCT STABILITY (Cont.)

□ Commitments:

- Place at least one batch annually on stability at shelf-life storage conditions (25°C/60% RH)
- Report data to FDA in the Annual Report
- May have to withdraw batches market that fail stability studies
- Expiration Date may be extended with additional CRT stability data for 3 commercial batches by an annual report

BIOEQUIVALENCE IS KEY

Bioavailability studies assess the rate and extent of absorption and levels of concentration of a drug in the blood stream needed to produce a therapeutic effect.

Bioequivalence studies compare the bioavailability of one drug product with another, in this case the innovator's product. When bioequivalence is established, it indicates that the rate of absorption and the levels of concentration of a generic product are substantially equivalent to the branded product.

BIOEQUIVALENCE IS KEY (CONT.)

If the performance of the chemical entity in the immediate release drug product is highly variable in the human body, then it suggested to conduct a PILOT BE study with 6 to 12 healthy volunteers, before spending the money for expensive PIVOAL studies. A PILOT study can cost minimum \$50K.

If the Drug is indicated to be taken with FOOD (MEALS) as per the label, then a FED (FOOD) study will also be required in addition to the FASTING BE Study for the product. Otherwise only a FASTING BE study will be required.

BIOEQUIVALENCE IS KEY (CONT.)

On the average for a drug that does not have much subject to subject variability in the GI absorption then a 24 Subject FASTING study would cost about \$ 200K. And if FED study is required, then an 18 subject study would cost about \$ 150K.

If the Drug is highly variable in absorption in the body, then FSASTING study can cost anywhere from \$ 250K to 500K and FED study from \$ 200K to 500K.

Now there are many CROs in India that can conduct good studies and can do them at as low as 40% of the cost on the CROs in USA.