DECISION TREE #1: ESTABLISHING ACCEPTANCE CRITERION FOR A SPECIFIED IMPURITY IN A NEW DRUG SUBSTANCE

Determine impurity level in relevant batches¹

Determine mean + upper confidence limit for the impurity (Let this = A)

Is impurity also a degradation product?

YES

Estimate maximum increase in impurity at retest date using data from relevant accelerated and long-term stability studies

NO

Is A or B greater than the qualified level?

NO

Acceptance criterion = A or B (as appropriate)

YES

Determine maximum likely level as: A + increase in degradation product at appropriate storage conditions. (Let this = B)

Acceptance criterion = qualified level or establish new qualified level²

¹ Relevant batches are those from development, pilot and scale-up studies.

² Refer to ICH Guideline on Impurities in New Drug Substances

Definition: upper confidence limit = three times the standard deviation of batch analysis data
Does degradation occur during product manufacture?

Estimate maximum increase in degradation product at shelf life using data from relevant accelerated and long-term stability studies. (Let this = D)

Determine maximum likely level as drug substance acceptance criterion. ((A or B) + C + D)

Is maximum likely level greater than the qualified level?

Acceptance criterion = maximum likely level. NO

NO

Acceptance criterion = qualified level or establish new qualified level or new storage conditions or reduce shelf life. YES

1 Relevant batches are those from development, pilot and scale-up studies.
2 Refer to Decision Tree 1 for information regarding A and B.
3 Refer to ICH Guideline on Impurities in New Drug Products.
DECISION TREE #3: SETTING ACCEPTANCE CRITERIA FOR DRUG SUBSTANCE PARTICLE SIZE DISTRIBUTION

Is the drug product a solid dosage form or liquid containing undissolved drug substance?

- **NO**
  - No drug substance particle size acceptance criterion required for solution dosage forms.

- **YES**
  1. Is the particle size critical to dissolution, solubility, or bioavailability?
  2. Is the particle size critical to drug product processability?
  3. Is the particle size critical to drug product stability?
  4. Is the particle size critical to drug product content uniformity?
  5. Is particle size critical for maintaining product appearance?

- **If NO to all**
  - No Acceptance Criterion Required

- **If YES to any**
  - Set Acceptance Criterion
DECISION TREE #4: INVESTIGATING THE NEED TO SET ACCEPTANCE CRITERIA FOR POLYMORPHISM IN DRUG SUBSTANCES AND DRUG PRODUCTS

Drug Substance

   Can different polymorphs be formed?  
     NO → No further action
     YES → Characterize the forms: e.g., - X-ray Powder Diffraction - DSC / Thermoanalysis - Microscopy - Spectroscopy

2. Do the forms have different properties? (solubility, stability, melting point)
   NO → No further test or acceptance criterion for drug substance
   YES → Is drug product safety, performance or efficacy affected?
     NO → No further test or acceptance criterion for drug substance
     YES → Set acceptance criterion for polymorph content in drug substance

GO TO 2.  GO TO 3.
Drug Product - Solid Dosage Form or Liquid Containing Undissolved Drug Substance

N.B.: Undertake the following processes only if technically possible to measure polymorph content in the drug product.

3. 

- **Does drug product performance testing provide adequate control if polymorph ratio changes (e.g., dissolution)?**
  - **YES**: Establish acceptance criteria for the relevant performance test(s).
  - **NO**: Monitor polymorph form during stability of drug product.

- **Does a change occur which could affect safety or efficacy?**
  - **NO**: No need to set acceptance criteria for polymorph change in drug product.
  - **YES**: Establish acceptance criteria which are consistent with safety and/or efficacy.
Consider the need for verifying chiral identity in drug substance release and/or acceptance testing.

Is the new drug substance chiral? YES AND RACEMIC

Chiral identity, assay and impurity procedures are not needed.

NO

YES AND ONE ENANTIOMER

Needed for drug substance specification:  
- chiral identity
- chiral assay
- enantiomeric impurity

Needed for drug product specification:  
- chiral assay
- enantiomeric impurity

1 Chiral substances of natural origin are not addressed in this Guideline.

2 As with other impurities arising in and from raw materials used in drug substance synthesis, control of chiral quality could be established alternatively by applying limits to appropriate starting materials or intermediates when justified from developmental studies. This essentially will be the case when there are multiple chiral centers (e.g., three or more), or when control at a step prior to production of the final drug substance is desirable.

3 A chiral assay or an enantiomeric impurity procedure may be acceptable in lieu of a chiral identity procedure.

4 An achiral assay combined with a method for controlling the opposite enantiomer is acceptable in lieu of a chiral assay.

5 The level of the opposite enantiomer of the drug substance may be derived from chiral assay data or from a separate procedure.

6 Stereospecific testing of drug product may not be necessary if racemization has been demonstrated to be insignificant during drug product manufacture and during storage of the finished dosage form.
DECISION TREE #6: MICROBIOLOGICAL QUALITY ATTRIBUTES OF DRUG SUBSTANCE AND EXCIPIENTS

Is the drug substance/excipient capable of supporting microbial growth or viability?

YES

Is the drug substance/excipient sterile?

YES

No further microbial limits testing or acceptance criteria are necessary.

NO

Does drug substance/excipient synthesis/processing involve steps which inherently reduce microorganisms?

YES

Establish microbial limit acceptance criteria as per the harmonized pharmacopoeial monograph.

NO

Are monitoring microorganism/indicator levels consistently below acceptance criteria levels?

YES

Test lots on a skip-lot basis for microbial limits and freedom from compendial indicator organisms.

NO

Test each lot for microbial limits and freedom from compendial indicator organisms.

Does scientific evidence demonstrate that reduction steps result in microorganism levels < acceptance criteria limits (and the absence of compendial indicator organisms) in the drug substance/excipient?

YES

Provide supporting data. Microbial limits acceptance criteria and testing may not be necessary.

NO

Establish microbial limit acceptance criteria as per the harmonized pharmacopoeial monograph.

Provide supporting data. Microbial limits acceptance criteria and testing may not be necessary.
1. What type of drug release acceptance criteria are appropriate?

- Is the dosage form designed to produce modified release?
  - YES
    - Establish drug release acceptance criteria.
      - Extended release: multiple time points
      - Delayed release: two stages, parallel or sequential
  - NO

- Is drug solubility at 37 ± 0.5°C high throughout the physiological pH range? (Dose/solubility ≤ 250 mL (pH 1.2 - 6.8))
  - NO
  - YES
    - Is dosage form dissolution rapid? (Dissolution > 80% in 15 minutes at pH 1.2, 4.0, and 6.8)
      - NO
      - YES
        - Has a relationship been determined between disintegration and dissolution?
          - NO
            - Generally single-point dissolution acceptance criteria with a lower limit are acceptable.
          - YES
            - Generally disintegration acceptance criteria with an upper time limit are acceptable.
      - NO
        - Continued on next page.
2. What specific test conditions and acceptance criteria are appropriate? [immediate release]

- **Does dissolution significantly affect bioavailability?**
  - **YES**
    - Attempt to develop test conditions and acceptance criteria which can distinguish batches with unacceptable bioavailability.
  - **NO**

- **Do changes in formulation or manufacturing variables affect dissolution?**
  - **YES**
    - Are these changes controlled by another procedure and acceptance criterion?
      - **YES**
        - Adopt test conditions and acceptance criteria which can distinguish these changes. Generally, single point acceptance criteria are acceptable.
      - **NO**
        - Adopt appropriate test conditions and acceptance criteria without regard to discriminating power, to pass clinically acceptable batches.
  - **NO**

(e.g., have relevant developmental batches exhibited unacceptable bioavailability?)

(Use appropriate ranges. Evaluate dissolution within pH 1.2 - 6.8)
3. What are appropriate acceptance ranges? [extended release]

- Are bioavailability data available for batches with different drug release rates?
  - NO
  - Is drug release independent of in vitro test conditions?
    - YES
    - Can an in vitro / in vivo relationship be established?
      - NO
      - Use all available stability, clinical, and bioavailability data to establish appropriate acceptance ranges.
      - YES
    - (Modify in vitro test conditions if appropriate.)
    - YES
    - Use the in vitro / in vivo correlation, along with appropriate batch data, to establish acceptance ranges.
  - YES
- Are acceptance ranges >20% of the labeled content?
  - YES
  - Provide appropriate bioavailability data to validate the acceptance ranges.
  - NO
  - Finalize acceptance ranges.
Is the drug product a dry dosage form (e.g. solid oral or dry powder)?

- NO

  - Does production lots consistently meet microbial limits acceptance criteria?
    - NO
      - Establish microbial limit acceptance criteria as per the harmonized pharmacopoeial monograph.
    - YES
      - Do production lots consistently meet microbial limits acceptance criteria?
        - NO
          - Perform microbial limits testing on a lot-by-lot basis.
        - YES
          - Perform skip-lot testing for microbial limits, or provide scientific justification for no routine microbial limits testing.

- YES
  - Establish preservative chemical acceptance criteria and perform preservative effectiveness validation of product containing less than or equal to the minimum specified preservative concentration, or demonstrate the inherent antimicrobial activity of the drug product.

Does the drug product contain antimicrobial preservatives or possess inherent antimicrobial activity?

- YES

  - Does the drug product contain antimicrobial preservatives or possess inherent antimicrobial activity?
    - NO
      - Does scientific evidence demonstrate growth inhibitory properties of the drug product?
        - NO
          - Establish microbial limit acceptance criteria as per the harmonized pharmacopoeial monograph.
        - YES
          - Microbial limits acceptance criteria and testing may not be necessary.
    - YES
      - Establish preservative chemical acceptance criteria and perform preservative effectiveness validation of product containing less than or equal to the minimum specified preservative concentration, or demonstrate the inherent antimicrobial activity of the drug product.