
EFFECTIVE HANDLING OF REGULATORY QUERIES



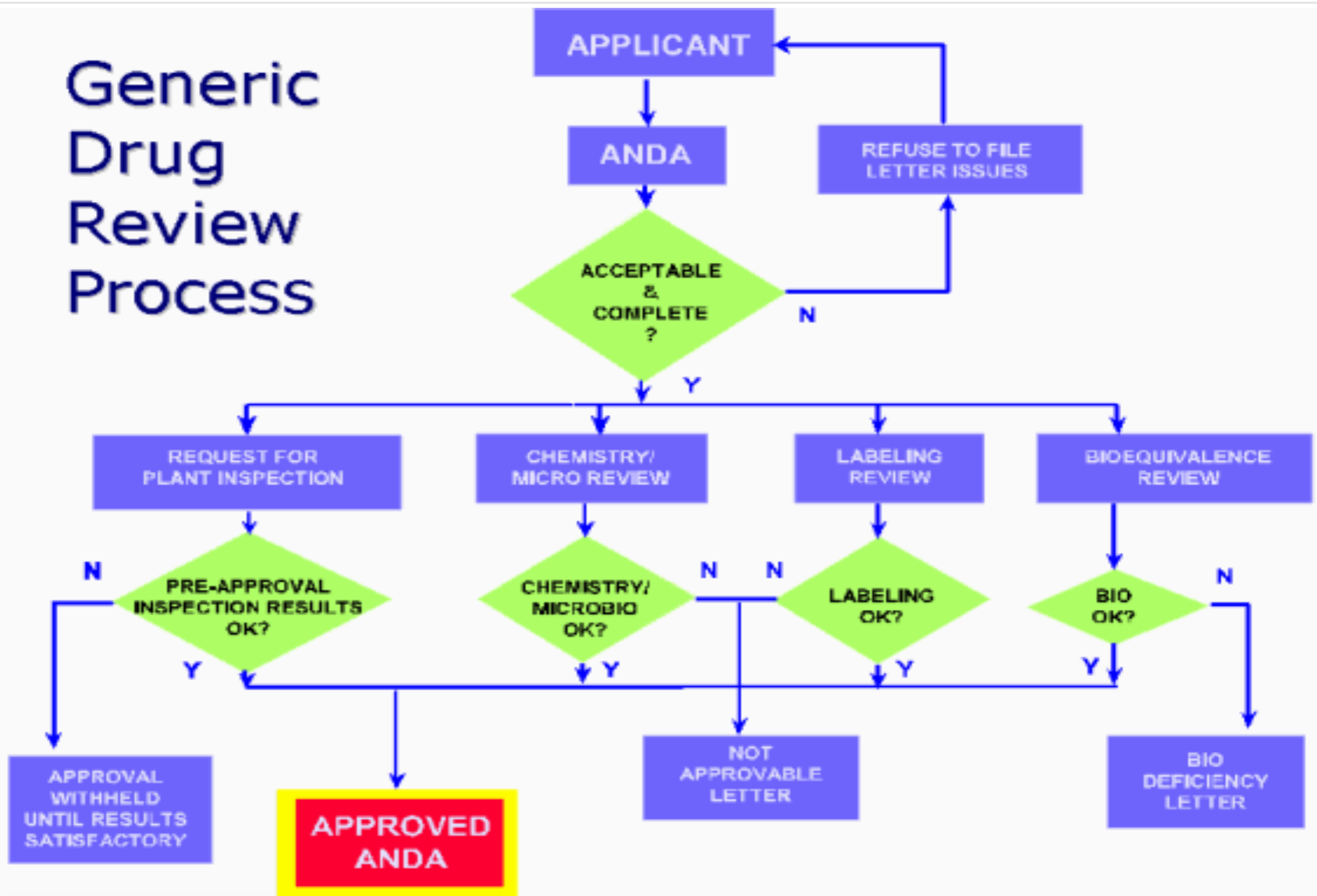
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SCOPE OF THIS PRESENTATION

- ❑ Deficiencies related to CMC review
- ❑ Drug Substance (DS) Filing (DMF)
- ❑ Drug Product (DP) Filing (ANDA/Dossiers)
- ❑ Learning through case studies
- ❑ Review Process of both DMF and ANDA
- ❑ Risk Based Review
- ❑ Common Gaps
- ❑ Risk Mitigation Measures (SMART Filing)

Generic Drug Review Process



Center for Drug Evaluation & Research
U.S. Food & Drug Administration

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NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

Generic Drug ANDA Requirements

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

EXPLAIN THE DISTORTED MASS BALANCE?

- During the review of 24 M CRT stability data of ABC Tablets, it was found that mass balance is getting offset gradually going up to 104.8% though Assay results obtained by specific HPLC method were consistent.
- Authorities asked explanation for the distorted mass balance [...\My Documents\CRT Stability Data.doc](#)

RESOLUTION OF DISTORTED MASS BALANCE?

- Response factor for Impurity A was found to be 21 times higher as compared to the active substance. In absence of response factor impurity which was actually low was calculated very high e.g. 0.01% impurity was calculated as 0.21%. This has offset the mass balance.

EXPLAIN INCREASING PLACEBO IMPURITY?

- The ACC stability data that was presented showed increasing level of impurity A (0.78% at 6 Months) which was disregarded as it comes from placebo. Initial sample too showed impurity A but it was much less (0.06%). CRT sample showed consistent results. Authority said that it can't be just disregarded and asked for the explanation?



RESOLUTION OF INCREASING PLACEBO IMPURITY?

- ❑ Degradation study was carried out for placebo.
- ❑ Placebo was found to degrade over a period of time at ACC condition.



QUALIFY LIMITS OF EPICHLOROHYDRINE, ISOPROPOXY ETHANOL AND ISOPROPYLAMINE IN YOUR DS ?

RESOLUTION

- As per the ICH Q3C, the PDE (Permitted Daily Exposure) has been calculated for the above solvents using the LD50 value of solvents from literature (MSDS). From the PDE value the limit for solvent has been calculated as per ICH Q3C (M).
- The detailed formula and calculation were attached
- Solvent Limits in PPM as per Inhouse specification and Permitted limit based on PDE were as follows.
Epichlorohydrine: 2/750,
2-Isopropoxyethanol: 100/6667
Isopropylamine: 100/925

EXPLAIN USE OF ACETONE WHICH CAN INTRODUCE MESITYL OXIDE, POTENTIAL GENOTOXIC IMPURITY IN DS?

RESOLUTION

- ❑ Issue was taken up with the manufacturer
- ❑ GC method was developed to detect Mesityl Oxide in traces (1PPM)
- ❑ 3 consequent lots were tested and found to comply. Data was submitted.



JUSTIFY BORON LIMIT IN YOUR DS?

Justification:

- The Acute oral toxicity data (LD50) is 560 mg/kg for Mouse and 650 mg/kg for Rat as per MSDS.
- Boron contamination in water is upto 600 micrograms/liter. If you assume a daily intake of 5 liters of water/day this equates to 3.0 mg Boron. The maximum daily dose of our DS is 10 mg. As per inhouse limit of Max 0.015%, this equates to max 0.0015 mg of Boron/day, which is well below the acceptable limit of 10 – 25 mg discussed in the published article.

JUSTIFY MICROBIAL LIMIT/SWAB ?

□ This was regarding Microbial contamination studies done for equipment surfaces during Cleaning Validation

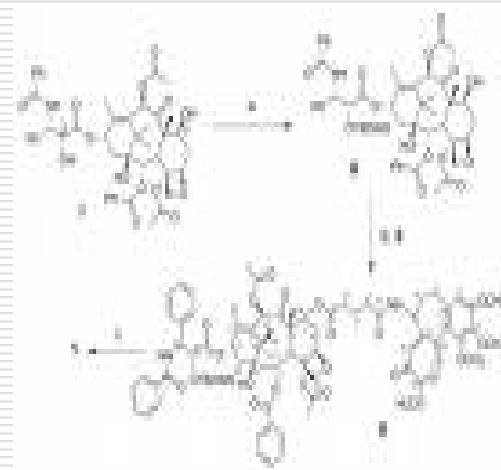
□ Resolution

Limit specified was NMT 40 CFU per swab of 4 Sq. Inch. Amount of adhered purified water on the surface was determined, found to be 0.4 ml.

Considering max permitted 100 CFU per ml of purified water, limit of 40CFU/Swab was justified.

CHEMISTRY

- ❑ Components and composition
- ❑ Manufacturing and controls
- ❑ Batch formulation and records
- ❑ Description of facilities
- ❑ Specs and tests
- ❑ Packaging
- ❑ Stability



CMC REVIEW

- ❑ Qualitative and quantitative listing of all active and inactive ingredients; including grade of each component
- ❑ Process for manufacturing
- ❑ Controls (Inspections, sample points, test, methods, specification, COA, acceptance criteria) in place from the receipt of the raw material to the labeling and storage of the finished product

CMC REVIEW Contd.

- ❑ Synthesis of the active pharmaceutical ingredient's (API) or authorization to refer a Drug Master File (DMF)
- ❑ Impurity profile of the API
- ❑ Stability of the API
- ❑ Characterization of degradation products with drug substance and drug product
- ❑ Microbiological testing when appropriate (Reviewed by Microbiologists)
- ❑ Batch formulation and batch records

CMC REVIEW Contd.

- Description of manufacturing facilities
- Stability profile
- Container and closure system
- Method validation information
- Environmental Assessment
- Stability Indicating Methods
- Justification of proposed limits

QUESTION BASED REVIEWS

- ❑ QbR utilizes CTD module 2 Quality Overall Summary for addressing pertinent issues
- ❑ Submissions are encouraged in CTD format
- ❑ QbR based QOS also serves as template for CMC review
- ❑ Outline structured as series of questions
- ❑ Questions have area/topic focus
- ❑ Approximately 150 applications from Jan 2006 to Apr 2007
- ❑ Helps the reviewer in explicit identification of critical parameters

COMMON GAPS ?

- ❑ Reporting/Identification/Quantitation threshold not as per ICH
- ❑ BSE (Bovine Spongiform Encephalopathy)
- ❑ Stability Indicating Methods
- ❑ LOD/LOQ for Impurities/Degradants
- ❑ Justification of proposed limits for impurities?
- ❑ Justification of expiry date, retest period?
- ❑ Non-consideration for Genotoxic impurities
- ❑ Inadequate Polymorphism study

COMMON GAPS Contd.

- ❑ Inadequate studies w.r.t. Melting point of DS which undergoes degradation at Melting Point
- ❑ Inadequate characterization of impurities
- ❑ No determination of trace level of Penicillin's /Cephalosporin's in environment and in general products (non Beta Lactum products) where the potential exists.

RISK BASED APPROACH

- ❑ Based on periodic reviews of deficiencies received, identify the weak areas
- ❑ Do the Gap analysis against the applicable regulatory requirements and prepare a risk mitigation plan
- ❑ Develop a check list for each type of country specific submission
- ❑ Inadequate review of documents is a major risk which has to be attended on priority

RISK MITIGATION MEASURES

- ❑ Both eCTD and paper submissions should have electronic QOS
- ❑ Provide QOS both as PDF and Word file, readable by Word 2003
- ❑ Never delete a QbR question if N/A
- ❑ All amendments to an application under review should use the same format as that of original submission
- ❑ Provide actual values of solubility rather than descriptive phrases like 'slightly soluble'.

RISK MITIGATION MEASURES Contd.

- ❑ Provide pH solubility profile for the polymorphic form present in the drug and relative solubility (at one pH) for other more stable forms
- ❑ When the drug substance contains one or more chiral centres, indicate whether it is a racemate or a specific enantiomer
- ❑ Discussion of chirality should include the potential for interconversion between enantiomers (racemization/epimerization)
- ❑ Classify each impurity as process impurity and/or degradant

RISK MITIGATION MEASURES

Contd.

- ❑ Verify USP Assay/RS methods for specificity and submit the proof
- ❑ Check the compliance of the analytical method for reporting/Identification /Quantification Threshold which is generally 0.05/0.10 & 0.15 % respectively for MDD of less than or equal to 2 gram.



REFERENCES

- ❑ ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
- ❑ FDA Guidance for Industry, M4Q: The CTD-Quality
- ❑ ICH Q3C, Guidance on Residual solvents
- ❑ ICHQ1A (R2) Stability testing of new drug substances and drug products
- ❑ FDA, CDER, Question-Based Review for CMC Evaluations of ANDAs
- ❑ ICH Q9, Quality Risk Management



*Thanks a
Million!*