Acta Scientific Pharmaceutical Sciences

Volume 2 Issue 4 April 2018

Mini Review

Impurity Profile Validations of API- Challenges for GMP Inspection-Part 1

BK Chakravarthy*

Capic Laboratories Private Limited, Hyderabad, India

***Corresponding Author:** BK Chakravarthy, Capic Laboratories Private Limited, Hyderabad, India.

Received: February 22, 2018; **Published**: March 22, 2018

Abstract

Impurity profile validations test the competence of GMP auditors as impurities are added up at various stages of new routs of synthesis of API manufactured in different manufacturing units (done when different from the original R&D routes and conditions). Hence there is a need for more focused audits and key role to be played by GMP auditors in the validations of impurity profiles. GMP auditors should examine critically for batch to batch aberrations and their views not only can provide substantial inputs for the audited company's research team for critical evaluations but also prevent many potential and time tested API being sidelined due to newly attributed clinical toxicity reported for API's manufactured by synthetic routes other than original research done at the stages of commercial launch of API's. There are no reports available for such new research findings if any newly added impurities due to changes made in synthesis route to reduce cost or process time and perhaps some new impurity may be responsible for freshly found toxicity/side effects rather the main API itself.

Keywords: Active Pharmaceutical Ingredients (API); Critical Process Parameters (CPP); Critical Process Variables (CPV); Good Manufacturing Practices (GMP); Micro, Small, Medium Enterprises (M S M E)

Introduction

Impurity profile of API and its validation always challenge for the GMP auditors. Many a times the decisions taken by GMP evaluators are not the true reflections of the prevailing conditions of the audited company, due to possibility of multiple sources for impurities as contaminants which may or may not have direct impact on the toxicity attributed to API. Specification of impurities in the API, residual solvents, validation of analytical procedures of impurity profile does not provide reasonable assurance for the accuracy and precision, not only the product quality but also the process and systems of the organizations' ability to reproduce. It is known fact that most of the API's are manufactured by contract manufacturing agents (MSME) subleased by parent company which has original R&D technology of API's. Focus on impurity source validations by GMP auditors and issues raise with respect to some impurity validations process steps of API are discussed here.

While preparing validation of a process for a new route of synthesis of API, care to be taken that the impurity profile should be comparable to or better than the profile determined during original process development of API. Each and every step in the process parameters that could affect the critical quality attributes of the API (CPP, CPV) should be determined by scientific judgment and be based on knowledge derived from research, scale-up batches, or manufacturing experiences. Sometimes the inspectors reject the product based on the facts that the approved protocol failed to establish inter-laboratory acceptance criteria for impurities in the drug product; the approved method for executing the above protocol failed to establish a single integration parameter for analyzing the concentration of oligomictic peaks for the entire sequence. The firm re-integrated the sequence using different integration parameters for these peaks. This resulted in independent selection of desired peak width. Many potential toxins as impurities are not directly analyzed.

The GMP auditors' dilemma all the way increases when the site visited is biotech product manufacturing area like insulin production area (the cause for immune response isn't the insulin itself, but often impurities in the insulin) or contract manufacturing of API/formulations unit. Growth of medical devises and implants all over the world added additional areas challenges like metallic and polymer components and their cross contaminants assembled in different locations widens auditors scope more complicated and can be discussed separately. Several factors like process, environmental influences, Technology transfers, communication gaps between R&D/FP&D/plant personals, usage of high reactive toxins like cyanides/PCA etc. in the chemical process influence the impurity profiles of the product and some of the related key issues of impurity validations of API are discussed. If manufacturers of API do have sufficient protocols and documentary proofs for impurity validations also at different stages, the GMP auditor can fairly be assured for the quality of API being maintained for different batches manufactured.

Preparing for GMP Inspection: Preparations for GMP inspection normally give more stress and burden to the executives of the plant to be inspected and the key focus will be on how to prove that entire unit is working with systems for maintaining the purity API/Formulation/or related biotech molecules or devises. However, the most of GMP auditors look not only for reproducible systems to maintain batch consistency with allowed purity parameters but also for possible lapses for impurities to develop or dominate the overall impurity profile (within pharmacopeia/in house standards allowed percentage) and batch to batch variability.

Our experiences advocate some critical points need to be addressed by inspectors to review closely the records as how many times the process was modified to suite techno-commercial benefits of the products and as how technology development at R&D and P&D labs of the company done and how the modified technology been transferred, and any critical analysis done to verify total impurity profile with each process modification.

Various important points for preparations of GMP inspection are discussed earlier by Pharmaceutical Inspection convention for API [1]. The adoption of ICH Q7 as the first truly harmonised GMP guideline for active pharmaceutical ingredients (APIs) and the associated development of regulatory frameworks to implement the guideline as a regulatory standard mark the beginning of a new

era of regulation for medicines. The adoption of ICH Q7 by PIC/S occurred in May 2001 with the current version of the guideline having been available since 1 September 2007 as GMP PE 009 (Part II) [1]. The primary objective for implementing ICH Q7 is the reduction of the risks associated with the manufacturing quality of APIs and this cannot be achieved without an effective inspection system which addresses the specific aspects of the global API industry

It is recognized that the expertise and experiences of GMP auditors/inspectors are not similar and not necessarily suite to all API industries audits. It is attempted here to provide some critical points to be taken for consideration for those who have new/little experience in API industry GMP audits.

Various points needed for GMP validations are discussed in detail [2] which provide critical points to maintain/validate purity profiles of API/biotech molecules. GMP validation is an element of quality assurance program for a pharmaceutical/biotech product or process. To ensure that the products are absolutely fit for intended use, the company has to demonstrate in a documented form that the processes, methods, tests, activities and equipments they deploy are capable of repeatedly producing the desired product. Therefore, each critical step in the manufacturing process must be verified to perform as intended under defined conditions.

ICH limits for impurities for formulations is

Maximum daily dose[a]	Reporting Threshold[b,c]	Identification Threshold[c]	Qualification Threshold[c]
≤ 1 g	0.05%	0.10% or 1.0 mg per day intake	0.15% or 1.0 mg per day (whichever is lower) intake (whichever is lower)
> 2g	0 .03%	0.05%	0.05%

Table 1: Thresholds for impurities in New Drug substances [2]. a: The dosage of drug administered per day. b: Higher reporting thresholds should be scientifically validated. c: Lower thresholds may be appropriate if the impurity is unusually toxic.

Types of Validation

Validation procedures need to cover all the aspects related to facilities, procedures, processes and activities are to be documented. The validation process has been categorized into following parts:

Prospective Validation: To be conducted before the new drugs are released into market or when the existing drugs are manufactured using a revised process and protocol. The authorities ensure prior to drug distribution that the characteristics of interest are functional and comply with the safety standards.

Retrospective Validation: Done by Regulators to get assurance from time to time that the drugs already being produced and distributed are of highly quality. Documents related to historical data, batch records, recorded evidences, log books, control charts, customer complaints and audit reports to perform validation are reviewed by GMP auditors and it is conducted for products or processes already in use.

Concurrent Validation: The validation is conducted during the normal process of manufacturing or services. The inspectors review sample analysis for a chemical assay to trace the impurities if any.

GMP Validation: An Important and key tool towards consistent and safer API /Medicines

1. **Process Validation:** FDA has mentioned the requirements for process validation in Section 820.75 of the Quality System Regulation (QSR). Reproducibility of the process is inspected to obtain documented assurance that the manufacturing process successfully meets the pre-defined acceptance criteria. The activities in process validation that focus on machines, systems and equipments are called "qualifications". They include: design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

2. **Cleaning Validation:** FDA auditors conduct GMP validation for cleaning to ensure that no cross-contamination occurs between different batches. For example one batch 'X' has been just finished with manufacturing tablets for fever and soon a batch of dysentery tablets using those same equipments are initiated. What if the residues of first batch couldn't be cleaned properly and got mixed with the ingredients of the next batch? Cleaning validation documents provide assurances for such cross contaminations possibilities.

3. **Method Validation:** Ensuring the precision, accuracy and consistency of analytical tests in very important. A test method must be verified to be acceptable for intended use before it is applied to test the analytical samples. The methods have to be reliable as per the pre-established results under the defined conditions based on the original R&D requirements of API developed.

4. **Computer System Validation:** FDA issued a guide especially for the inspection of computer systems in pharmaceutical industries. The guide was first published in 1983 and is commonly called 'bluebook'. Annex 11 was added to EU GMP regulations (EMEA) for the purpose of computer system validation which provide ample scope for the auditors as well the companies to validate all computed materials related to pharmaceutical manufacturing,, tissue culture establishments and clinical trials.

Life Cycle of GMP Validation

1. Validation of master plan 2. Validation protocol 3. Execution of validation 4. Validation reports 5. Preparation of SOPs

These five steps specified to be are the key to preparation, documentation and implementation of GMP validation for regulatory audits.

However, in-spite of many protocols and SOP's for validations of purity profiles of API often the GMP auditors either give more importance to documentations on verifying consistency in preparing pharmacopeia/in-house standards with respect to purity of API and giving lesser importance of impurity profile if found within accepted % limits of impurities, not giving importance to

chemical nature of impurities either developed due to batch variability in production or due to process modifications done by R&D developments.

It is a known fact that any newer API once has a commercial success will undergo rapid innovative research all over the globe in order to reduce manufacturing cost as well production time and in the process attaining accepted purity limit given importance than maintaining impurity profile.

Thus, sometimes newer impurities develop(may be some of them are highly toxic even at very low doses) and may overshadow the clinical toxic limits of main API analysed with original R&D API molecule synthesized or biotech molecule developed by cell culture techniques.

The intelligence of GMP auditors play a key role in validating consistency of batch to batch variability of manufactured API with respect to purity while maintaining impurity profile same or nearer to original R&D batches which have been thoroughly validated for clinical efficacy and various toxicological effects including teratogenicity.

Discussions

Due to possibility of multiple sources for impurities as contaminants validation of impurity profile of API always pose challenges for the GMP auditors and often decisions taken are not the true reflections of the prevailing conditions of the audited company. Specification of impurities in the API, residual solvents validation of Analytical procedures impurity profile does not provide reasonable assurance for the accuracy and precision of not only the product quality but also the process and systems of the organizations' ability to reproduce.

As per FDA Guidance Part 6.1 [3] the process validation should confirm that the impurity profile for each API is within the limits specified and is comparable to the profile determined during process. For validation of a process to prepare a new API, the impurity profile should be comparable to or better than the profile determined during process development.

Identification of process parameters that could affect the critical quality attributes of the API. Critical parameters should be determined by scientific judgment and typically should be based on knowledge derived from research, scale-up batches, or manufacturing experiences.

Many a times the inspectors reject the product based on the facts that "The approved protocol failed to establish inter-laboratory acceptance criteria for impurities in the drug product "The approved method for executing the protocol failed to establish a single integration parameter for analyzing the concentration of oligomoiety peaks for the entire sequence. Then the audited company re-integrated the sequence using different integration parameters for these peaks. This resulted in independent selection of desired peak width of one impurity. However, many potential toxins as impurities are not directly analyzed.

Classification of impurities

Impurities can be classified into the following categories [4-6].

Organic impurities (process- and drug-related), Inorganic impurities and Residual solvents.

However, in order to have better understanding more focused R&D is needed on impurity profiles like

1. Extensive Use of Generic Drugs over Branded Drugs.
2. Failure of proper documentations in many manufacturing units on Critical Process Parameters and Critical Process Variables.
3. Drug expiration date and revalidations
4. Impact of GMP/FDA audits on commerce.

The relevance of GMP/GLP-audits to Pharmaceutical industry

1. Impurities play catastrophe and may influence the closure of the entire manufacturing unit itself.
2. Many manufacturing units lost recognition and commerce due to lack of impurity profile validations.
3. R&D inputs on newer impurity profiles other than the accepted original parent rout are very less. (Chemical/Natural/Biotech products and also medical diagnostics and surgical implants).
4. Impurity identification is easier when carried out at stages earlier to the formation of the final API, i.e. at an intermediates stage. It helps in dealing with the impurity at the point of its formation which provides ample time to address various aspects of its formation and control. However, the thresholds and guidelines of the International Council of Harmonization do not apply to the impurities at the developing stages and thus overlooked many a times.

Impact

1. Many R&D molecules have been successful commercial drugs with known Pharmacopoeia Analytical STANDARDS (100 ± 10% variance for commercial use).
2. No issue if all manufactures follow the same original

R&D route but in reality, it is not so.

3. Many process innovations are done at Plant level to reduce cost of API (unmindful of new and potential impurity developments).

Sources of Impurities at Commercial scale manufacturing

1. The lack of R&D/P&D level inputs on all process changes to batch process records for possible impurity developments
2. Non-evaluation of CPP and CPV in each step of BPR.
3. Change of instruments/equipment's from Batch to Batch.
4. Process modification without due consent from online plant personals.
5. Solvents, pH, Temperature and Time and duration of reaction.
6. Analytical techniques used for detection of API.
7. Variations impact due to man power changes or improper HRM policies/management of the manufacturing units.

Possibility of impurity developments to check for the validation

1. Process parameters
2. Proper Transfer of Technology
3. No process changes controls
4. Environmental factors
5. Proper vendor validations
6. Usage of deadly chemical toxins in the process.

R&D scope at academic institutions: 1. For developing Novel Drugs Due to cost factor and time (3 - 4 billion USD and 13 - 14 yrs for R&D for each new molecule), budget constraints and fund-raising problems. 2. Focus on impurities identification and validation to be for short term thesis work may bring and strengthen academic –industry relations 3. Direct work on process impurities at industries have immense use for FDA audits

Potential time-tested APIs' Trimethoprim, Sulfamethoxazole, Loratadine, Ciprofloxacin, Chlorhexidine digluconate are sidelined due to newer clinical toxicity reports other than evaluated and identified in the pre-commercialized research stage and attributed to main molecule or API but no data available if it was due to newer and more toxic impurities developed due to synthetic process altered/changes made from original R&D synthesis route as a part of techno-commercial needs.

Different routes generate different impurities: Many known molecules are reported to have developed toxic effects due to process modifications like Loratadine (sudden allergic rashes due to batch variability), Ciprofloxacin (reduced bio-efficacy/allergy/batch variability), Trimethoprim/Sulfamethoxazole (fatalities associated with the administration of Sulfonamides although rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic Epidermal necrolysis, fulminant hepatic necrosis and other blood disorders. Many more to cite similar draw backs and side effects generated not known during parent research stage but after commercially introduced and establishing due clinical efficacy and the process of synthesis from original research being altered at manufacturing plant/MSME sites keeping purity profile same but variable impurities (only in terms of quantities but not structural similarities).

Loratadine molecular weight of 382.89, and empirical formula of $C_{22}H_{23}ClN_2O_2$; its chemical name is ethyl 4-(8-chloro-5,6-dihydro-11H-benzo [5-7] cyclohepta[1,2-b] pyridin-11-ylidene) -1-piperidinecarboxylate and has the following structural formula:

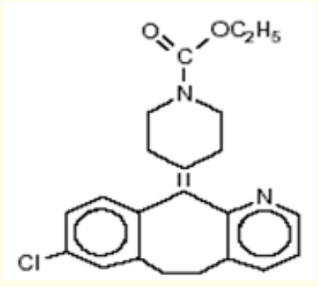

Figure 1

The isolated impurity showed potent anti-inflammatory activity, 58.6% at 5 mg kg^{-1} and evaluated for locomotors activity showed significant loss of activity at 50 mg kg^{-1} The impurity was isolated from an intermediate stage formed at the 9th stage of the synthesis) [7].

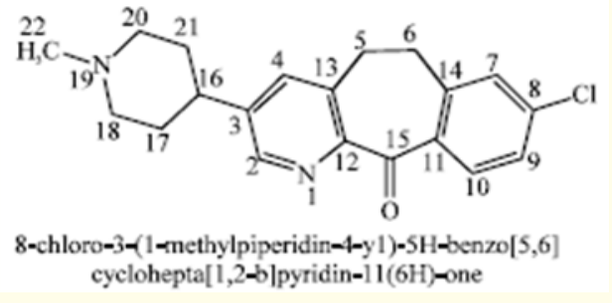

Figure 2

Expiration dates and impurity generation: Loss of revenue due to recalled expired medicines is increasing in all countries. In INDIA Expired drugs cost pharmaceutical companies INR 500 cr every year [8] on account of destruction of expired drugs. Some studies find that Expired Medications may still be effective, and what if expired medications were still effective- it could be an enormous cost-saver for consumers. However much less research data is available on such usage of a drug which may have acceptable potency at the end of its shelf life, but impurities could be forming will definitely do have adverse role. Some studies on analytical parameters of expired drugs that effect lifespan of drug is moisture, increased temperature, manufacturing impurities, and, for some drugs, light and so on are there [9]. The expired sample and unexpired sample of Metformin showed new peaks in UV, X-ray diffraction, FTIR for impurities but the principle peaks remained more or less same. Many reports are available on expiration of drugs (API and API as its formulations.) Expiration dating is not the true measure of the physical stability of the drug but rather is an estimate in the worst possible storage conditions and accelerated stability testing of the final drug product which simulates by being at variable conditions of temperatures, humidity, time and nature of packing. Reports are available on the physical stability of expired drugs and for some drugs it may have been over years before the degradation of the drug occurs. It is also seen some drugs that are not stable beyond 3 years. It is a difficult one to answer or predict whether depending upon the degradation the compound in testing may have a pharmacological activity? and does it create any toxic effects, is a question that depends upon the drug itself. In most cases the degradation of the drug is not as toxic as the primary drug and so toxicity is not a problem. One example of a drug that has toxicity upon going past its expiration date is Ascorbic acid or Vitamin C which has been documented to cause kidney damage.

It is established fact that Analytical method validations are done in the following areas: 1. Pharmacopoeia recommended methods, 2. Newer validated methods and equipments, 3. Minimum 3 batch validations, 4. Chemical structural elucidation for all impurities above 2% of total impurity profile. It is needed that redesigning R&D efforts to be done on impurity profile developments with a quality of interaction with the pharmaceutical academic and industries, updating academic syllabus as per current industrial needs. Due to rapid and upcoming new techno-commercial activities with enhanced R&D capability and alliance formation in the focused areas of Pharmaceuticals, Biotechnology and medical devises industries the contribution of GMP auditors is undeniable.

The challenges for GMP auditors: GMP auditors do many times provide unbiased evaluation of inspected API manufacturing unit. However, it is also likely that due to non-expertise in all areas of API the auditor may over look certain parameters for impurities while focusing on validations of attaining and maintaining purity profile of concerned API, which may lead to some unknown impurities being generated from batch to batch due to process modifications done in the plant R&D to attain more yields or reduce process cost. The auditor should review all record related to technology transfers with special emphasis on the analytical results of IR/NMR/Mass spectra and HPLC/HPTLC data of at least three consecutive batches immediately prepared soon after any process modification done and find if any validation done on the impurity profile.

Conclusion

Impurities are generated or added raw materials remain non-reacted at various stages of new routs of synthesis of API (away from the original R&D routes and conditions). Hence there is a need for more focused audits and key role to be played by GMP auditors in the validations of impurity profiles. GMP auditors who have an access to all confidential documents of the inspected company right from the stages of Site Masters Plan to final Distribution and storage facilities of API synthesized should provide vital clues for batch to batch aberrations which not only provide substantial inputs for the audited company's research team for critical evaluations but also prevent many potential and time tested API being sidelined due to newly attributed clinical toxicity reported other than original research done at the later stages of commercial launch of API's.

There are no reports available for such new research findings if any newly added impurities are/may be responsible for freshly found toxicity/side effects or it is specially only due to API alone as the clinical research teams work with API formulations synthesised and marketed from different sources. R&D and focused validations on API impurities by the GMP auditors will have 1. Direct impact on commercial products 2. Provide regulatory auditors updated focus to ensure quality products 3. Provide cost effective research topics for graduates (Pharmaceutical Chemistry, Analysis and Pharmacology students) and bring M S M E's to effectively participate in cost reduction with high quality API manufacturing. If a manufacturing company/MSME develops reasonably good procedures for the validation of Impurity profiles of API, the GMP auditor can get assured of the reproducible purity of the same for recognizing the consistency of quality of API being manufactured there.

Bibliography

1. Inspection of active pharmaceutical ingredients - pharmaceutical inspection convention pharmaceutical inspection co-operation scheme 1 (2009): 30-113.

2. GMP Validation - GMP Good Manufacturing Practice SOP (2006).

3. FDA Guidance Part 6 Pharmaceutical CGMPs (2003).

4. U.S. Department of Health and Human Services. Food and Drug Administration Office of Generic Drugs Revision 1 (2009).

5. Center for Biologics Evaluation and Research (CBER) ICH 2 (2008).

6. Susanne Keitel. EU/Swissmedic GMP Workshop Beijing University, Federal Institute for Drugs and Medical Devices (BfArM), Germany (2006).

7. R Krishna Reddy., *et al*. "Impurity profile study of loratadine". *Journal of Pharmaceutical and Biomedical Analysis* 32.1 (2003): 29-39.

8. Expired drugs cost pharma cos Rs 500 cr every year - The Economic Times (2007).

9. R Kayalvizhi., *et al*. "Spectroscopic Analysis of Expired and Pure Melmet". *Journal of Minerals and Materials Characterization and Engineering* 11.4 (2012): 427-435.

Volume 2 Issue 4 April 2018
© All rights are reserved by BK Chakravarthy.