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Annual product quality review: Guidance for industry by regulatory perspective

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Abstract
Annual Product Quality Review (APQR) is an evaluation which is prepared according to the CGMP requirements of different regulatory authorities. A Good Manufacturing Practice ensures that the products are consistently produced and controlled according to quality standards. Annual Product Quality Reviews not only are required by GMP but also required for robust quality improvement for manufacturing the pharmaceutical product. Annual product review is an evaluation conducted annually to assess the quality standard of each drug product with a view to verify the consistency of existing process and to check the appropriateness of current specifications and to highlight any trend in order to determine the need to change any drug product specifications or the manufacturing processes or control procedures. It is a written report is required for every drug product, based on data collected at least annually. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. It is universally accepted by the industry and contents must specify a list of manufactured batches, release data and reviews of deviations, complaints, recall and returned goods. This article gives brief overview of regulatory aspects and regulatory requirements for Annual Product Quality Review of pharmaceutical product. It mainly focuses on the documentation required for the preparation of Annual Product Quality Review. Thus the article is based on the regulatory requirements or standards to manufacture and maintain the quality of any pharmaceutical product.

Keywords: product quality review, quality, Good manufacturing practice, annual product review

Introduction

Annual product Quality review [1, 2, 3].

Annual product quality review is an evaluation conducted at regular periodic or rolling quality reviews of all registered medicinal pharmaceutical products, including export (US market & Europe market, UK, Canada, Australia and Row market) to assess the quality standard of each drug product with the view to verify the consistency of existing process and to check the appropriateness of current specifications and to highlight any tends in order to determine the need to change any drug product specifications or the manufacturing processes or control procedures.

It is an effective quality improvement tool to enhance the consistency of manufacturing process and overall quality of the product. It will capture broader review of product data and capturing trends will help determine the defects and possible improvements of the methods and Process. Where no significant changes have been made to the system or manufacturing process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

Significance of Annual Product Quality review

- Verify the consistency of the existing manufacturing process and minimize the risks to pharmaceutical products which will be helpful for the pharmaceutical companies to develop their products consistently of best quality on yearly basis.
- It determines the quality and process defects of the products. It also determines possible improvements of the analytical methods and manufacturing process.
- Trend of yield, analytical results, manufacturing parameters of the product are also highlighted. It is helpful to identify the process and product defects.
- It reviews the quality of the raw material and packaging material which is used for the product. Mainly it indicates the quality of material.
- Verifies the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements.
- Out of Specification parameter helps to determine the product defects and the prospective actions are defensing the product from possible risks.
- If any of the batches is failed, then it is also included in the Annual Product Quality Review to determine reasons for the batch rejection.
- The review of the stability study results of any long term and on-going stability of the bulk product and the marketed product should be done.

Requisite of periodical Annual Product Quality Review for Drug Manufacturing and Control of Pharmaceutical Products & Active Pharmaceutical Ingredients[4]

The US Food and Drug Administration proposed a necessity to prepare written summary for each product in its February 13, 1976 by rewriting the good manufacturing practices (GMPs) for drug products.

The purpose of this proposed GMP requirement was to provide reliable procedures for a drug manufacturer to review the quality standards for each drug product.

After numerous comments from industry objecting to the preparation of written summaries, US FDA revised the proposal to allow each company to establish its own procedures for the evaluation of product quality standards, by reviewing the records required by the GMPSs on annual basis. This requirement was published as final current good manufacturing practices (CGMP) regulations for drug products (21 CFR 211.180(e)).

Since its publication, 21 CFR 211.180(e) has been commonly referred by FDA and the pharmaceutical industry as the "Product Annual Review" (PAR) or the "Annual product review" (APR).

In august 2001, FDA also adopted and published the guidance for industry ICHQ7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.

This guidance was developed within the expert Working Group of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

This guidance was then incorporated as Part II of the European Community Guide to GMP (EU GMP Guide) in October 2005.

Product Quality Review by Various Regulatory Agencies

1. European Commission volume 4, Part II [13, 14]

Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results;
- A review of all batches that failed to meet established specification(s);
- A review of all critical deviations or non-conformances and related Investigations;
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program;
- A review of all quality-related returns, complaints and recalls; and
- A review of adequacy of corrective actions.

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

Periodic Review of Validated Systems

Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

2. 21 CFR Part 211 [17, 18].

Sec 211.115 states about reprocessing one that fails to confirm with all established standards, and characteristics. Reprocessing shall not be performed without the review and approval the quality control unit.

Sec 211.180 states about general requirements for any production, control, or distribution record shall be retained for at least 1 year after the expiration date of the batch and in case of OTC drug products lacking the expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the batch.

The quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedure. Written procedures shall be established and followed for such evaluation and include provisions for:

1) A review of representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.
2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted for than 211.192 for each drug product.

Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 211.198, 211.204 or 211.208 of these regulations, any recalls, reports of inspectional observations issued by FDA.

Sec 211.192 states about Production Record review,

Sec 211.198 states about the all the complaint files related to the product, and then

211.204 are about the returned Drug Products etc.

Just because of this, it is not always clear exactly what is expected by the regulatory authority. So it is presently a standard FDA practice to make additional and quite reasonable demands that make it possible to improve the evaluation possibilities for products.

This development is then consistent of with the requirement s of the Guidance for industry Quality Systems Approach to Pharmaceutical CGMP Regulations Published in Sep 2006.

The US FDA regulations describe very limited the contents for the review and evaluation of the product but as per EUROPE the contents for the preparation of the APQR are well described.

Frequency and procedures for Annual Product Quality Review

- FDA requires an annual frequency for the Annual Product Quality Review (APQR), which is stated in all three GMP regulations and the guidance document.
- FDA and EU require an annual frequency for the PAR/PQR, which is stated in all three GMP regulations and the guidance document.
- FDA does not allow the extension of the review frequency beyond an annual basis, regardless of the number of batches produced in the preceding 12-month period.
- FDA expressed the concern that "Potential problems with product quality standards could go undetected and thereby delay recognition of a need to revise specifications or manufacturing or control procedures"
- The Product Quality Review requires that the account should be kept of the previous reviews.

Table 1: Comparative evaluation of annual product quality review with respect to us and europe

Parameter	US	EUROPE
The regulations required for the preparation of the APQR.	21 CFR 211.180(e)	EMEA- Part I of the EU GMP, Chapter-1 Items For Review
Study and review of all the quality related data, returned products, if any complaints and recalls are there for the Product and the investigations performed at that time during the review.	It is specified under the 211.192	It is specified in the European guidelines
The review of adequacy of any other previous product processes or corrective actions of the equipment	It is not specified	It is specified
The qualification status of the equipment's and utilities used for that product for e.g. HVAC. Water, compresses gases, etc.	Not specified	Specified
The study and review of the starting materials used for the preparation of the product	It is not specified	It is specified in EU
The review of any contractual agreements signed for that pharmaceutical product which is well defined in the chapter-7 to ensure that they are up to date.	Not specified	Specified
The evidence and information related to the salvaged products and the review of the same.	It is specified	Not specified
The review and data related to the in-process controls	It is not specified	It is required and specified
The reviewing of the packaging materials used in the preparation of the product.	It is not specified	It is specified
The critical insignificant deviations and the non-conformances observed	Not specified	It is specified
The reviewing of the data of stability results of the product	Not specified	Specified
The study and reviewing of any adverse trends found during product development.	Not specified	It is specified
The study and review of any marketing authorization variations which are submitted, granted or refused	Not specified	It is specified
The data of post marketing commitments if any	Not Specified	Specified
The inclusion of review of the exported products only	Not Specified	They are specified
The data of total no. of batches whether they are approved or rejected	Specified	It is not specified
The analyzed data of the batches that failed to meet the specifications should be included in the APQR report.	Not specified	It is specified
The adequacy of any equipment's corrective actions taken or any previous processes corrective actions taken (from the Previous product quality reviews).	Not specified	Specified
The responsibility of the QA personnel to ensure the accurate review and in the timely manner	It is not specified	It is required as per the European guidelines (it is done by the qualified QA person
The written reports of all the data.	Not specified	Specified
The documented data for the reason of corrective actions taken.	Not specified	Specified
The frequency of the review of all the manufactured batches.	It is annually done	It is annually done
The account of the previous reviews to be kept.	Not specified	Specified
Procedure or SOP for the preparation of the APQR of the product.	There is a written procedure of the preparation of the APQR of the pharmaceutical product	There is no such written procedure for the preparation of the APQR of pharmaceutical product.
Annual Product Quality Review (APQR) – In US and Europe	It is known as Annual Product Review (APR) / Product Annual Review (PAR) in US.	It is known as Product Quality Review (PQR) in Europe.
The regulatory authority for the preparation and documentation of the APQR	USFDA, Centre for Drug Evaluation and Research (CDER)	EMEA, The Committee for Medicinal Products for Human Use (CHMP)

3. PIC/S- Quality Management PE009-13 (Part -I) Sub Part 1.4) [15, 16].

Given the variability inherent in many biological substances and products, steps to increase process robustness thereby reducing process variability and enhancing reproducibility at the different stages of the product lifecycle such as process design should be reassessed during Product Quality Reviews.

Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

- A review of starting materials including packaging materials used in the product, especially those from new sources.
- A review of critical in-process controls and finished product results.
- A review of all batches that failed to meet established specification(s) and their investigation.
- A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.
- A review of all changes carried out to the processes or analytical methods.
- A review of Marketing Authorization variations submitted/granted/refused, including those for third country (export only) dossiers.
- A review of the results of the stability monitoring programmer and any adverse trends.
- A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- A review of adequacy of any other previous product process or equipment corrective actions.
- For new marketing authorizations and variations to marketing authorizations, a review of post-marketing commitments.
- The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.
- A review of any contractual arrangements to ensure that they are up to date.

The manufacturer and marketing authorization holder should evaluate the results of this review and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorized person responsible for final batch certification together with the marketing authorization holder should ensure that the quality review is performed in a timely manner and is accurate.

4. WHO – WHO Technical Report Series No. 961, [Annexure 4] [19].

Regular periodic or rolling quality reviews should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications in order to highlight trends and to identify improvements in both product and process.

A product quality review may also be considered as an instrument for surveying the overall quality status of a blood component and its manufacturing processes, including the collection of starting materials. Such a review should normally be conducted annually and should be documented. In accordance with international and/or NRA requirements and recommendations it may include:

- Review of starting materials;
- Review of critical in-process controls;
- Review of results of quality control and quality monitoring;
- Review of all changes;
- Review of the qualification status of equipment;
- Review of technical agreements and contracts;
- Review of all significant deviations, errors and non-conformances, and the corrective actions implemented;
- Review of the findings of internal audits and other inspections, and the corrective actions implemented;
- Review of complaints and recalls;
- Review of donor acceptance criteria;
- Review of donor deferrals;
- Review of look-back cases.

5. Product Quality Review by ICH Q7 [20].

Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results;
- A review of all batches that failed to meet established specification(s);
- A review of all critical deviations or non-conformances and related investigations;
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program;
- A review of all quality-related returns, complaints and recalls; and
- A review of adequacy of corrective actions.

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

A). Regulatory aspects for preparing APQR [5, 6, 7, 8, 9, 10, 11, 12].

Table 2

Parameters	Data to be reviewed
Ware House review	Identify all starting and packing materials used for the product
	All analytical tests, specification changes and deviations
	Packing material approval and release and rejections
	Use of appropriate electronic or electromechanical equipment to conduct a 100% examination for correct labeling during, after completion of finishing operations.

	If any automated tech to prevent incorrect labeling name of tech should also be included. It should also contain the inspection rejection rate.
Quality control review	Written procedure for production and process controls design to assure that the drug products have the identity, strength, quality and purity they purport.
	Changes in the procedures, reviewed, approved by the Quality units.
	Trending of in-process, finished product test results in both manufacturing and packaging process and microbiology considerations should also be included.
	Evaluation of CPK at bulk and finished product stage is essential.
	Laboratory incidents, OOS and OOT in drug products
	Review of long term and on-going stability of the bulk product and marketed drug product.
Production review	Product description and Master formula description
	Equipments involved in manufacturing and packing
	Manufacturing area classification
	Process flow diagram
	Qualification status of equipment/utilities and process
	Number of batches manufactured and vendors of raw materials and packing materials
	Hold time reviews such as bulk hold time, filling time and total processing time
	Optical inspection data such as critical defects, major defects and minor defects
	Product /processing yields such as manufacturing yield, filling yield and good product packing yield
	Changes to the system such as document & facility related
Quality assurance Review	Process deviations and investigations, corrective and preventive actions
	Rework(Repacking) batches
	Rejected batches
	Market complaints
	Product recalls
	Quality related returns
	Control samples
	Environmental reviews such as bio-burden
	Review of Quality Technical agreement
	Review of marketing authorizations/ variations
	post marketing commitments
	Contractual agreements

B). Calculation of process capability index [C_{pk}] [21, 22].

In process improvement efforts, the process capability index or process capability ratio is a statistical measure of process capability: the ability of a process to produce output within specification limits. Assumes process output is approximately normally distributed.

$C_{pk=}$ min [Upper Specification Limit-Mean/3σ; Mean-Lower Specification Limit/3σ]

Table 3

Situation	Recommended minimum process capability for two-sided specifications	Recommended minimum process capability for one-sided specifications
Existing process	1.33	1.25
New process	1.50	1.45
critical parameter for existing process	1.50	1.45
critical parameter for new process	1.67	1.45
Six Sigma quality process	2.00	2.00

C). Relationship to measures of process fallout:

Table 4

C_{pk}	Sigma level (σ)	Area under the probability density function	Process yield
0.33	1	68.27%	68.27%
0.67	2	95.45%	95.45%
1.00	3	99.73%	99.73%
1.33	4	99.99%	99.99%
1.67	5	99.9999%	99.9999%
2.00	6	99.99999998%	99.99999998%

D). Process Capability Analysis

Process capability ratio (C_p), when the process is centered at nominal dimension, is defined below

$$C_p = \frac{USL - LSL}{6\sigma}$$

where USL and LSL stand for upper specification limit and lower specification limit respectively and σ refers to the process standard deviation.

$100(1/C_p)$ is interpreted as the percentage of the specifications' width used by the process.

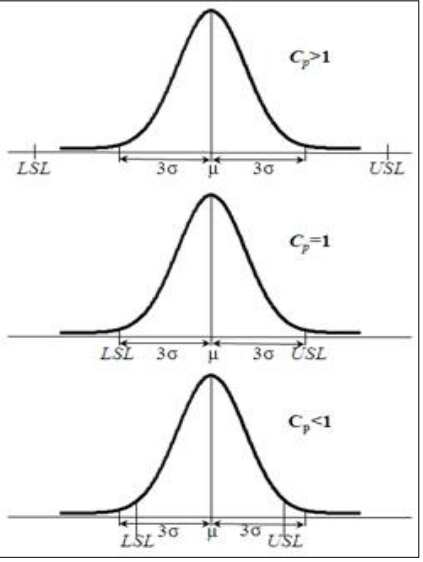


Fig 1: Measure of Process Capability: Cp

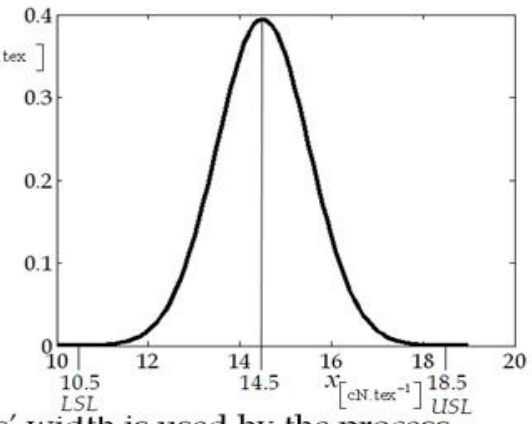
Illustration

Suppose the specifications of yarn strength are given as 14.50±4 cN.tex^{-1}. As the process standard deviation σ is not given, we need to estimate this

$$\hat{\sigma} = \frac{\bar{R}}{d_2} = \frac{3.110}{3.078} = 1.0104$$

We assume that the yarn strength follows normal distribution with mean at 14.50 cN.tex-1 and standard deviation at 1.0104 cN.tex^{-1}.

$$C_p = \frac{18.5 - 10.5}{6 \times 1.0104} = 1.3196$$



That is, 75.78% of the specifications' width is used by the process.

Fig 2: Measure of Process Capability: Cpu and Cpl

The earlier expression of Cp assumes that the process has both upper and lower specification limits. However, many practical situations can give only one specification limit. In that case, the one-sided Cp is defined by

$$C_{pu} = \frac{USL - \mu}{3\sigma} \quad \text{(upper specification only)}$$

$$C_{pl} = \frac{\mu - LSL}{3\sigma} \quad \text{(lower specification only)}$$

Fig 3

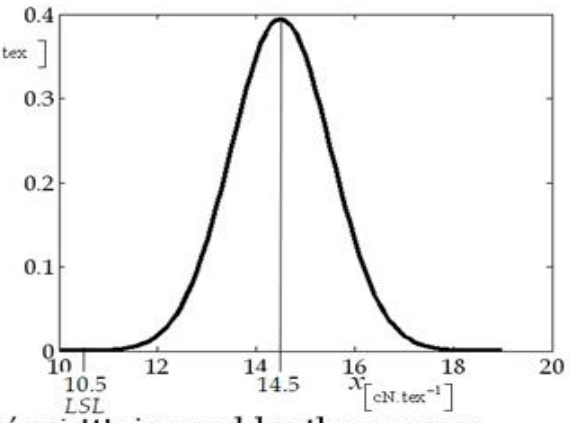
Illustration

Suppose the low specification limit of yarn strength are given as 14.50 - 4 cN.tex^{-1}. As the process standard deviation σ is not given, we need to estimate this

$$\hat{\sigma} = \frac{\bar{R}}{d_2} = \frac{3.110}{3.078} = 1.0104$$

We assume that the yarn strength follows normal distribution with mean at 14.50 cN.tex-1 and standard deviation at 1.0104 cN.tex^{-1}.

$$C_{pl} = \frac{14.5 - 10.5}{3 \times 1.0104} = 1.3196$$



That is, 75.78% of the specifications' width is used by the process.

Fig 4: Process capability ratio versus process fallout

Assumptions

1. The quality characteristic is normally distributed.
2. The process is in statistical control.
3. The process mean is centered between USL and LSL.

Measure of Process Capability: Cpk

We observed that Cp measures the capability of a centered process. But, all process are not necessarily be always centered at the nominal dimension, that is, processes may also run off-center, then the actual capability of non-centered processes will be less than that indicated by Cp. In the case when the process is running off-center, the capability of a process is measured by the following ratio

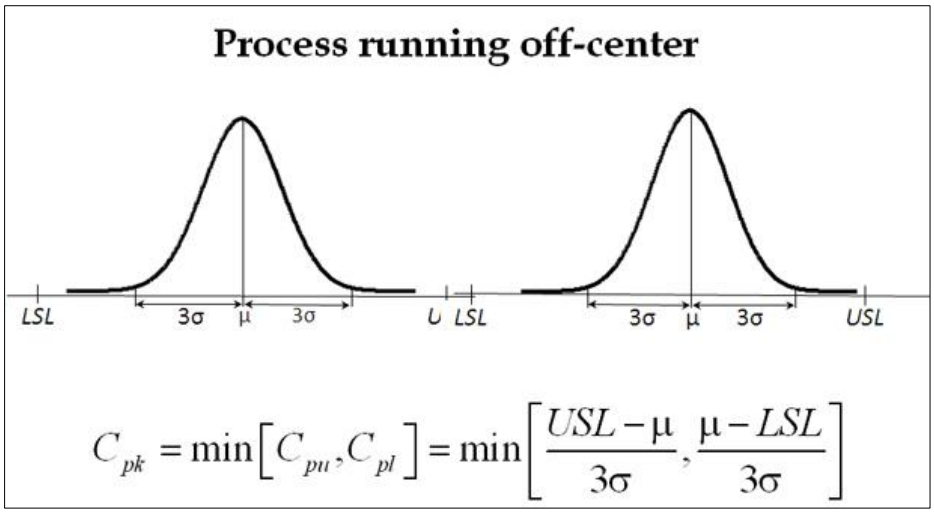


Fig 5

Interpretations

1. When Cpk=Cp then the process is centered at the midpoint of the specifications.
2. When Cpk < Cp then the process is running off center.
3. When Cpk=0, the process mean is exactly equal to one of the specification limits.
4. When Cpk<0 then the process mean lies outside the specification limit.
5. When Cpk <-1 then the entire process lies outside the specification limits.

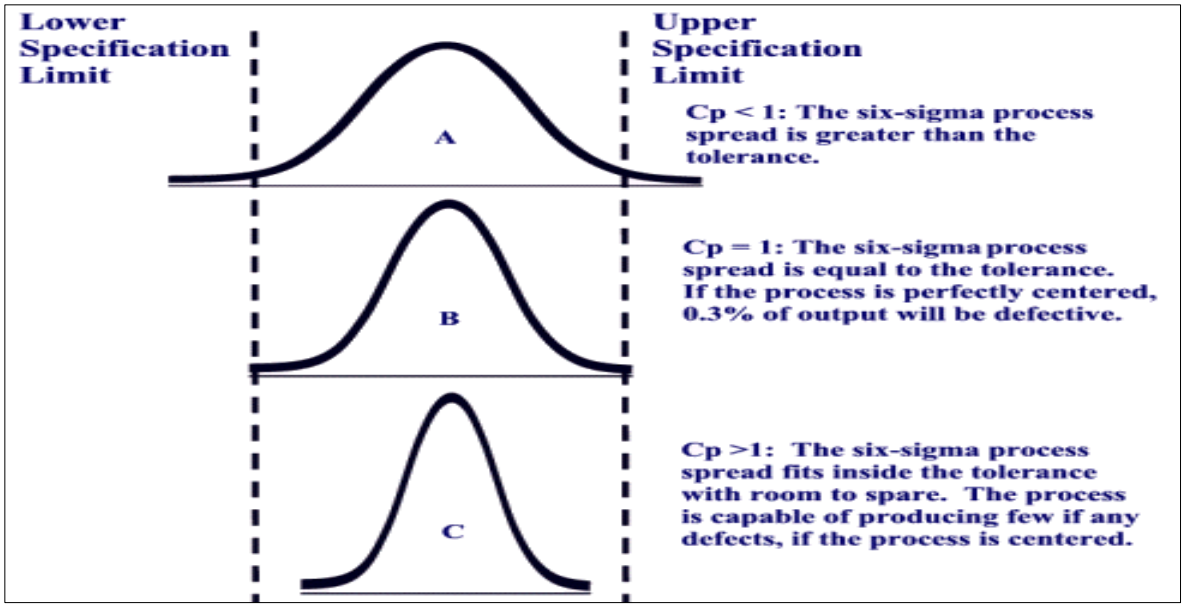


Fig 6

E). Illustration

A). Cisplatin injection finished Dosage form Analytical Data of pH and Assay values are tabulated in below to explain the process capability index of pharmaceutical drug products.

Table 5

S. No	Batch No	pH Limit (6.2 – 7.0)	Assay of Cisplatin by HPLC Limit: 95.0%-105.0%
1.	ZX601	6.6	99.1
2.	ZX602	6.7	99.5
3.	ZX603	6.5	99.3
4.	ZX604	6.5	99.3
5.	ZX605	6.5	99.3
6.	ZX606	6.5	99.7
7.	ZX607	6.7	99.6
8.	ZX608	6.7	98.7
9.	ZX609	6.7	99.3
10.	ZX610	6.6	98.8
11.	ZX611	6.6	99.1
12.	ZX612	6.6	98.8
13.	ZX613	6.6	99.3
14.	ZX614	6.6	99.1
15.	ZX615	6.7	99.8
16	ZX616	6.6	99.1
17.	ZX617	6.6	98.6
18.	ZX618	6.8	99.0
19.	ZX619	6.6	99.8
20.	ZX620	6.6	99.4
21.	ZX621	6.6	98.9
22.	ZX622	6.7	99.4
23.	ZX623	6.5	99.9
24.	ZX624	6.6	99.4
25.	ZX625	6.5	100.9
26.	ZX626	6.5	100.2
27.	ZX627	6.6	100.9
28.	ZX628	6.6	99.8
29.	ZX629	6.6	98.3
30.	ZX630	6.7	100.0

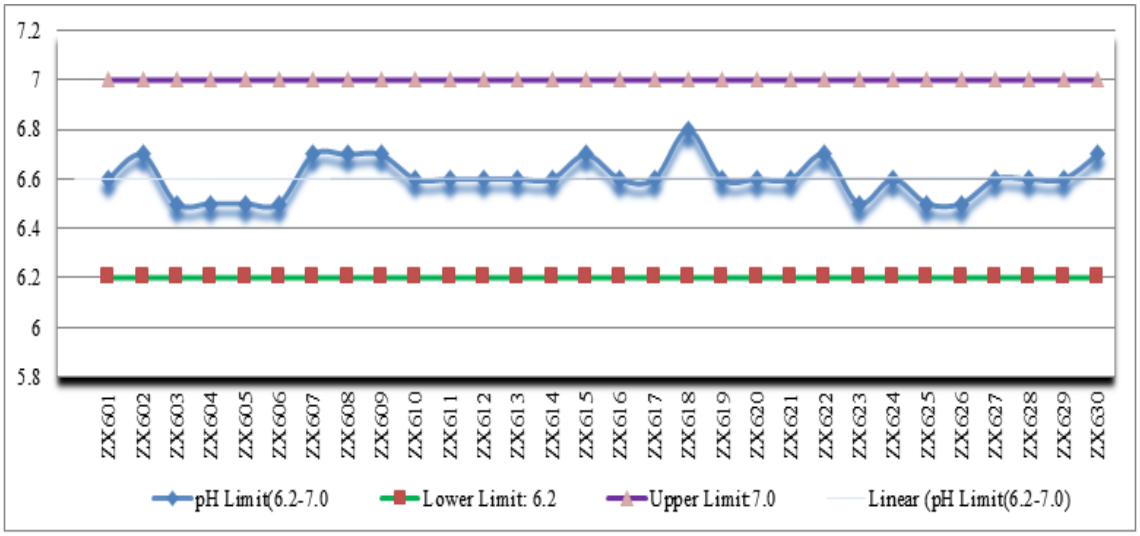


Fig I: Trend data for finished dosage form pH

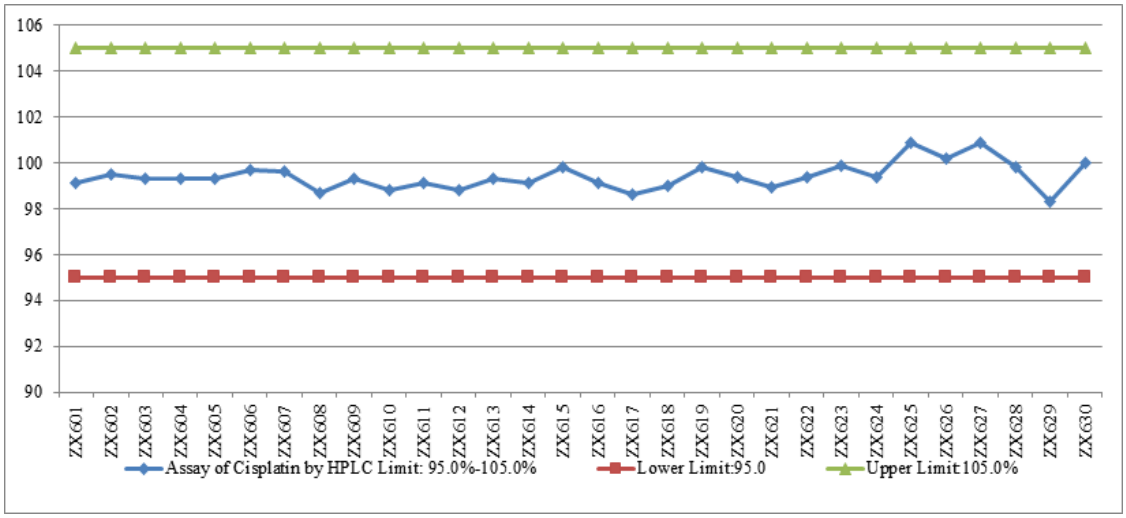


Fig II: Trend data for finished dosage form assay by HPLC

Evaluation of process capability index at bulk and finished stage is applicable, here only finished stage interpreted.

The review of process capability and trends parameters of finished dosage form is carried out and given below.

Table 6: Process parameter: pH (Specification Limit: 6.2-7.0)

S. No	Statistical parameter	C_{pk} Process value
1.0	Average (Mean)	6.594
2.0	Standard Deviation	0.079
3.0	Process Capability Index	1.663

Table 7: Process parameter: Assay of Cisplatin by HPLC (Specification Limit: 95.0%-105.0%)

S. No	Statistical parameter	C_{pk} Process value
1.0	Average (Mean)	99.517
2.0	Standard Deviation	0.638
3.0	Process Capability Index	2.361

Evaluation of process capability index

To evaluation of data by using control charts for any out of trends and estimating the process capability through statistical tools like C_{pk} (Minimum 30 batches data required) to define the status of existing process that is the distance from process mean to the nearest specification divided by three standard deviation for critical quality attributes for examples., pH and assay of bulk and finished product shall be reported. C_{pk} value indicates reflection of the process capability and these values depends upon the limits that are adopted. The C_{pk} value shall be targeted to less than 1is process is in-capable and it indicates improve by reducing common cause of variation in process variables use 100% inspection. Between 1& 3 it indicates process is capable; do nothing or some process improvement depending upon sample size. Greater than 3 it indicates very capable. Do nothing or reduce specification limits. No inspection necessary.

Conclusion

The regulations, regulatory requirements and the procedures mentioned as per US and Europe should be strictly followed to prepare and document the annual product quality review of the pharmaceutical product this should be done to avoid the dis-satisfied results.

On comparison of regulations between the US and Europe it was found that the regulations and requirements for annual product quality review in Europe are stringent as compared to

US. European regulations have more number of basic requirements to be fulfilled and it strictly follows GMP to maintain the quality of the pharmaceutical product and to make consistent good quality batches of the product after reviewing the results.

Just because of this, it is not always clear exactly what is expected by the regulatory authority. So it is presently a standard FDA practice to make additional and quite reasonable demands that make it possible to improve the evaluation possibilities for products.

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