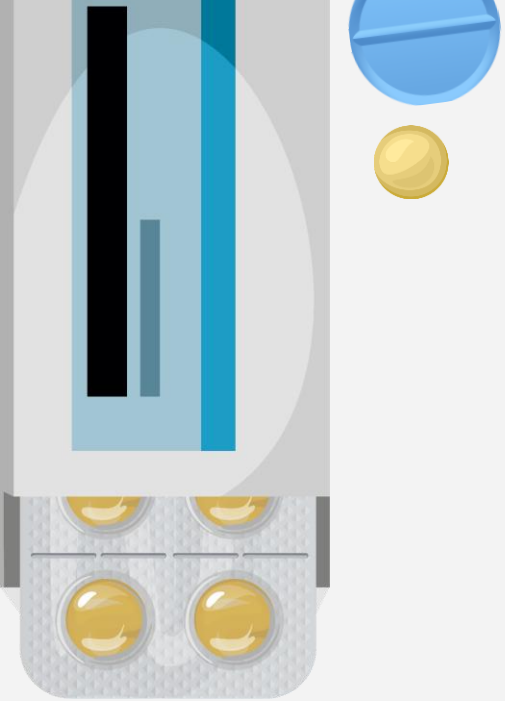
Pengembangan Produk

Pertemuan 9

apt. Catharina Apriyani W.H., M.Farm



01

CPOB & Mutu Produk

CPOB

- **GMP (*Good Manufacturing Practice*)** atau dalam Indonesia disebut **CPOB (Cara Pembuatan Obat yang Baik)** cara pembuatan obat dan/atau bahan obat yang bertujuan untuk memastikan agar mutu obat dan/atau bahan obat yang dihasilkan sesuai dengan persyaratan dan tujuan penggunaan
- **CPOB (Cara Pemuatan Obat yang Baik)** bertujuan untuk menjamin Obat dibuat secara konsisten, memenuhi persyaratan yang ditetapkan dan sesuai dengan tujuan penggunaannya.
- CPOB mencakup seluruh **aspek produksi dan pengendalian mutu**.

CPOB

- **CPOB** mengatur: produksi obat, pengawasan mutu, personalia, sanitasi, dokumentasi, penyimpanan, distribusi
- **Sertifikat CPOB** adalah dokumen sah yang merupakan bukti bahwa Industri Farmasi atau sarana telah memenuhi standar CPOB dalam membuat Obat dan/atau Bahan Obat.

Tujuan

- Menjamin obat aman, bermutu, dan berkhasiat
- Meminimalkan risiko kontaminasi
- Mengurangi kesalahan produksi
- Menjamin konsistensi mutu produk

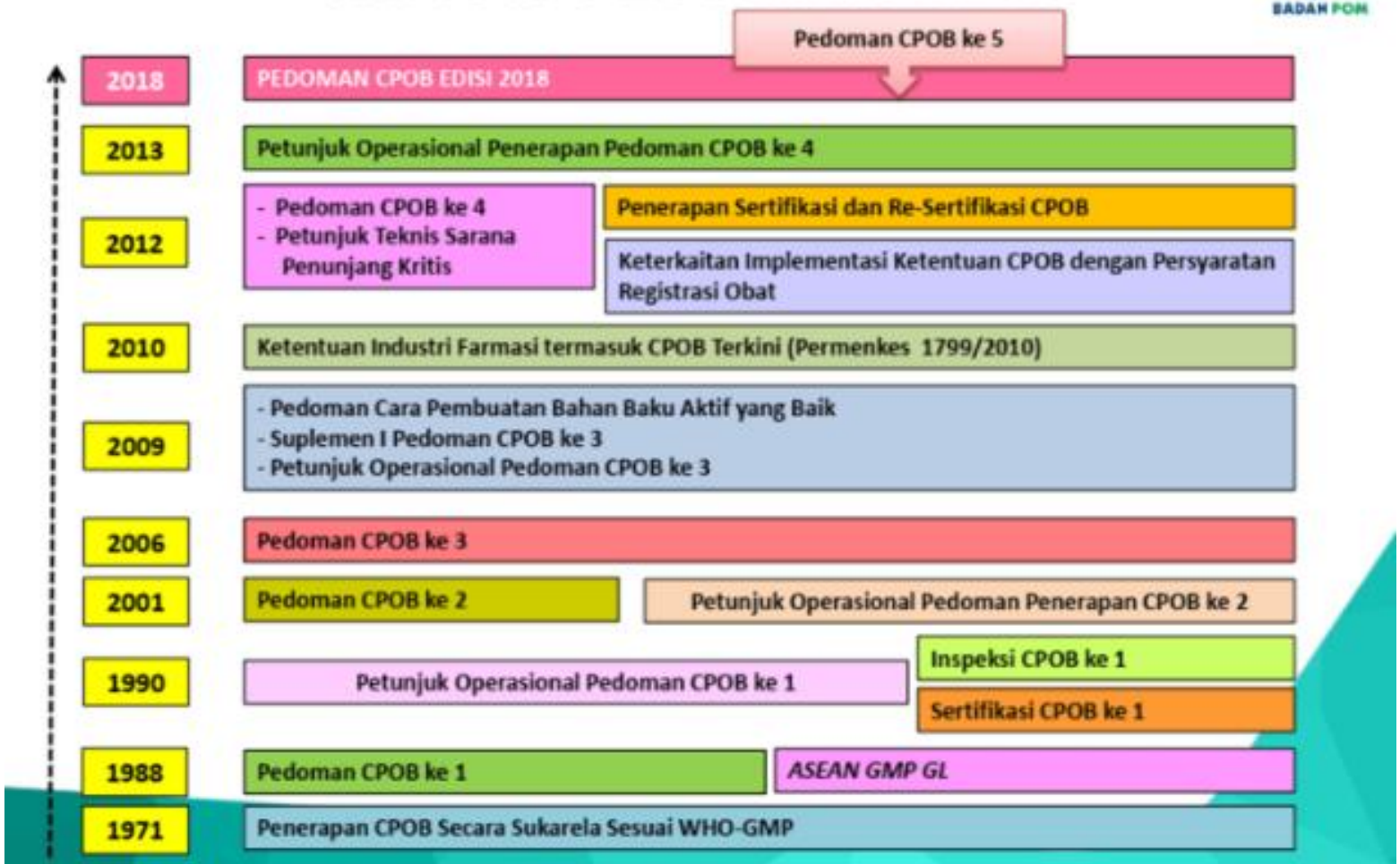
Dasar Hukum

- Saat ini yang berlaku adalah CPOB 2024 menggantikan CPOB 2018 berdasarkan peraturan kepala **BPOM nomor 7 tahun 2024** tentang standar cara pembuatan obat yang baik

CPOB 2024

- Standar ini merupakan menggantikan standar CPOB sebagaimana telah diatur dengan Peraturan Badan Pengawas Obat dan Makanan Nomor 34 Tahun 2018 tentang Pedoman Cara Pembuatan Obat yang Baik, yang mengacu pada **PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PIC/S GMP Guide) doc. PE 009-16 Tahun 2022, WHO Technical Report Series (TRS) 981 Tahun 2013 (Annex 2), WHO TRS 986 Tahun 2014 (Annex 5), WHO TRS 992 Tahun 2015 (Annex 3 dan Annex 5), WHO TRS 996 (Annex 5) Tahun 2016, WHO TRS 999 Tahun 2016 (Annex 2), dan WHO TRS 1025 Tahun 2020 (Annex 2)**.

HISTORI PEDOMAN CPOB



Mutu Produk

Mutu produk farmasi adalah kemampuan suatu produk obat memenuhi persyaratan:

- Aman
- Berkhasiat
- Bermutu
- Stabil selama penyimpanan

Hubungan CPOB dengan Mutu Produk

CPOB memengaruhi mutu melalui:

- Pengendalian proses produksi
- Pengawasan bahan baku
- Sanitasi dan hygiene
- Validasi proses
- Dokumentasi
- Pengawasan mutu (QC)

Hubungan CPOB dengan Mutu Produk

Tanpa CPOB:

- Produk dapat terkontaminasi
- Dosis tidak konsisten
- Produk tidak stabil
- Risiko bagi pasien meningkat

Faktor CPOB yang Mempengaruhi Mutu Produk

The 5 Ps of GMP Compliance

1

PEOPLES

Trained staff ensure quality and safety.

2

PREMISES

Clean, controlled spaces prevent contamination.

3

PROCESSES

Standardized methods guarantee consistency.

4

PRODUCTS

Each batch tested for purity and strength.

5

PRECCURES

Detailed records maintain compliance.

Fasilitas Produksi Farmasi sesuai CPOB

A. Bangunan dan Fasilitas

Pengaruh terhadap mutu:

- Layout buruk meningkatkan *cross contamination*
- Ventilasi buruk menyebabkan kontaminasi udara

Contoh:

- Area produksi antibiotik harus terpisah.


Personalia

B. Personalia

Pengaruh terhadap mutu:

- ***Human error*** dapat menyebabkan cacat produk
- Operator tidak terlatih meningkatkan risiko kontaminasi

Contoh:

- Salah timbang bahan → dosis tidak sesuai

C. Peralatan

Pengaruh terhadap mutu:

- Mesin tidak terkalibrasi → bobot tablet tidak seragam
- Alat kotor → kontaminasi produk

Contoh:

- Mesin filling sirup harus divalidasi.

Sanitasi & Higiene

D. Sanitasi & Higiene

Pengaruh terhadap mutu:

- Sanitasi buruk → cemaran mikroba
- Kebersihan personel memengaruhi sterilitas

Contoh:

- Operator wajib mencuci tangan sebelum masuk *cleanroom*.

Dokumentasi dan Quality Control dalam CPOB

E. Dokumentasi dan Mutu Produk

Prinsip:

“If it is not documented, it did not happen.”

Fungsi dokumentasi:

- Traceability
- Investigasi masalah
- Bukti kepatuhan GMP

Dokumen penting:

- SOP
- Batch Record
- Logbook
- Certificate of Analysis

F. Quality Control (QC)

Peran QC

- Menguji bahan baku
- Menguji produk antara
- Menguji produk jadi

Contoh pengujian:

- Disolusi
- Kadar zat aktif
- pH
- Sterilitas

SAMPLING

TESTING

HIGH QUALITY

DOCUMENTING

REPORTING

G. Quality Assurance (QA)

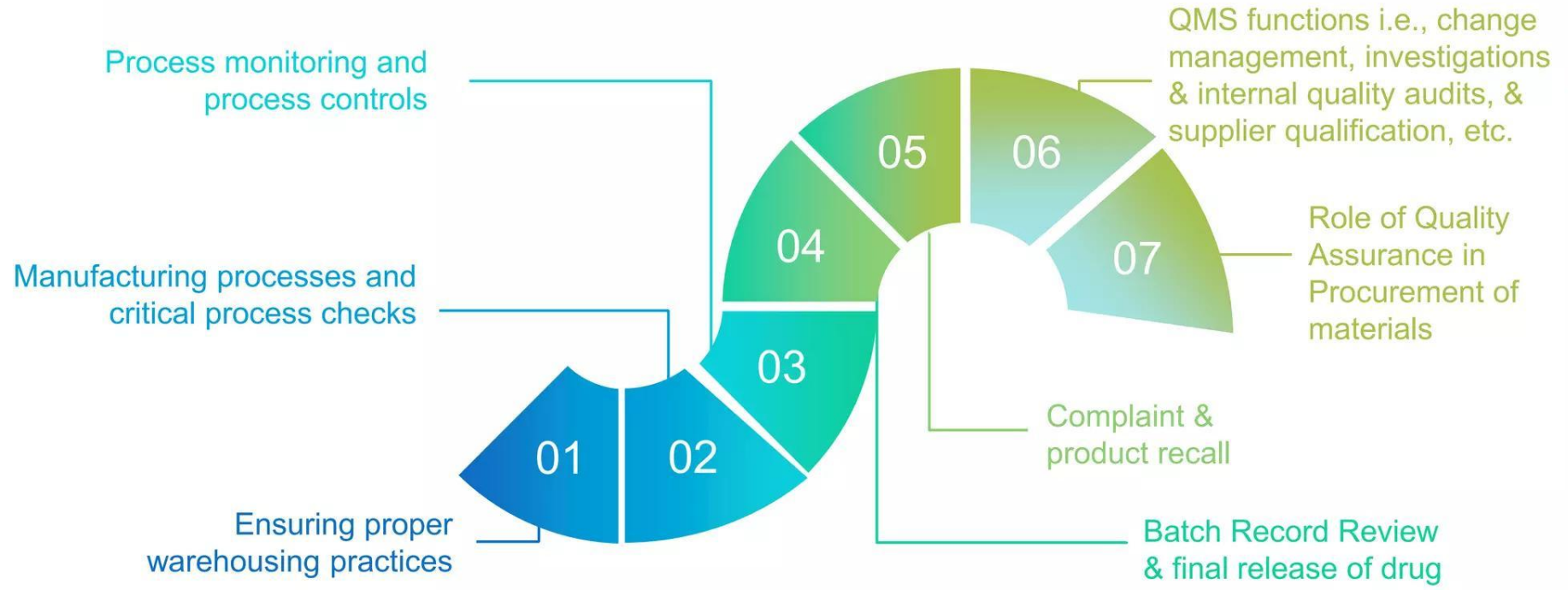
Peran QC

- Menjamin sistem mutu berjalan
- Audit internal
- Approval batch
- Menangani deviation

QA memastikan:

Produk hanya dilepas jika memenuhi spesifikasi mutu.

Functions of Quality Assurance in Pharmaceutical Industry:



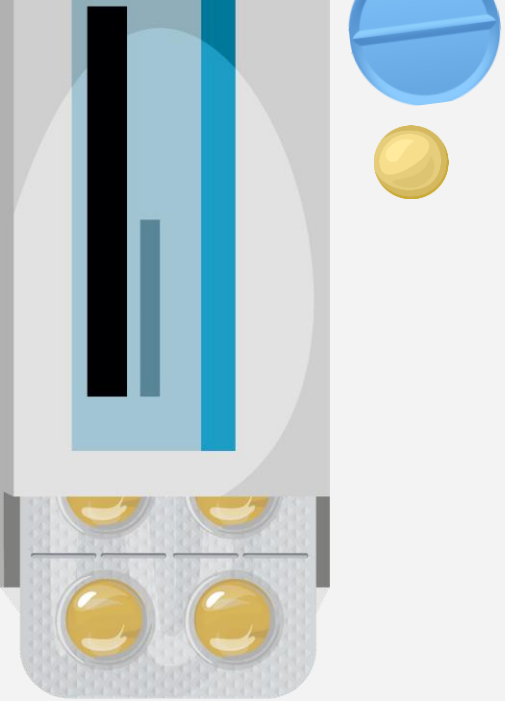
H. Validasi dan Mutu Produk

Jenis validasi:

- Validasi proses
- Validasi pembersihan
- Validasi metode analisis

Tujuan:

Menjamin proses konsisten menghasilkan produk bermutu.



02

QRM (*Quality Risk Management*)

Quality Risk Management in Pharmaceuticals

Pengertian

Pendekatan sistematis untuk:

- Identifikasi risiko
- Analisis risiko
- Pengendalian risiko

Berdasarkan:

ICH Q9 (R1)

Tahapan QRM

- Risk Assessment
- Risk Control
- Risk Communication
- Risk Review

Quality Risk Management

RISK ASSESSMENT

1. Identify risks
2. Analyse risks
3. Evaluate risks

RISK CONTROL

1. Reduce risks
2. Accept risks

RISK COMMUNICATION

RISK REVIEW

Risk Assessment

- Identifikasi bahaya
- Analisis risiko
- Evaluasi tingkat risiko
- Menentukan prioritas risiko

Metode QRM

- FMEA (*Failure Mode and Effects Analysis*)
- Fishbone Diagram
- HACCP
- Risk Ranking

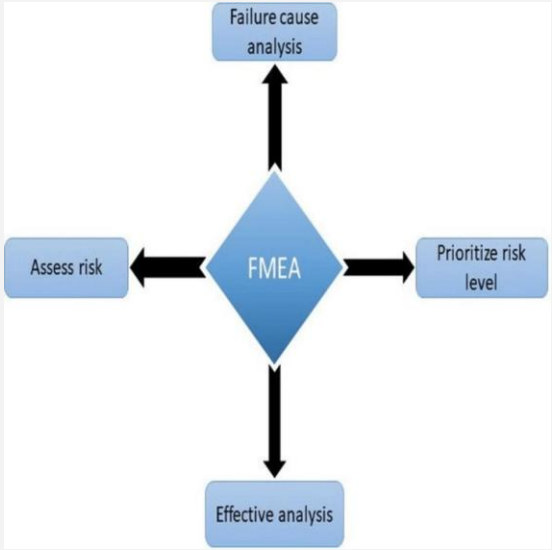
FMEA - *Failure Mode and Effects Analysis*

FMEA (*Failure Mode and Effects Analysis*) adalah metode sistematis untuk:

- Mengidentifikasi potensi kegagalan,
- Menilai tingkat risiko
- Menentukan tindakan pencegahan.

Menilai:

- Severity
- Occurrence
- Detection



FMEA - *Failure Mode and Effects Analysis*

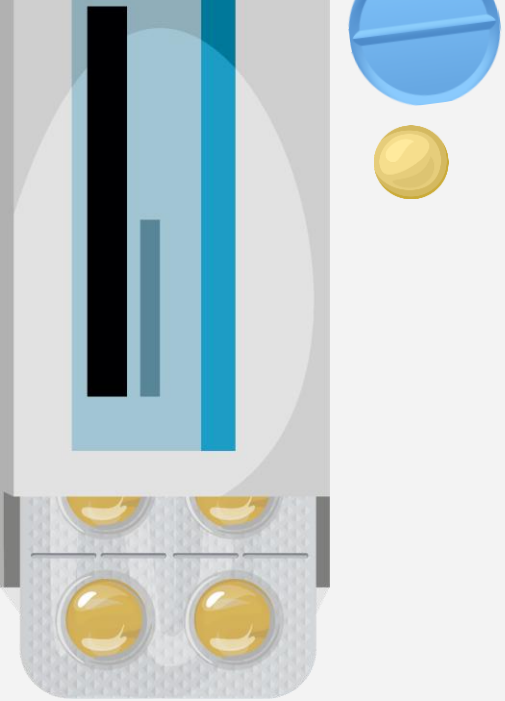
Istilah	Pengertian
Failure Mode	Bentuk kegagalan yang mungkin terjadi
Effect	Dampak kegagalan
Cause	Penyebab kegagalan
Control	Pengendalian yang sudah ada
Risk Priority Number (RPN)	Nilai prioritas risiko

Contoh FMEA

- Risiko: tablet pecah
- Penyebab: tekanan mesin tidak stabil
- Dampak: mutu produk menurun
- Tindakan: kalibrasi mesin dan monitoring

Hubungan CPOB dan QRM

- QRM mendukung penerapan CPOB
- Pendekatan berbasis risiko meningkatkan efisiensi
- Membantu pengambilan keputusan mutu



03

Tugas Mahasiswa

Tugas

Mahasiswa membaca artikel lalu menganalisis:

- Risiko mutu apa yang paling kritis?
- Apa dampak terhadap patient safety?
- Bagaimana GMP mencegah kontaminasi?

Link Jurnal:

https://drive.google.com/file/d/1x8BMTQquxYeGGltS4tWtPYrKX3DYGZk5/view?usp=sharing

Isi Kasus

- Filling produk steril
- Penanganan vial dan stopper
- Risiko kontaminasi
- *Cross contamination*

Risiko Paling Kritis

Kasus	RPN Awal	Risiko
Line clearance tidak dilakukan dengan benar	270	Product mix-up & GMP violation
Filter integrity test gagal/tidak dilakukan	200	Kontaminasi mikroba
Tidak ada QA approval sebelum filling	200	Kesalahan produksi
Dynamic pass box tidak digunakan	128	Kontaminasi cleanroom
Botol kosong tertinggal dalam mesin	112	Kontaminasi & mix-up

Dampak terhadap Patient Safety

- Kontaminasi Mikroba
- Particulate Contamination
- Product Mix-Up
- Ketidaksesuaian Volume Produk

Peran GMP Mencegah Kontaminasi

Cleanroom Control

- Klasifikasi cleanroom
- Tekanan udara
- HEPA filter
- Monitoring partikel
- Prosedur masuk-keluar personel

Peran GMP Mencegah Kontaminasi

Line Clearance

Sebelum produksi:

- Area harus diperiksa
- Sisa batch sebelumnya dibersihkan
- QA melakukan approval.

Dalam jurnal disebutkan:line clearance tanpa QA approval memiliki RPN sangat tinggi (270).

Peran GMP Mencegah Kontaminasi

Sanitasi dan Higiene

GMP mewajibkan:

- Gowning procedure
- Hand hygiene
- Sanitasi alat
- Cleaning validation.

Thanks!

Do you have any questions?

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Research & Reviews: Journal of Pharmaceutics and Nanotechnology

An Overview on Design of Experiment in Product Formulation

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Review Article

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ABSTRACT

The pharmaceutical product development process requires specific domain knowledge and expertise in specific area. Design of Experiment is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Keywords: Design of Experiment, Product Formulation, Drug-Excipients, Tablet Granulation, Dissolution testing

INTRODUCTION

A drug candidate must be chemically, physically stable and manufacturable throughout the product life cycle and manufacturing process,). In addition, many quality standards and special requirements must be met to ensure the efficacy and safety of the product. It is always essential to establish the (target product profile) TPP so that the formulation effort will be effective and focused [1,2]. The TPP usually includes dosage form, route of administration, special-delivery requirement, maximum and minimum doses, and aspects of pharmaceutical elegance (appearance). The TPP guides formulation scientists to establish formulation strategies [3-12] and keep formulation effort focused and efficient. After the TPP is clearly defined, many studies must be conducted to develop a formulation. DOE is an effective tool for formulation scientists throughout the many stages of the formulation process and can help scientists make intelligent decisions. These steps include optimization of product, drug-excipient compatibility [13-19], process feasibility studies, formulation, and scale-up, and characterization of manufacturing process.

DESIGN OF EXPERIMENT

Design of Experiment [20-22] is a systemic approach to determine the relation between independent process/product variable and their effect on response variable **(Figure 1).**

Terminology used in Design of Experiment

1. Independent Variables: These variables are directly under the control of formulation scientist
2. Dependent variables: These variables are result or response
3. Factors: There are two types of factors are there Qualitative and Quantitative factors
4. Level: These are the values assigned or designated for factors
5. Responses surface plot: A 3-D graphical representation between independent factor and dependent factor
6. Interaction: It gives the overall effect of two or more variables means lack of additivity of factor effects
7. Effect: Magnitude in change in response

8. Contour plot: These are two dimensional representation of response obtained by plotting one independent variable against another keeping the response and other variable constant
9. Contour lines: curves obtained over counter plot to a response value
10. MLRA (Multiple Linear Regression Analysis): The technique which express mathematically in form of quadratic equation the linear relationship between various independent variable and dependent variable (Response)
11. Orthogonality: When effect is due to the main factor of interest and no interaction
12. Confounding: Lack of Orthogonality is termed as confounding or aliasing
13. Resolution: Measurement of degree of confounding

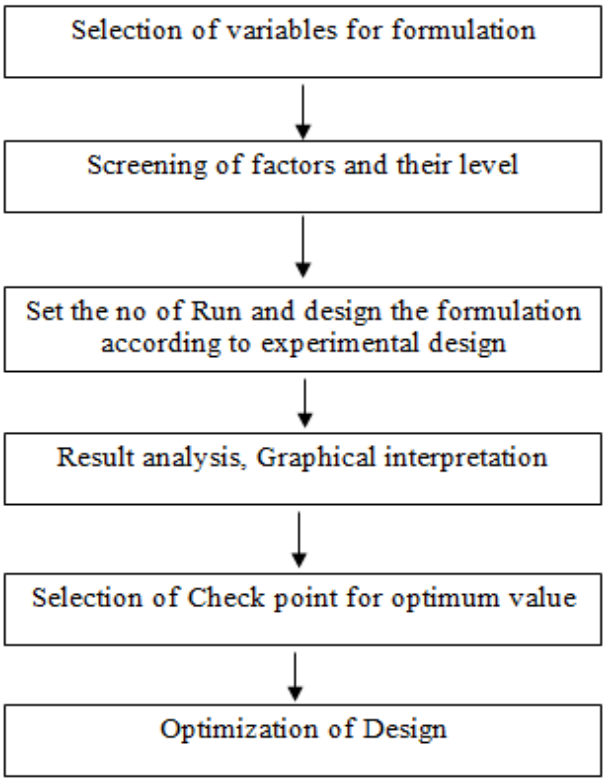

Figure 1: Flow Chart in Design of Experiment.

Types of Experimental Design

A. Completely randomized designs.
B. Full Factorial designs.
- Two-level full factorial designs.
- Full factorial example.
- Blocking of full factorial designs.

C. Fractional factorial designs.
- A 23-1 half-fraction designs.
- How to construct 23-1 designs.
- Confounding.
- Design resolution.
- Use of fractional factorial designs.
- Screening designs.
- Fractional factorial designs summary tables.

D. Randomized block designs.
- Latin squares.
- Graeco-Latin squares.
- Hyper-Graeco-Latin squares.

E. Plackett-Burman designs.
F. Response surface (second-order) designs.
- Central composite designs.
- Box-Behnken designs.
- Response surface design comparison.
- Blocking a response surface design.

G. Adding center points.
H. Improving fractional design resolution.
- Mirror-image foldover designs.
- Alternative foldover designs.

I. three-level full factorial designs.
J. Three-level, mixed level and fractional factorial designs

Application of Experimental Design

- Compatibility studies between Drug-Drug [23] and Drug-Excipients
- Granulation
- Pre Tablet Granulation [24-29]
- Oral-controlled release formulation [30-33]
- Modelling of properties of powder [34-41]
- Dissolution testing [42-62]
- Tablet formulation [63-78]
- Coating of tablets
- Extrusion-Spheronization
- Inhalation formulation [79-90]

Software used in Experimental Design

- DESIGN EXPERT
- FACTOP
- OPTIMA
- XTAP
- OMEGA
- ECHIP
- MULTI-SIMPLEX
- NEMRODW
- GRAPHPAD PRISM
- DoE PC IV
- MINITAB
- MODDE

CONCLUSION

Over the past decade the practice of optimization of formulation has increased. DoE optimization would further gain increased acceptance as a priceless developmental tool. DOE is an effective tool for formulation scientists starting from pre-formulation stage to various stages of clinical trial in product development. What is essentially needed for realization of this quality breakthrough is the workable basic knowledge of computers and statistics, coupled with persistence, patience, perseverance and passion. Different techniques used in optimization [91-100] mainly reduces the number of trial thereby cost and time consumed in product development.

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Method validation: A complex concept

I welcome all to the current issue of Pharmaceutical Methods, and thank all our contributors.

The reader will find that many of the articles that are published in the current issue refer to method validation and in particular to the International Conference on Harmonization (ICH) guidelines as the basis for their approach. The ICH was launched in 1990, with the objective of harmonizing technical and regulatory approaches in the Pharma-Chem industry between international markets, with the ultimate objective being the protection of human health.

Every analytical chemist and process owner knows the sequence of analytical validation requirements [linearity, level of detail (LOD), level of quantification (LOQ), precision, accuracy, robustness, etc.]. The requirements are universal; a measure to assure the quality of the results. However, the ICH along with organizations like the International Organization for Standardization (ISO) and the Food and Drug Administration (FDA) view their role as progressing and evolving the concept of analytical quality assurance into a multidimensional approach. Consider for example the 'simple' concept of 'precision'. In the Pharma-Chem industry there are no simple concepts, only 'far reaching' concepts. Determining the precision of the quantitation of a particular drug component using a given method demands the evaluation of system precision, sample precision, intermediate precision, and long-term and intra-laboratory precision; refer to the onion-like diagram below [Figure 1].

Precision (and of course accuracy) is also linked with the determination of process capability, process stability, and process improvement measures. Along with these considerations, regulators demand extensive investigative procedures to be deployed in the case of out-of-specification results.

Additionally, the analytical chemist and process operator must of course display a high level of competence, and along with the competence comes a personal responsibility. A veritable sword of Damocles is suspended above the head of each analyst, which extends right up, along the hierarchical chain of the organization! Naturally these measures are in place for

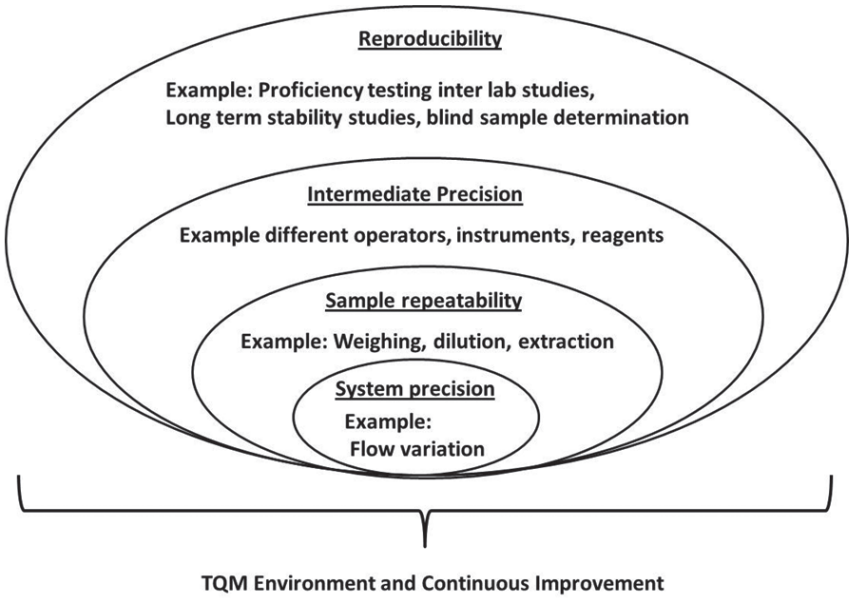

Figure 1: Multiple levels of precision

a very good reason: to prevent harm to the consumer, sometimes a very vulnerable customer.

In my opinion, one very innovative and enabling approach to the quality assurance of analytical methods is the process approach, advocated in recent years by ISO and a stalwart of process engineers. In its simple form, this involves producing a comprehensive and interlinked flow diagram of the process (the process may be a single analytical method using this definition) and sub-processes, and using this map as a basis for comprehending the process, controlling it, identifying the regions where data must be collected and analyzed, where SOPs must be written, and so on.

The other advantage of the process approach is that it facilitates a logical approach to quality risk analysis and thus management by expert teams. Quality risk management is indispensable in the analytical environment of the pharmaceutical sector. Risk management is a systematic and team-driven approach that tries to anticipate possible quality aberrations, their probability, their severity, and their consequences for the consumer.

Ultimately the point of all of this is that method validation is the tip of the iceberg when it comes to the control of quality of analytical methods in the pharmaceutical environment, where events of the past have taught us that there can be no room for complacency.

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