IPEC FEDERATION

The International Pharmaceutical Excipients Council

Incorporation of Pharmaceutical Excipients into Product Development using Quality-by-Design (QbD)

First Version
2020

This document represents voluntary guidance for the excipient industry and the contents, unless otherwise specified, should not be interpreted as regulatory requirements. Alternatives to the approaches in this Guide may be used to achieve an equivalent excipient quality assurance level.

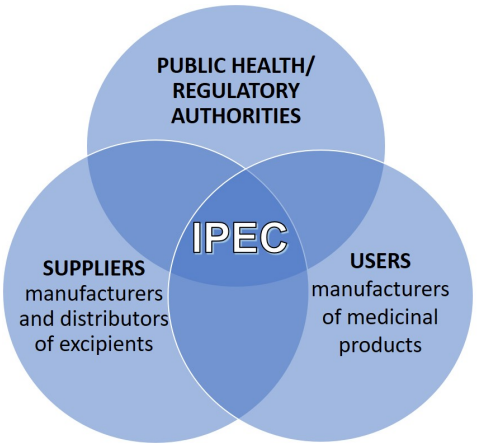
This guide was created to help companies understand current expectations on this topic and is not intended for use by third parties to conduct audits. The content of this guide cannot be reproduced without the written authorisation of the IPEC Federation Management Body.

FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and end-users. At the current writing, there are regional pharmaceutical excipient industry associations located in the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to international excipient standards development and harmonization, new excipient development and introduction, and best practice and guide development concerning excipients.

IPEC has three major stakeholder groups;

1. Excipient manufacturers and distributors, defined as suppliers in this document
2. Pharmaceutical manufacturers, defined as users in this document
3. Public health and regulatory authorities



This Guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the rules and regulations applying to excipients will vary from region to region and country to country. In addition, the rules and regulations are continually evolving. It is the responsibility of users of the Guide to determine whether there are any additional legal or regulatory requirements, in addition to the recommendation given in this Guide, applicable to a particular region or country in which they are doing business.

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This Guide offers current best practice and voluntary guidance on the incorporation of excipients and excipient variability into Quality-by-Design (QbD) pharmaceutical finished product development programs. It is important that the reader confirms this is the latest version of the guide as found on www.ipec-federation.org or regional IPEC websites.

NOTE: Refer to the "International Pharmaceutical Excipient Council Glossary: General Glossary of Terms and Acronyms" for definitions [1]. The first use of a term found in the glossary will be in **BOLD**.

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ACKNOWLEDGEMENTS

This guide was developed by the International Pharmaceutical Excipients Council members representatives. IPEC Federation, or in short the Federation, is a global organisation that promotes quality and safety in pharmaceutical excipients. The Federation consists of the five existing regional IPECs: IPEC-Americas, IPEC China, IPEC Europe, IPEC India, IPEC Japan. The representatives who worked on this Guide are listed below:

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1 INTRODUCTION

1.1 Purpose

This **Guide**'s intent is to:

- introduce Quality-by-Design (QbD) and pharmaceutical formulation development concepts to **excipient** manufacturers and suppliers,
- provide an explanation of how changes in pharmaceutical formulation practices, due to the introduction of QbD, impact excipient manufacturers and suppliers,
- provide understanding for excipient manufacturers and suppliers as to what excipient **user**s will likely require when applying QbD principles during product development, and
- provide understanding to excipient users and regulatory agencies regarding what may or may not be possible when considering the impact of excipient variability in the application of QbD principles during product development.

This Guide includes recommendations related to impact of excipient variability on drug product quality during development and to justify management of excipient variability in the control strategy.

It contains useful explanations and suggestions for pharmaceutical excipient makers and users.

1.2 Scope

This Guide is applicable to excipient use throughout the pharmaceutical product development process using a Quality by Design (QbD) approach described by the International Conference on Harmonization (ICH) Q8 [2] as well as other applicable ICH **Guidelines** such as ICH Q9 [3], Q10 [4], Q11 [5], and Q12 [6].

Persons using this Guide should apply appropriate risk management principles to ascertain what options may apply for excipients in their intended use. This Guide's intent is to enhance communication between excipient maker and excipient user related to QbD relevant information. The excipient maker and excipient user should discuss and negotiate the necessary parameters for control and who will accept responsibility for the testing.

The QbD concepts in this guide are applicable to both new drug applications and generic drug applications. The pharmaceutics primer in Sections 2 and 3 is based primarily on small molecule oral solid dose form development but the general principles introduced in Sections 4 and 5 can be applied in other development areas, including biologics.

Other relevant guides may complement this guide, such as:

- IPEC Qualification of Excipients for Use in Pharmaceuticals [7]
- IPEC Excipient Composition Guide [8]

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- The Joint IPEC-PQG **Good Manufacturing Practices** Guide for Pharmaceutical Excipients [9]
- IPEC-Americas Quality by Design (QbD) Sampling Guide [10]
- The IPEC Risk Assessment Guide for Pharmaceutical Excipients: Part 1 – Risk Assessment for Excipient Manufacturers [11]
- NSF/IPEC/ANSI 363 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients [12]

Note: While this Guide is concerned with excipients, APIs are also a source of variability (common cause and special cause variation).

1.3 Principles Adopted

This guide is intended to apply internationally. Excipients are a diverse group of materials that often have primary use in non-pharmaceutical applications. It is not possible to address every option or alternative related to all excipient types. Rather, broad principles will be discussed, and the reader can then apply those principles to their operations as appropriate. The extent of QbD adoption by different global regulatory authorities varies, and feedback from regional regulatory authorities should be sought early in development.

This Guide is intended as an advisory document. When considering use of this Guide, each manufacturer, **distributor**, or **drug product** manufacturer should consider how the Guide may apply to that specific manufacturer's product and processes. Excipients should always be sourced from original manufacturers or authorized distributors. Suppliers unable or unwilling to identify an original manufacturer are unlikely to provide excipient data required to apply a QbD strategy. QbD requires an understanding of excipient attributes impacting finished product performance making excipient data essential. Due to excipient diversity, some principles in the guide may not be applicable to certain products and processes. The terminology “should” and “it is recommended” do not necessarily mean “must” and common sense should be used during guide use.

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2 BACKGROUND AND GENERAL GUIDANCE

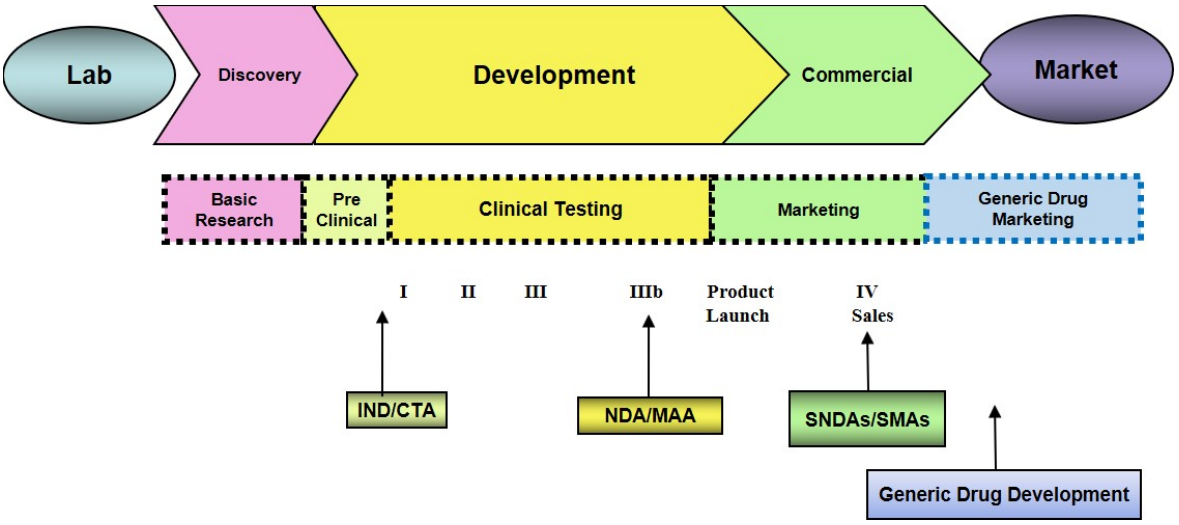
2.1 An Introduction to Drug and Drug Product Development

Pharmaceutical drug development (small molecules and biologics) is a highly regulated undertaking. Development often requires several stages over multiple years, including:

- candidate selection,
- preclinical testing,
- phase I clinical testing,
- phase II clinical testing,
- phase III clinical testing,
- phase IV post launch (post marketing surveillance), and
- generic drug development.

Refer to Annex A for pharmaceutical development activities.

Figure 1 Pharmaceutical Drug Development Timelines



IND – Investigational New Drug / CTA – Clinical Trials Application
NDA – New Drug Application /MAA – Marketing Authorization Application
SNDAs – Supplemental New Drug Applications / SMAs – Supplemental Marketing Applications

An initial regulatory review takes place prior to commencing development and is then ongoing throughout the clinical testing, prior to submitting the marketing application, and post launch.

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Different formulations may be used at the different stages during development and for different study types. These differences often depend on drug molecule type (for example, small molecules vs. biologics). The formulation requirements for product safety testing may be different from those for clinical testing. In addition, formulations used in early clinical testing may differ markedly from that used in later clinical testing and/or for the commercial product. It is common for the targeted commercial formulation to be used in Phase III clinical trials, but not obligatory. Typically, with small molecule active pharmaceutical ingredients (APIs), it is unlikely for a Phase I clinical formulation to be used as the commercial formulation and very unlikely for the safety testing formulation to be used for commercial purposes.

Regulatory authorities require that all pharmaceutical products to be administered to humans, or to animals as veterinary medicines, be manufactured to the requisite standards of current good manufacturing practice (cGMP) based upon development stage [13]. As a result, APIs (drug substance) and excipients also must be manufactured to appropriate GMP standards and meet appropriate **specification**s.

Pharmaceutical products may be manufactured by **batch** or **continuous processing** methods. For drug products manufactured using batch processing, pharmaceutical formulation manufacturing process scale-up must be considered also. For continuous processing, an extension of run time should also be considered. Commonly, formulation projects begin with small laboratory experiments and are scaled up as clinical or commercial needs demand and API supplies become available. During scale-up activities, in addition to defined GMP requirements, drug product manufacturers need to consider what, if anything, regulatory authorities might require for equivalence.

Under traditional pharmaceutical development approaches (prior to the issuance of the most recent FDA **Guidance** on process validation in January 2011 [14], and the corresponding EU Guidance of February 2014 [15]), commercial formulations were subject to formal **validation**, based on three commercial-scale batches. Aspects of the qualitative and quantitative formulation and the manufacturing process are fixed depending on the detail and content of the individual regulatory filings, and many post-validation changes require some form of regulatory review (see e.g. the FDA SUPAC Guidances [16-18]). Under the 2011 FDA Process Validation Guidance, the traditional 'minimum of three batches' approach to validation is no longer applicable. "The number of batches should not be considered as an acceptance criterion, instead, it should be considered as a means to acquire the samples and information needed to ensure process control" [19]. Compliance is neither predictive nor a measure of robustness, so according to QbD principles, all batches contribute to continued **verification** throughout the product lifecycle. Using this QbD approach, discussions related to excipient **critical material attributes** (CMAs) may be necessary to ensure robust drug product formulation development. A CMA is an attribute requiring additional control in order to control a **critical quality attribute** (CQA) of the finished product. CMAs are defined and discussed in more detail in Section 4.3

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Scale-up at the excipient manufacturer can potentially confound results of preceding experiments. Univariate change control and compliance conceal hidden risk of drift due to change in manufacturing scale. Comparability protocols should include multivariate analysis (MVA) [37]. Absence of drift is a useful complement to compliance data. If drift is detected by MVA, causes should be investigated. Uncontrolled drift increases risk of an excipient variability interacting with a finished product criticality, potentially invalidating models and control strategies based on data from experiments performed at smaller scale.

For drug products manufactured using continuous processing methods, scale-up may refer to increased throughput in the existing processing line, addition of a like-for-like or a new line, or a larger continuous processor. It will be necessary to demonstrate that longer running times, increased throughput, or increased capacity do not adversely impact product quality design space or control strategy. In batch manufacturing, as scale increases, the number of experimental batches decreases such that smaller scale design of experiments (DoE) cannot be replicated, which confirms the importance of continued verification and monitoring using multivariate analysis in QbD. DoE applies to both continuous manufacturing and batch processing.

2.2 Quality-by-Design

QbD is a systematic approach to pharmaceutical drug product design and development, taking into account the many variables associated with drug product manufacture including a full understanding of ingredients (APIs and excipients), their inherent variability, and the processes and equipment used during their manufacture. QbD is part of the larger Quality Planning initiative proposed by J. M. Duran in the mid-1980s [20]. QbD is NOT new but the concepts are being more frequently adopted by the pharmaceutical industry. The basic elements of QbD as they relate to the pharmaceutical industry include:

- scientific, risk-based, holistic, and proactive approaches to pharmaceutical development,
- deliberate design effort from product conception through commercialization, and
- understanding how material attributes and process parameters relate to finished drug product performance.

In 2009, QbD was included in the ICH Q8(R2) Guideline and eventually became one of the cornerstones of the ICH Quality Roadmap:

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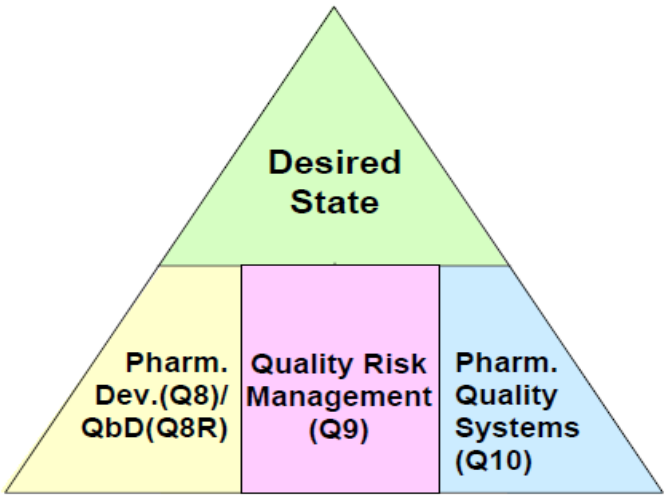
Figure 2 ICH Quality Roadmap [21]



It was also one of the cornerstones of the US FDA's 'Quality in the 21st Century' initiative. The basic philosophy is that, "Quality cannot be tested into a product or operation, it must be built in during the whole development and manufacturing cycle."

QbD is based on the premise that during development of pharmaceutical finished products, pharmaceutical companies invest time and effort up-front to identify and obtain enhanced understanding of the material attributes and **critical process parameters** (CPPs) which significantly affect product CQAs.

This should result in more robust products and processes, and may reduce the post approval regulatory burden. For example, it may be possible to show that changes within the design space (see below) will no longer require prior approval, but will simply be reported in the annual report.

When used effectively, QbD will ensure that every drug product batch manufactured within the design space conforms to specifications and that the control strategy is still valid, thus potentially eliminating the need to reject, **rework**, or **recall** batches due to out-of-specification (OOS) failure. Results from manufactured batches can be leveraged to support a continued verification program. Regulatory process validation guides [14,15] seek to provide additional flexibility for process validation approaches across the process life-cycle (e.g., through the application of continued process verification).

Although formulations designed and manufactured for safety testing and early phase clinical trials may not require the same level of understanding and process optimization as required for the final commercial product, experience gained from such formulations can provide a scientifically valid framework for identifying key process and formulation parameters, and thus facilitate effective process optimization used to support a robust commercial formulation (i.e., the design space).

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It is also important to emphasize that QbD is not just about experience. QbD requires product design using techniques (e.g., statistical DoE) that provide a scientifically valid framework for identifying all key process and formulation parameters, thus facilitating effective process optimization. This, coupled with an effective risk assessment strategy to identify interactions between different material attributes and/or process parameters, can be used to ensure that factors potentially impacting product quality are clearly identified and assessed. QbD requires the use of appropriate experimental designs (e.g. DoE – see Section 2.2.1) and analysis of the results by means of multivariate statistics. A univariate approach to QbD projects is less likely to succeed [22].

2.2.1 Design of Experiments (DoE)

DoE by itself is not QbD, but rather, it is a tool to investigate interactions between different material attributes and process parameters having the potential to influence pharmaceutical finished product performance. It is sometimes also referred to as experimental design (see also ICH Q8(R2)). There are numerous DoE approaches which may be appropriate for drug product design, development, and scale-up.

Statistically justified experimental designs, when properly executed, will allow confirmation and/or identification of CMAs, CPPs, and any interactions between them that can impact product CQAs. Based on the DoE results and a subsequent risk assessment, a design space can be created that will establish the operating range (formulation and process), within which a product can be routinely manufactured to consistently meet required quality standards and performance attributes. This design space can be used to establish the control strategy (see below).

2.2.2 Design Space

Design space is defined in ICH Q8(R2) as follows:

> "*The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.*"

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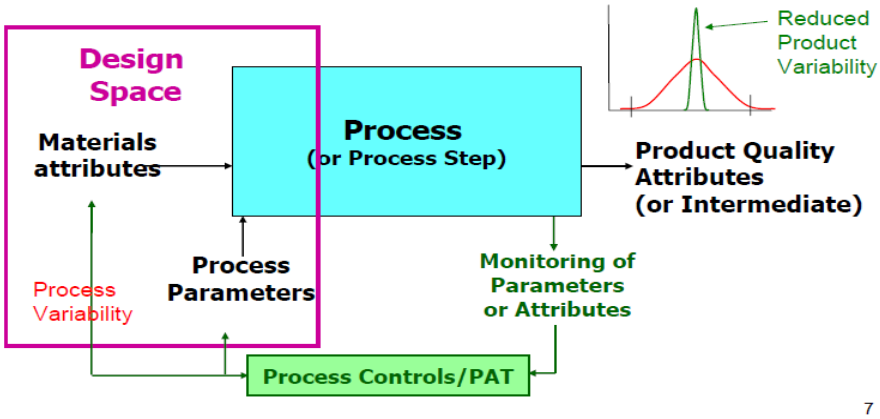
Figure 3 Reducing Product Variability [21]



Thus, the design space concept, when utilized and approved by the appropriate regulatory/health authority, would permit the drug product manufacturer to continue to optimize the formulation and process within the design space during routine commercial manufacture, e.g. through the use of evolutionary operations (EVOP) or an equivalent technique and reporting such changes through appropriate regulatory mechanisms without the need for prior authorization.

2.2.3 Control Strategy

Control strategy is defined in the ICH Q8 (R2) document as follows:

> "*A planned set of controls derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10).*"

The control strategy is developed from the design space. It is the total of in-process controls, finished product testing, and any other checks and balances that control final product quality and consistency. ICH Q10 highlights the importance of effective processes for maintaining the control strategy through the product lifecycle.

2.2.4 Change Control

Products are subject to numerous changes throughout their lifecycle, and ideally subject to on-going multivariate monitoring. Univariate change control based on compliance risks cumulatively builds inherent risk of hidden drift, which may lead to unexpected failures and possibly invalidating models and the control strategy. Enhanced understanding using a QbD approach also will likely provide information supporting design space expansion.

Note: Expansion of the design space requires prior authorization.

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2.2.5 QbD Stages

QbD generally has several iterative stages, covering the product lifecycle, and should include a continuous improvement loop based on additional information learned [14].

QbD stages would be as follows:

- Define the CQAs [1] as formalized in the quality target product profile[2] (QTPP).
- Characterize API properties (pre-formulation).
- Review relevant prior knowledge.
- Identify potential manufacturing approaches.
- Identify potential excipients (from excipient compatibility studies).
- Design potential formulations and processing.
- Complete initial risk assessment to identify potential excipient CMAs and CPPs.
  Note: ensure dialog with the supplier to identify needs and determine risks
- Define the DoE.
- Evaluate robustness of the formulation and process to determine if formulation and/or process changes may be needed.
- Finalize risk assessment.
- Establish the design space and control strategy (optional).
- Scale-up
  Note: There may be more than one scale-up.
- Confirm design space and control strategy for commercial manufacture.
- Submit marketing authorization application.

Note: There are other activities that will be undertaken in support of QbD formulation development, including, but not limited to: analytical method development (chemical, physical and microbiological), stability, bioequivalence, etc.

A new product development project incorporating QbD is outlined in Annex A.

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1 ICH Q8(R2) defines a CQA as: a 'physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality'.

2 ICH Q8(R2) defines a QTPP as 'A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product'. The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include: intended use in clinical setting, route of administration, dosage form, delivery, systems; dosage strength(s); container closure system; therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed; drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

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2.3 Excipients

2.3.1 General

Excipients are 'substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system' [1] and/or pharmaceutical formulation.

Excipients are a very diverse group of substances and include solids, liquids and gases, and semi-solids. Chemically, excipients include simple gases (e.g. nitrogen), inorganic chemicals (e.g. sodium chloride, calcium carbonate, etc.), and organic chemicals of either natural or synthetic origin ranging from comparatively simple molecules such as ethanol through larger molecules such as fatty acid esters to high molecular weight polymers.

Together with APIs, container-closure systems and the unit processes, excipients are essential to pharmaceutical products. Unformulated, most APIs are not convenient for patients, and may not provide optimum therapeutic benefit. Excipients are used to help formulate APIs into medicinal products (for clinical or commercial use), which can be administered to patients and provide the intended therapeutic benefit.

2.3.2 Excipient Manufacture

Excipients are manufactured by many different processes. These processes may range from harvesting and extraction of natural products, mining natural minerals through to entirely synthetic manufacture. Manufacturing scale also varies; most excipients are typically manufactured in significantly greater quantities than APIs or pharmaceutical finished products. Manufacturing processes may include **batch manufacture**, continuous processing or a combination of batch and continuous processing. The latter combined operations may be referred to as hybrid manufacturing.

2.3.2.1 Batch Manufacture of Excipients

In batch manufacture, one or more operations are carried out over a period on defined quantities of raw materials. Batch size is determined by a limiting equipment working volume or capacity. The batch of finished excipient is traceable to the input **lot**s of raw materials.

2.3.2.2 Continuous Processing in the Manufacture of Excipients

In continuous processing, raw materials are continually supplied, and product removed, from the equipment train, at predetermined rates. The quantity of finished excipient produced is a function of run time and cannot be unequivocally linked to the lots of raw materials. The equipment train will typically consist of equipment for all the processing steps linked in series. For high volume production the risk of failure is mitigated by dividing the output into sublots to minimize comingling of out-of-specification material. The excipient batch/lot number may therefore be specific to output during a defined time period or specified amount of material.

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2.3.3 Excipient Composition

There is often a balance between excipient composition and **functionality**. Excipient functionality can depend on **concomitant components** (substances in addition to the main components). Concomitant components are part of the excipient **composition profile** and should be not construed as being undesirable, nor confused with the presence of added substances (**additives**, **processing aid**s or other components).

> **Note 1:** Water can be classified as either a concomitant component or an undesirable inorganic component depending on its role in the excipient or effect on finished drug product.
>
> **Note 2:** Fatty acid esters synthesized from homologous series of acids and alcohols may yield tens of esters in addition to the nominal excipient entity.
>
> **Note 3:** The nominal excipient entity may not even be the major component**.** For example, pharmacopeial grades of stearic acid may contain as little as 40% stearic acid, with up to 50% palmitic acid.

There are some exceptions to this, most notably for excipients intended for parenteral administration, where chemical purity may override some aspects of performance. Excipients may also contain permitted additives and residual processing aids. **Co-processed excipient**s are multi-component by design [36]. Further information and discussion on excipient composition are provided in the IPEC Excipient Composition Guide [8].

2.3.4 Excipient Performance

Finished pharmaceutical products typically contain excipients because they assist in drug product manufacture and API delivery. Excipients may contribute to pharmaceutical finished products by allowing product manufacture, assisting in product stability, and/or allowing the product to function as intended after administration. These properties are referred to as 'functionality' or 'performance' [23]. Functionality is the rationale for excipient selection but excipient performance in a specific formulation may be dependent on overall formulation composition and manufacturing process.

2.3.5 Excipient Variability

Excipients are inherently variable as they are not controlled at an individual parameter level. For example, with polydispersity of particle size, molecular weight and/or chemical composition, which may be process/supplier dependent. Excipient variability may impact drug product robustness and performance, but not all causes of variability are well understood. Excipient manufacturers can control excipient variability only within the limits of their process capability and for which the processing equipment was designed and constructed [7]. Process capability is a general statistical concept based on the ratio of the specification limits to the process variability. If the variability is the same as the specification range the process capability is one, with no room for error. The higher the process capability the lower the risk of failure. Less than one means that not

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all batches will meet specification. Therefore, arbitrary narrowing of a specification by users may adversely impact sustainable excipient supply. Robust formulations are not critically impacted by typical excipient variabilities, not all of which may be reflected in the specification.

Variability in the raw materials used in excipient **manufacture** can arise from causes such as, but not limited to:

- Excipients derived from plants or animals can vary from:
  - ***Weather conditions during:***
    - growing season,
    - harvesting,
    - transportation to processing sites,
    - raw material storage,
    - processing,
    - packaging, storage, and **distribution**,
    - climate change, and
    - natural disasters.
  - ***Composition related to environmental conditions in different geographic regions (e.g. soil, ocean)***
    - nutrient levels,
    - heavy metals (elemental impurities),
    - pollution, and
    - other cations.
- Mineral excipients can vary with:
  - ***Geographic source of the excipient or crude ore***
  - ***Processing conditions***
    - calcining temperature and
    - type of milling
- Synthetic materials can vary with:
  - ***The composition of products derived from crude oil or gas feedstock varies with well location:***
    - sulfur content,
    - heavy metals content and range,
    - distribution of the different organic components, and
    - multiphase vs single phase reactions.

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In addition, the equipment train used in the process and the type of processing and unit operations included may all influence variability. Various excipients are continuously manufactured in many metric tons per annum. Results reported on a CoA will often be a composite or average, potentially underestimating variability. Not all excipients will have the crystallization or precipitation steps typically used to purify fine chemicals. Users should discuss inherent variability with the supplier and their capability to supply product as it relates to the user's needs. It is the responsibility of the user to identify potential CMAs for the excipients used in their formulations but the suppliers may be able to assist. A risk-based approach will probably be appropriate.

2.4 Pharmaceutical Products

2.4.1 General

API(s), excipients, manufacturing process(es), and packaging components are combined to make pharmaceutical products suitable for patient administration.

There are many pharmaceutical formulation types and several different routes of administration.

It is important to understand both the potential formulation type and intended route of administration, the components (API(s), excipients, and packaging), and the unit processes likely used in pharmaceutical product manufacture in order to perform a relevant risk assessment, which properly supports the DoE and thus project success.

QbD principles apply to all dosage forms. There may be additional constraints on excipient specifications imposed by the route of administration.

2.4.2 Excipient Function

Excipients may function to aid processing, improve stability, aid in drug product administration, or influence its performance after patient administration (e.g. modified release). An excipient may perform more than one function in a formulation.

Excipients may also have properties detrimental to the proper drug product performance. These potential disadvantages should be recognized (e.g. the effects of over blending magnesium stearate on dissolution and tablet hardness). Potentially detrimental effects should be part of the risk analysis performed in support of the development program.

2.4.3 Excipient Grades

Excipients may be offered in different **grades** for different routes of administration or to provide performance characteristics in the formulation. Grades are typically differentiated based on physical attributes, e.g. particle size or viscosity. However, in some cases, differentiation may be based on chemical differences, e.g. degree of substitution for hypromellose, degree of neutralization for sodium starch glycolate. Different grades may perform differently depending on application but not in all cases.

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Evaluation of potential CMAs may include investigation of non-pharma excipient grades as part of the risk assessment supporting the DoE. This is discussed further in the IPEC-Americas QbD Sampling Guide [10].

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3 INCORPORATION OF EXCIPIENTS INTO THE FORMULATION

Typical pharmaceutical formulations comprise API(s) and excipients, which are combined to produce dosage forms. Excipients are used to formulate APIs into pharmaceutical products, which are administered to patients. Excipients typically exhibit variability (see Section 2.3.5 Excipient variability). It is the responsibility of the user to assess the impact of API, excipient and process variability on finished product CQAs.

3.1 Excipient Selection

Excipient selection will be governed by route of administration, process and formulation type (from the QTPP).

Excipients selected should neither adversely impact the API(s) (e.g. absence of any chemical interactions) or be adversely impacted by the process (e.g. no unacceptable degradation of the excipient due to the processing conditions). To this end, the excipient selection process should include excipient compatibility studies. A full discussion of excipient compatibility testing is beyond the scope of this Guide. However, it should be noted that excipient compatibility testing will only indicate those excipients to be avoided. Absence of problems on compatibility screening does not mean problems will not arise during drug product stability testing. Excipient incompatibilities may not be due to interaction with the labelled entity but with minor components, which might be source dependent. Excluding too many excipients using aggressive screening conditions runs the risk of compromising finished product quality due to limited excipient choices, which are chemically compatible but are of less than optimal manufacturability.

In order to avoid the time loss associated with stability failures, it is common for more than one preliminary formulation to be developed using different excipients (where possible). From knowledge of QTPP requirements and results from excipient compatibility testing, a list of potential excipients can be assembled. Final selection of preferred excipients will depend on:

- The nature of the API (dose, solubility and other physical properties), and
- The type of processing required to manufacture the dosage form.

Excipient choice will also likely be influenced by formulation scientist experience and company policies and procedures (e.g. platform formulations, preferred excipients, etc.). Even in the case of formulation development for a new drug candidate, it will be possible to leverage experience gained from other projects. Other useful excipient information sources and their application include: The Handbook of Pharmaceutical Excipients [24], USP-NF General Chapter <1059> Excipient Performance [25] and Ph. Eur. General Chapter 5.15 Functionality-related characteristics of excipients [38].

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3.2 Formulation and Process Design and Development

Once excipients are identified and preliminary formulations defined, formulation and process design can commence. Early formulation and process design objectives are two-fold:

- establish formulation composition, and
- establish processes necessary for formulation manufacture.

Once formulation and processes are defined at laboratory scale, the project can advance to achieve the enhanced understanding required of QbD development through the stages of:

- excipient risk assessment with respect to the formulation and processing,
- design of experiments (DoE),
- design space and control strategy identification, and
- scale-up.

Both excipient performance and excipient variability impact on CQAs should be a DoE output. However, as discussed in Section 2.4.3, some excipient characteristics will have a greater influence on performance than others in any given application.

3.3 Risk Assessment

An understanding of the excipient's advantages and limitations as they relate to the intended application, coupled with an appropriate risk analysis, will facilitate identification of excipient characteristics most likely to impact product performance (manufacturing, stability or *in vivo* performance). The risk assessment should evaluate the potential for the individual excipient characteristics to impact the final pharmaceutical product performance [11, 39, 40].

Risk has been defined as [26]:

> "*The combination of the probability of occurrence of harm and the severity of that harm.*"

For risk assessments related to pharmaceutical products, the likelihood of detection of the harm should also be considered. The risk will be higher if the likelihood of detection is low. In the context of pharmaceutical excipients, risk of harm can arise in several ways:

- direct harm to the patient through inclusion of the excipient in their medicine (e.g. use of arachis oil in a formulation given to a patient with a peanut allergy), and
- indirect harm to the patient because the formulation does not deliver the drug to the patient in the required manner (e.g. the formulation fails to release the drug at the required rate and there is insufficient therapeutic effect, or the drug is released too quickly and the patient suffers from side-effects).

In addition, there are other potential risks associated with the use of the excipient, including:

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- the risk that the excipient will somehow not perform as intended and/or interfere with the manufacturability of the medicine,
- the risk that there is an unanticipated interaction between the excipient and the API leading to the degradation of the API and sub-therapeutic dosing, and
- the excipient could potentially interfere with the API absorption, distribution, metabolism, or excretion.

In order to assess the potential risks associated with excipients, it is necessary to consider the following:

- excipient chemistry, including its composition profile,
- physical properties of the excipient,
- excipient microbiological characteristics,
- how it will be used (route of administration and type of dosage form),
- process(es) used to manufacture the pharmaceutical product, and
- necessary performance attributes of the finished product (from the QTPP).

There are several ways in which risk analysis may be assessed; however, risk analysis is typically performed in several stages:

- Identify potential risks associated with excipient use in specific applications.
- Examine each risk and classify it according to:
    - severity of the harm,
    - probability of it occurring, and
    - likelihood of the harm being detected.
- Assess which excipients to exclude because the risks are unacceptably high and which excipients to include in the DoE.

There are several means by which risks may be identified, including Ishikawa diagrams (also referred to as 'fishbone' diagrams, or cause and effect diagrams) and bow tie diagrams. The choice of a technique is beyond the scope of this Guide. Risk classification is usually by means of some form of risk matrix.

> **Note:** risks are known entities which can be quantified and mitigated. However unknown factors can also impact product quality and need to be factored into the design, as discussed in Section 4.1.1.

Once excipients have been selected, further assessment should be performed to determine which excipient attributes may become CMAs in the application and thus impact finished product CQAs. These potential CMAs should be included in the DoE.

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3.4 Design of Experiments

Upon completion of the risk analysis it should be possible to create a DoE that incorporates variability in the potential excipient CMAs and CPPs in order to assess potential impact on finished product CQAs. Excipient incorporation into the QbD DoE is discussed in detail in the IPEC-Americas QbD Sampling Guide [10]. There are many potential statistical designs of experiments. Commercial software packages are typically used to develop the DoE. The experimental design chosen should be based on the nature of the formulation, the potential CMAs and CPPs to be included, and scientifically justified. The order of execution of the experiments in the DoE should be randomized to avoid bias.

> **Note**: results from a DoE are a snapshot at time of execution. Hence, the QbD emphasis on continuing verification and monitoring throughout the product lifecycle ensures model fidelity and adjustment of the control strategy as required.

Serial experimentation: stepwise change of a single parameter or quality attribute, and full factorial experimental designs are inefficient methods of finding a position of robustness. Better matrix statistical treatments such as DoE can be used to map plateau regions for operational and ingredient specifications. In addition, PAT can be used to monitor manufacturing processes and deviations. MVA methods allow the extraction of information contained in large, complex data sets and contribute to increased product and process understanding.

3.5 Design Space and Control Strategy

Upon DoE completion and evaluation of the results obtained, it should be possible to confirm the excipient CMAs and CPPs, which can then be incorporated into the design space and control strategy.

In some instances, it will be necessary to justify why an excipient parameter is not included in the design space and control strategy; for example, when the parameter is listed as a potential functionality-related characteristic (FRC) in the European Pharmacopoeia (Ph. Eur.) monograph.

To preempt the special cause variation associated with too many degrees of freedom from excipient, process and product, the control strategy ideally includes continued multivariate monitoring during the product lifecycle. Multivariate monitoring is preferred because quality depends on multiple variables, which individually may remain within univariate limits but interact to cause a quality problem.

It is essential to monitor for trends instead of waiting for out-of-specification (OOS) results. MVA can contribute to an early warning system that enables effective management review (Quality Assurance instead of reliance on Quality Control). Potential risk from excipient variability can be addressed by further development batches to expand the excipient experience domain before production, if the risk is deemed unacceptable. Alternatively, if the risk is deemed acceptable,

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comparability protocols (including MVA) in production can allow expansion of the excipient experience domain during the product lifecycle.

Another advantage of applying MVA to excipient data is that it provides a convenient means of demonstrating user oversight of excipient quality, as required by cGMP. Excipient users should anticipate lot-to-lot and supplier-to-supplier variability in excipient properties and therefore should have appropriate controls in place to ensure consistent excipient performance.

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4 EXCIPIENTS IN QUALITY-BY-DESIGN

4.1 Introduction

As defined in Section 2.3.1, excipients are substances, other than the API, which are included in the manufacturing process or are contained in the finished pharmaceutical dosage form. After a prototype formulation and process have been developed, emphasis shifts to assessing impact of excipient variability on finished product quality. Excipient suppliers and users should identify and, if possible, control relevant excipient material attributes, which may not be included in pharmacopeial specifications. Reliance on pharmacopeial compliance alone may not be sufficient for QbD.

In part, QbD seeks to minimize the risk that excipient variability will adversely affect finished product quality. The impact of excipient variability will depend on the excipient role in the formulation and the finished product CQAs. Formulation and process development scientists should anticipate lot-to-lot and supplier-to-supplier variability in excipient properties and address the following potential areas of concern:

1. unknowns and uncertainty,
2. complexity,
3. common vs special cause variation,
4. finished product criticalities,
5. excipient, process, and product drift, and
6. ensuring representative sampling of excipient variability to inform design robustness and determine control strategy [see Excipient QbD Sampling Guide, 10].

4.1.1 Unknowns and Uncertainty

A pharmaceutically plausible formulation is not a guarantee against quality excursions. The design quality depends on how well the product performs against predictions based on (known) design inputs. Unknowns may subsequently adversely affect product quality. Unknowns may be unknown to the user, the excipient manufacturer, or both. Risk management requires that the impact of unknowns (uncertainty) be minimized by involving all **stakeholder**s, including excipient suppliers. Excipient unknowns include:

- composition and its impact on functionality and performance,
- attributes not included in pharmacopeial specifications,
- variability, and
- potential for interaction with latent criticalities in the finished product.

Unknown does not mean unknowable. What may be unknown to users may be known to excipient makers and thus discoverable in discussion with the maker. Justification of reliance on pharmacopeial specification should include the results of such discussions.

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4.1.2 Complexity

Excipient complexity, and products into which excipients are formulated, should not be underestimated. A definition of complexity, which is very relevant to excipients in QbD is: -

> "*the repeated application of simple rules in systems with many degrees of freedom that gives rise to emergent behavior not encoded in the rules themselves*." [27]

Pharmaceutical product development, control, and regulation have traditionally relied on simple rules, such as fixed formulae, fixed processes, and (over-)reliance on pharmacopeial compliance. Some of the many degrees of freedom (variability) associated with excipients have been illustrated in the preceding discussion of excipient unknowns, and they are complemented by additional degrees of freedom from processes and operating procedures. The resulting unpredictable emergent behaviors means that the excipients (and API), even if fully compliant, represent a reservoir of potential special cause variation. Finished product quality may unexpectedly and disproportionately become susceptible to the impact of excipient variability.

4.1.3 Common Cause Variation (CCV)

CCV is the intrinsic noise or variation due to phenomena constantly active within the system. CCV is predictable probabilistically from a historical experience base and is characterized by irregular variation around a mean with no significance in individual high or low values. CCV data shows zero trend (no time or batch dependency).

4.1.4 Special Cause Variation (SCV)

The term "*special cause*" was established by Deming [28] and is characterized by: -

- new, unanticipated, emergent behaviors,
- inherently unpredictable,
- outside historical experience, and
- inherent change in the system.

SCV is attributable to a specific disturbance. Removing all special causes leaves the intrinsic system noise, CCV. Deming's reference to inherent system change is consistent with finished product criticalities.

Due to the complexity of excipients, and the products into which they are formulated, excipients represent a reservoir of special cause variation in the finished product, which must be addressed by the designer. As SCV is, by definition, unpredictable, it is not experimentally accessible during development, and must be factored into the control strategy. Paradoxically, the more rigid or fixed the system is, the more susceptible it is to the impact of excipient variability. Flexibility built into the system to cope with SCV then becomes a criterion of design quality. There is little benefit in having products that work perfectly so long as nothing changes. Products are subject to

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cumulative changes throughout their lifecycle. Serial univariate changes often lead to eventual failure as quality is a combination of multivariate attributes. The failure need not correlate with a so-called "critical excipient." It could also correlate with an attribute of a so-called "non-critical" excipient, within its norms of variability.

4.1.5 Finished Product Criticalities

A criticality, or critical transition, is defined as "*being in a state, or at a point, where some quality, property, or phenomenon undergoes a definite change*" [29]. An example of criticality is critical micelle concentration, where the properties of dilute solutions below critical concentration are not predictive of the micellar system above, and vice versa. Polymer solution gelation occurs above a critical concentration, meaning that the dilute solution viscosities commonly used to characterize polymer excipients are not predictive of higher application-specific concentrations.

Criticalities may exist within pharmaceutical products, unknown to the designer, and are therefore known as latent conditions. Criticalities, as points of transition from one state to another, were not included in the ICH Q9 criticality definition but can be critical if encountered during production. Excipients may disproportionately impact CQAs and manufacturability if their variability interacts with product criticality. A previously unknown, unremarkable excipient variability may unexpectedly start to govern the transition from one state to another. This may be what Deming meant by "inherent change in the system" when describing special cause variation. Criticalities in pharmaceutical products are most commonly associated with percolation effects or conflicting technological objectives.

4.1.5.1 Percolation Effects

Percolation thresholds are common in pharmaceutical systems, especially in powder mixes and tableting physics. An example is increasing the water content in a water-in-oil emulsion. The oil is the continuous phase in which the water is dispersed, but at a critical water concentration, the system may invert to give an oil-in-water emulsion, where the water is now the continuous phase. Powder mixes may exhibit similar behavior with particles of one component (A) dispersed in another (B). As A increases beyond a critical concentration, or percolation threshold, the mix becomes a dispersion of B in A. If the properties of A & B are different there may be a marked discontinuity in the properties of the mix. In his review of the application of percolation theory to powder technology Leuenberger [30] warns that:

> "*formulations which contain a component with a critical concentration, i.e. close to the percolation threshold, may lead to non-robust conditions during scale-up and during subsequent large-scale production activities*."

An example is a disintegrant in a hydrophobic tablet matrix, at a level just sufficient to provide a contiguous network for water wicking. Even a slight variation in content uniformity could render parts of the tablet batch non-disintegrating.

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Leuenberger also gave an example of a percolation threshold in tablet hardness vs relative density. Below the criticality the granules disintegrate, above it they do not. Force transmission, and the resultant densities, within a compact are not homogeneous, and may be dependent on factors such as the tablet geometry.

Extreme cases may be described mathematically by a binary 0-1 step function where the system goes from one state to another with little or no warning, hence the term "*explosive percolation: From impossible to inevitable, without ever visiting the improbable*" [31].

4.1.5.2 Conflicting Technological Objectives

Conflicting technological objectives are another source of criticalities. Balancing compactability, dissolution and lubrication in a simple tablet formulation with a high load of poorly compactible drug may yield a very narrow operating region. Trying to balance too many multiple competing objectives within a narrow operating region will result in much greater susceptibility to excipient variabilities and unknowns.

Over-granulation is another example of conflicting objectives. Continuing the granulation beyond a certain point may provide better granule and tablet properties but often at the expense of dissolution. The more precise this end point, the greater the impact of excipient variability. Criticalities may arise from transitions among pendular, funicular, and capillary granulation states, which may be dependent on excipient variability, particularly with absorbent excipients such as cellulosics and disintegrants.

Proximity to performance margins or failure points also increases excipient variability impact risk. Good examples can be found with design-critical rate-controlling polymers in modified release. The higher the level of gelling-matrix-former in a hydrophilic matrix tablet formulation, the lower the impact from variability in the excipient attributes. If faster drug release is required, it is generally advisable to maintain a high level of a polymer having different viscosity (molecular weight) or chemistry rather than reduce the original polymer to a level where the impact of excipient variability is greater. Similarly, maintaining a high loading of a more permeable rate-controlling controlled release film-coating is preferable to reducing the level of a low permeability coating to the point where it is more susceptible to the impact of both the coating precision and variability of the excipient attributes.

4.1.6 Product, Process and Excipient Drift

Proximity to percolation thresholds, failure points, or balance point between conflicting requirements will predispose the product to excipient variability impact. During development, the variability of a basic excipient (or other attributes of a performance excipient) may be sufficiently far enough away from such finished product criticalities so as not to elicit a response under the experimental conditions. The question then arises how can so-called "non-critical" excipients be associated with special cause variation at some stage in the product lifecycle? Their impact is

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indirect, due to interaction with finished product criticalities. If no such interactions were observed during development, then something has changed resulting in product drift. This could include the cumulative impact of API, equipment, excipient and/or process changes as shown below.

$$\textbf{Impact} = f\ \textbf{(variability, drift, criticality)} \qquad (1)$$

Such drift may not be detectable by univariate change control; hence, the value of continued multivariate monitoring. Pharmaceutical product change control is nearly always univariate. Product performance is checked before and after the change to confirm that the product remains within specification and that the change has had no effect on CQAs. This may be formalized as a comparability protocol to cover foreseeable events such as switching excipient suppliers. The weakness of this approach is that other product attributes may change, which are not reflected in specification parameters or the CQAs. After several supplier changes and process adjustments, sequentially qualified one step at a time, the system may have drifted and the next change triggers an unexpected problem. Past performance is not predictive of future performance. Ideally, specification parameters or CQA monitoring should be complemented with multivariate monitoring.

> **Note:** The presenting excipient variability may not be causative. Excipients and their variability may not have changed but are now within range of a criticality and starting to correlate with finished product quality excursions.

Impact from drift can be illustrated by simple process capability models as shown in Figure 4.

Process capability is essentially the ratio of specification range relative to range of variability, usually quantified as ±3 standard deviations (±3σ), assuming only common cause variation. It is a measure of the ability of the process to yield product within limits. For the purposes of illustrating the combined impact of drift, variability and criticality, only a single limit is needed. This corresponds to an unknown limit within the product beyond where excipient variability will impact product CQAs.

$$\boldsymbol{Capability\ Index} = \boldsymbol{min}\left[\frac{(upper\ limit - mean)}{3\sigma}, \frac{(mean - lower\ limit)}{3\sigma}\right] \qquad (2)$$

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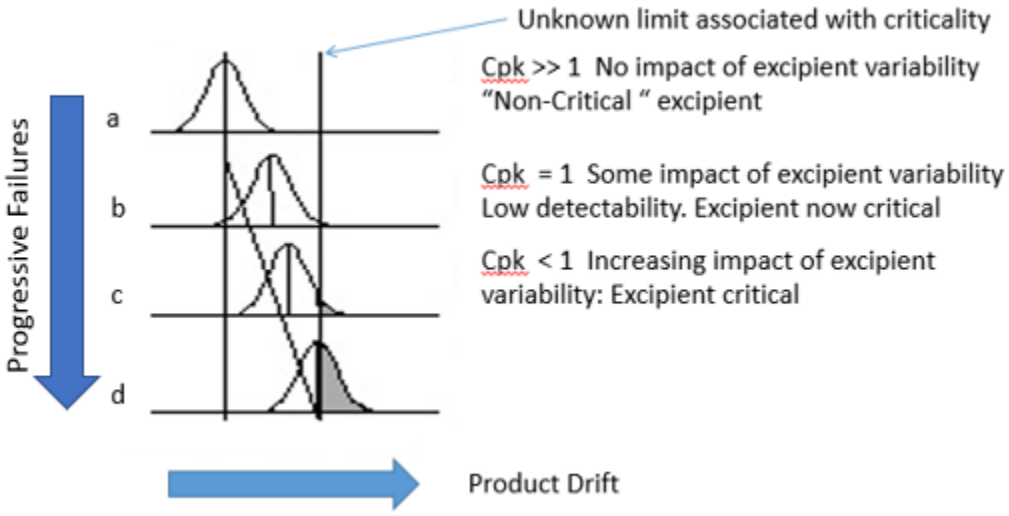
Figure 4 Simple Process Capability Model



In Figure 4a: the criticality limit is on the right-hand side. Excipient variability impact is not seen as it is well to the left of the criticality limit. The process capability is >1, and the product can tolerate some drift, with the 3σ limit being well away from the criticality. The excipient would be regarded as non-critical, as there is no discernible impact on product CQAs.

Figure 4b shows the 3σ limit drifting to the criticality limit. The process capability now has a value of one, and the previously non-critical excipient is now critical. Excipient variability is starting to correlate with product quality excursions. Detectability is low as incidence of excursions will still be parts per million, assuming a normal distribution. Further drift (Figure 4c and 4d) increases the incidence of quality excursion, and the process is no longer capable of producing product within limits.

> **Note:** excursion severity may be disproportionate if drift straddles a percolation threshold between two different regimes.

4.2 Excipient Impact Categorization

The level of effort, formality and documentation of the quality risk management process should be commensurate with risk level. Binary excipient categorization into critical versus "non-critical" has been criticized as being overly simplistic and not consistent with science and risk-based thinking. It is better to rank excipient criticality with the relative risk of not achieving desired quality attributes, a "*Spectrum of Importance*" [14] with respect to material attributes. All excipients are critical, but at a given time, some have more impact in an application than others. A suggested

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approach is to categorize excipients as either performance or basic using an adaptation of Kano Analysis [32] (see Annex B).

- Performance excipients have one or more material attributes which have direct, proportional and immediate impact on finished product quality. These are what would traditionally be regarded as critical excipients and are titrated into a formulation for specific performance.
- Variability in material attributes of basic excipients has no direct or immediate impact on finished product quality, above a minimum threshold. Such excipient attributes are generally taken for granted by users and only result in dissatisfaction if not present or insufficient. It is more appropriate to think of these excipients as potentially critical (below threshold) rather than non-critical.

The application of Kano Analysis to excipients in QbD has been published by Carlin & Wilson [35] and is discussed in more detail in Annex B.

4.3 Critical Material Attributes

Within this guide, a CMA is an excipient physical, chemical, or microbiological attribute, not necessarily reflected in supplier specifications or monographs:

1. that must be within appropriate limits, ranges, or distributions, OR

2. that are used in algorithms to control processes and/or formula.

to ensure that CQAs for a particular drug product are maintained throughout the product life cycle.

The degree of control via CMAs should be commensurate with risk from variability in such excipient attributes to the product quality and manufacturability: i.e. a higher degree of specification for excipients associated with higher risk. Excipient criticality in any formulation may be a continuum rather than a binary state.

CMAs are specific to a finished product and must be distinguished from application-specific FRCs. FRCs are potential CMAs. For example, in solid dose forms, particle size distribution (PSD) is an FRC, which only becomes a CMA if additional or tighter limits need be imposed in addition to pharmacopeial or grade specifications to control performance or the finished product quality.

PSD is irrelevant where excipients are in solution but are likely critical in solid dose forms. Table 1 illustrates the spectrum of criticality for Lactose PSD across a dosage form range.

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Table 1: The criticality of Lactose Particle Size Distribution in different dose forms

Dose Form	CMA	FRC	
Dry Powder Inhaler	Yes	Yes	Product specific, particle size nearly always critical
Solid Dose Form	Maybe	Yes	Application specific, particle size may be critical
Solution	No	No	Not critical

Attributes ensuring compliance with pharmacopeial specification are not CMAs, but minimum standards with limited relevance to fitness for purpose in specific applications. CMAs are complementary to compliance. Reliance on pharmacopeial compliance alone implies no CMAs are required, but this requires justification for products more complex than simple solutions.

CMAs should be discussed early in development with suppliers to ensure that desired limits, ranges, or distributions are within process capabilities. Suppliers also may be able to suggest other potential CMAs for specific applications.

CMAs are complementary to CPPs in controlling finished product quality. A fixed formula with a fixed process will be entirely dependent on CMAs as there are no compensatory controls. For example, a granulation process with a target performance endpoint (CPP), such as torque, may not need CMAs for the granulation excipients. However, the same process with a fixed endpoint, such as granulation time, may be dependent on CMAs.

CMAs can be used to either: -

- exclude excipient batches of outside of required limits, ranges, or distributions,

or

- control the process via process analytical technology (PAT) signal and/or algorithm based on the attribute(s) of interest.

The latter affords greater sourcing flexibility in that wider ranges or distributions can be used where compensatory process controls exist. Formulation control can also be applied by both user and manufacturer:

- Users can blend grades varying in CMAs to achieve a consistent, desired CMA.
- Manufacturers can supply standardized performance using agreed methods and an agreed diluent (batch-to batch compositional variability, but consistent performance in target application).

CMAs should be ranked in terms of severity of impact on patient safety (CQAs) followed by severity of impact on manufacturability. Detectability may be a secondary consideration but probably is of limited value in ranking CMAs given the potential for special cause variation, which is inherently unpredictable, even probabilistically. Failure to rank means that a reviewer will be

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unable to determine the relative importance of the CMAs. If there are large number of unranked CMAs, unnecessary scrutiny and delay may result, but the number of CMAs should not be minimized for fear of regulatory scrutiny.

In theory, the concept of incorporating excipients into QbD is deceptively simple:

$$\boldsymbol{QTPP} = \sum \boldsymbol{CQA} = \int(\sum \boldsymbol{CPP} + \sum \boldsymbol{CMA}) \quad \textbf{(3)}$$

In practice, this approach is overly simplistic, for several reasons. It assumes a simple linear relationship between excipient attribute or attributes and excipient performance in a finished product. This simplistic approach ignores interactions and assumes that relationships identified during development will hold during scale-up and throughout the product lifecycle.

4.3.1 Determining CMAs

4.3.1.1 Performance Attributes

CMAs are often performance attributes, which directly and proportionally impact finished product CQAs. For example, those polymer attributes which control rate of release may require narrower ranges or distributions (to be determined experimentally) than those allowed by pharmacopeial limits to ensure consistent release profiles.

Performance attributes require little experimental confirmation as they tend to be dominant, having already been titrated into prototype formulations. In addition to desired functionalities, side effects may also prompt CMA assignment. For example, magnesium stearate is intended to improve tablet manufacturability by easing ejection and reducing sticking. In practice, the well-known adverse effects on dissolution and compactability may outweigh functional benefits and require control via CMAs.

4.3.1.2 Basic Attributes

It is difficult to determine the criticality of basic attributes as they may exhibit a no response region above a threshold. Absence of impact under experimental conditions does not rule out potential impact if circumstances change e.g. during scale-up. Good experimental design using matrix statistical treatments is more likely to identify interactions than traditional serial experimentation (changing a single variable, one step at a time) and is more sparing in terms of **batch number**s. A significant advantage of continuous over traditional processing is that greater numbers of experimental variants can be evaluated, especially with automation/PAT.

Unexpected, significant interactions should be investigated. If they cannot be eliminated or reduced by formulation or process adjustments a CMA may be required to control impact.

If level of incorporation into a formulation is close to the minimum effective level, then impact risk from variability for that excipient is greater. Ranging experiments to determine concentration

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sensitivity are useful. If excipient levels can be substantially reduced without impacting product performance, there is lower probability of excipient variability impacting product performance.

4.3.1.3 Lifecycle Management: Addition of CMAs

During the product lifecycle, if variability in a previously non-critical excipient attribute starts to correlate with impact on finished product CQAs, then there are four options: -

1. alter the process,
2. alter the formulation,
3. alter a combination of process and formulation, or
4. include a new CMA, a modification of the control strategy.

A variation may need to be filed if the necessary process/formula changes fall outside the scope of the product approval, design space, or applicable waivers (e.g. US FDA Scale-up Post Approval Change [(SUPAC) [16, 17, 18] , EMA (EC) No 1234/2008 (the Variations Regulation) [41]). This could cause significant delays and expense. It is often difficult for excipient manufacturers to address such issues, as the problems may not be replicable in the laboratory (user or manufacturer). This can be the sign of a criticality specific to a product, at scale, on a particular site.

If the excipient manufacturer has not changed anything (or the user has not precipitated the crisis by changing excipient supplier), it is worth asking the excipient manufacturer what process or excipient variations are covered by product specifications. This could include different sites or equipment trains/scales. A representative selection of excipient batches can then be introduced into the user's production to identify "good" or "bad" batches in terms of the presenting quality issue. Specifying preferred excipient batch types should be accompanied by appropriate characterization to identify a CMA to distinguish "good" from "bad". The advantage of adding a CMA is that no prior regulatory approval is required. In the longer term (the next window of regulatory opportunity), a variation can be filed containing corrective formulation and/or process options, together with justification for retiring the now redundant added CMA if appropriate.

4.4 Analysis of the Design of Experiments (DoE)

Upon completion of the experimental work identified in the DoE, it will be necessary to analyze the data to obtain the necessary understanding of the formulation and process and to establish a scientifically justifiable Design space and thus a control strategy. It is important that all the data be considered in order to obtain maximum information and understanding.

If a statistics program with a DoE module has been used to provide the design of experiments, the data can also be analyzed using this same software. It is also possible to set up one's own DoE using standard models e.g. Plackett-Burman, Central Composite Design, etc., the equations for analysis of the data are published in the scientific literature and on the internet.

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Based on the results from the data analysis, assuming the DoE included all the requisite parameters, it should be possible to establish a scientifically justified design space and control strategy.

4.5 Scale-up

Having successfully completed the DoE and established the Design Space and Control Strategy, one of the next steps in the project progression will likely be to scale up the formulation and process. Scale-up, in pharmaceutical projects, may not be predictable. In addition, there are regulatory restrictions on how large a scale-up can be undertaken at one time. Generally, the maximum scale-up allowed by regulatory authorities is not more than a ten-fold batch size increase (for **batch process**ed formulations) can be undertaken in one step without having to undertake bioequivalence testing in human subjects (or appropriate animals for veterinary products).

It should be confirmed that after scale-up the Design Space and Control Strategy are still valid. However, this should not require repeating the original full DoE. With the increased understanding obtained during the initial DoE, and using experience of the unit operations in general, it may be possible to use a partial DoE to confirm the applicability of the Design Space and Control Strategy at the new scale of manufacture.

Once the continued applicability of the Design Space and Control Strategy are confirmed, further manufacture at the new scale can commence. If, however, the Design Space and Control Strategy are not confirmed at the new scale, further assessment is required. The options available include:

- data assessment to determine if a more restricted Design Space and Control Strategy would be applicable and can be scientifically justified based on available data,
- perform additional experiments to provide the necessary data to identify and scientifically justify an acceptable Design Space and Control Strategy for the new scale, and
- formulation and process redesign to address the issues identified during scale-up.

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5 LIFECYCLE MANAGEMENT

Quality or state of control at the time of filing does not guarantee ongoing quality and control throughout the product lifecycle. Maintaining a state of control, maintenance of commercial operations, and making improvements requires continued oversight. In the context of ongoing oversight or monitoring, this guide uses the FDA preferred term 'continued' [14] rather than 'continuous' [15] to distinguish from continuous manufacturing. Both batch and continuous processes require continued monitoring.

The traditional three batch validation of pharmaceutical finished products has been replaced by the continued monitoring of product and process, referred to as continued process verification [14]. In the process industries, the approach taken is that a sufficient number of batches are monitored to allow calculation of the probability of deviations from the mean for future batches. However, this assumes common cause variation (CCV, inherent variability) only, with batch results fluctuating randomly around the mean and not showing any trend.

Excipient users should also be aware of the risk of unpredicted events, including out of trend (OOT) and out of specification (OOS, failure), due to special cause variation (SCV). Unfortunately, prior compliance is not predictive of such events, thus, continued monitoring as part of the control strategy is essential to provide early warning. However, the onset of SCV may not always be easily detectable and can be difficult to distinguish from background CCV.

5.1 Continued Monitoring

Continued multivariate monitoring is preferred since quality itself is multivariate. Individual attributes may remain within univariate limits but interact to cause quality problems. Traditional **change control** and comparability protocols are univariate. If the product remains in specification before and after a change then that change is approved. A sequence of one-step at a time changes can be similarly approved during the product lifecycle. However, sequential compliance may mask product drift, which might only be detected by a trend in multivariate product data. Drift itself is not fatal but if it leads to the interaction of an excipient variability with a criticality in the finished product sudden failure may ensue. Drift may not be reflected in the specification attributes. Detection of drift by multivariate monitoring of all data, not just specification compliance, gives the best chance of detecting subtle changes early enough to investigate cause and take preventive measures before failure.

Another advantage of applying MVA to excipient data is that it provides a convenient means of demonstrating user oversight of excipient quality, as required by cGMP.

5.2 Multivariate Analysis (MVA)

MVA allows information extraction from large complex datasets in a manner not achievable by simple univariate statistical process control (SPC) where anything but the strongest correlations

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will be confounded by the interaction of multiple possibly correlated variables. Software may be required, and the reader should study the information provided by the software suppliers and/or the literature on statistics to determine which of the many available MVA techniques is suitable.

Principle Component Analysis (PCA) is one of the more commonly used techniques where large datasets with correlated measures are organized into a smaller set of uncorrelated variables, the principal components, PCs. If two or three PCs are sufficient to explain variability, then variability can be visualized in two or three dimensions. Mathematically, larger numbers of PCs can be used if required.

5.3 Continued Product Verification

In accordance with ICH Q8 [2] both US [14] and European [15] guidances on validation changed the emphasis from 3-batch validation to continued [14] or continuous [15] process verification. Continued Process Verification is defined as:

"*Assuring that during routine production the process remains in a state of control.*" [14]

This same thinking can be applied to the finished pharmaceutical product. MVA can aid in monitoring manufacturing trends and assessing the continued relevance of the Design Space and Control Strategy since it will encompass/summarize a broad range of underlying attributes.

5.4 Detection of Product/Excipient Drift and Out-of-Trend Results

Trends and OOS data for both finished product and excipients should be understood and addressed by the excipient users. MVA may help determine the underlying causes of such changes since it will aid in the identification of those excipient attributes that have the most impact on finished product quality. Although excipient manufacturers may monitor trends in their excipients, they are typically unaware of how excipient trends impact the finished drug product.

5.5 Excipient-related Special Cause Variation in Production

Several hundred batches of pharmaceutical product may have been manufactured within specification, but that does not mean that the next batch will also meet specification. There is always the possibility of special cause variation**.** Because such 'black swan' events [33] are unexpected and unpredictable, there is no definitive way to avoid them. (See also 4.1.4) However, it may be possible to mitigate the risk from black swan events by continued multivariate monitoring, including excipients and APIs. The more that APIs and excipients are understood, the less likely there will be issues triggered by special cause variation. This increased understanding should continue throughout the pharmaceutical product life cycle.

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5.5.1 Supplier Qualification and Multi-sourcing Qualification with Regards to Product Performance

In the absence of a CMA, the specification for an excipient should default to mandatory pharmacopeial standards. It is important to note that some attributes in the monographs do not have acceptance criteria, usually in the labelling section of USP/NF monographs or the FRC section of Ph Eur monographs. These attributes are non-mandatory and if not critical should not be (over) specified. Not only can limits vary from supplier to supplier but also the methods, making specification equivalence difficult to determine.

Qualifying multiple sources should be considered when establishing the design space to reduce the time required to switch to an alternative supply after launch.

> **Note:** If an alternative excipient source is qualified during development, the regulatory agencies will expect that it is used routinely during commercial manufacture in order to be interchangeable in the future. Without such routine use, it would be necessary to requalify the excipient prior to use. This restriction is to ensure that any changes in the alternate source material (and the finished product and its' processes) between original qualification and the switch date are properly assessed.

5.5.2 Excipient Change control

On occasion, and sometimes for reasons outside their control, it may be necessary for excipient manufacturers to make changes to their processes, which have the potential to impact excipient performance and thus finished product performance. The excipient manufacturer should consult the IPEC Significant Change Guide [34] whenever a change is to be made to the excipient raw materials, manufacturing process and/or finished excipient testing and assess the need for customer notification. It should be noted that excipient manufacture may be subject to on-going optimization for larger non-pharmaceutical markets. Based on a risk assessment, the excipient manufacturer should apply the same reasoning (as far as is practicable) to their own suppliers of **starting material**s, reagent, solvents, processing aids and additives used in the manufacture of the excipient.

When investigating potential impacts of notified changes, it is strongly recommended that a risk assessment be undertaken by the excipient user. Based on the results of the risk assessment, the excipient user should determine the need for further action.

Depending on the change and its potential impact on pharmaceutical finished product performance, it may be necessary for excipient users to inform the relevant regulatory authorities via either a supplemental filing such as a Prior Approval Supplement (PAS) or a Type II Variation for highest risk changes, Changes Being Effected or Type I Variations (CBE 0/IA or CBE 30/IB) for intermediate risks, or an annual report/product quality review for minor changes as assessed by the excipient user.

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Since filings may be subject to extended review times, it may be necessary for the excipient user to build product inventory, thus requiring excipient supplies from before the change is made. This may, in turn, require coordination between the excipient manufacturer and user. If prior approval of the change by the excipient user is required, this will almost certainly require inventory increase by the excipient manufacturer, user, or both.

It should also be remembered that not all changes to an excipient will be detrimental to the performance of the excipient or the pharmaceutical finished product. However, unless it can be scientifically justified as not a **significant change**, it should be assumed that all changes should be notified to the excipient user [34].

5.5.3 Mitigating Technological Risk from Excipients.

It is important to understand that continued excipient monitoring by both excipient manufacturer and user is just as important as continuous improvement. In addition, data sharing and transparency facilitate understanding, and will aid in mitigating risk for the excipient user. Feedback from the excipient user to the manufacturer may also be important as it may allow the manufacturer to make the excipient manufacturing process more robust for the excipient user.

Access to excipient manufacturers' data can accelerate product development and increase product robustness with respect to the impact of excipient variability. Such access requires collaboration. It is recommended that discussions/collaboration be conducted under a two-way confidentiality agreement, as pharmaceutically aligned excipient manufacturers cannot help if they are unaware of the application. The excipient manufacturer can help to identify CMAs for design-critical excipients during development and provide CMAs to counter special cause variation during the finished product life cycle. Continued multivariate monitoring of excipient data for drift may preempt drift and quality problems in the finished product.

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ANNEX A

PHARMACEUTICAL DEVELOPMENT PROCESS

The following overview of the pharmaceutical development process illustrates the incorporation of QbD throughout the project lifecycle. It describes a de novo product development project and is applicable to innovator or generic products.

Note: all stages should be fully documented using appropriate protocols and reports.

1. Define the QTPP: required product specifications, *in vivo* performance requirements, and any commercial requirements (including dosage strength(s), packaging, etc.).
2. Review of all the available information on the API relevant to the route of administration and the likely dosage form (including preformulation studies).
   Note: Preformulation comprises all physicochemical and biopharmaceutical studies undertaken on the API, alone or in combination with excipients, which support the formulation and process design, and development.
3. Identify likely excipients.
4. Identify likely formulations and processing options.
5. Review relevant information (prior knowledge) on excipients and processing options.
6. Identify potential product CQAs.
7. Assess variability of materials
8. Identify all potential CMAs relating to both the API and excipients used in, and CPPs relating to, the manufacture of the formulation(s).
9. Carry out a risk assessment regarding the potential CMAs and CPPs drawing on appropriate experience and knowledge (including the scientific literature).
10. Undertake preliminary experiments (if necessary) to confirm the criticality of any quality attributes or process parameters for which the risk assessment is not clear.
11. Establish the DoE at small scale (1x).
12. Execute the DoE for the small scale.
13. Analyze the results from the executed DoE.
14. Review the results and confirm there is nothing lacking in the DoE
15. Establish the design space for the small scale.
16. Establish the CMAs, CPPs and product CQAs and control strategy for manufacture at the small scale.
17. Establish the DoE for the intermediate scale (10x).
    Note: this will likely be a subset of the small-scale DoE.

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18. Execute the DoE for the intermediate scale.
19. Analyze the results from the executed DoE.
20. Review the results and confirm there is nothing lacking in the DoE
21. Confirm or re-establish the design space for the intermediate scale.
22. Establish the CMAs, CPPs and product CQAs and control strategy for manufacture at the intermediate scale.
23. Establish the DoE for the commercial scale (100x).
    Note: this will likely be a subset of the small-scale DoE and may be very similar to the intermediate scale DoE.
24. Execute the DoE for the commercial scale. *
25. Analyze the results from the executed DoE.
26. Review the results and confirm there is nothing lacking in the DoE
27. Confirm or re-establish the design space for the commercial scale.
28. Develop a control strategy
29. Establish the CMAs, CPPs and product CQAs and control strategy for manufacture at commercial scale.
30. Confirm all protocols and reports are complete, reviewed and approved.
31. Prepare QbD CMC submission.
32. Undertake technology transfer to commercial manufacturing site. *
33. Undertake continued verification and improvement.
34. Discontinue product.

*__Note__: It is likely that the commercial scale manufacture will be carried out at the commercial site, in which case the technology transfer step 30 could be combined with the execution of the DoE at commercial scale step 23 or could occur ahead of step 23.

As more experience is gained with QbD projects, it is possible that for certain projects some of the steps detailed above may be consolidated, particularly when information, understanding and experience are consolidated across several projects.

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ANNEX B

KANO ANALYSIS

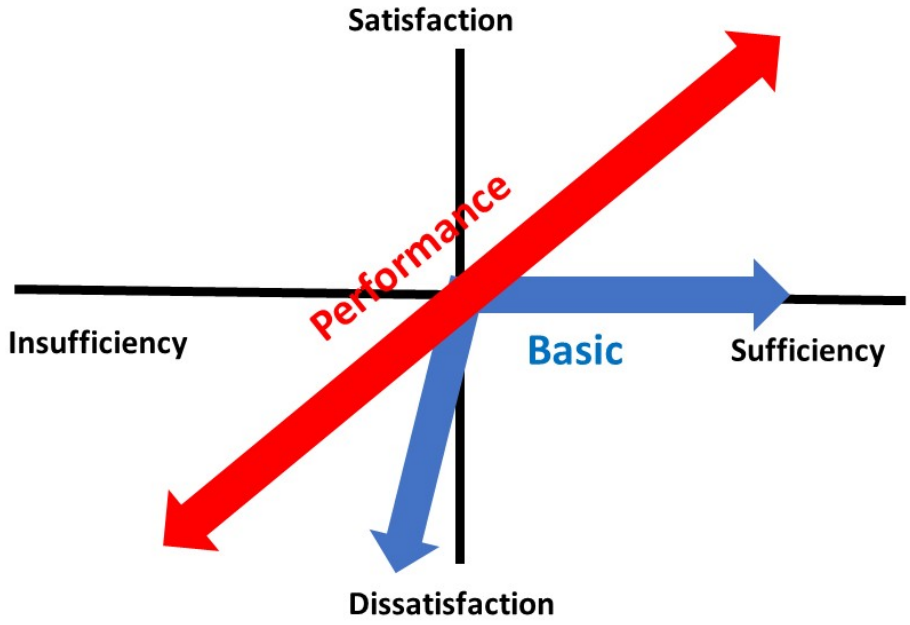
Kano Model

Kano models relate customer satisfaction to the degree of sufficiency of product or service design attributes. Kano models are used to guide investment in research and development (R&D). A simple two element Kano model divides design attributes into performance and basic:

- Performance, satisfaction proportional to degree of expression of attribute.
- Basic, no impact on satisfaction unless insufficiency of attribute

These categories are illustrated in Figure 1.

Figure 1 Kano Model



The Kano concept can be illustrated by the purchase of a car.

- Fuel economy is a performance attribute, the higher the miles per gallon the greater the customer satisfaction, and vice versa. The more important the fuel economy is to the buyer the steeper the gradient of the performance correlation.

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- The steering wheel is a basic attribute. A steering wheel is expected, so it is not a purchase criterion, but delivery of the car with the steering wheel missing would provoke extreme customer dissatisfaction.

Only performance attributes show correlation with customer satisfaction across the range of attribute sufficiency, and therefore merit more R&D investment than basic attributes above the minimum level of sufficiency.

This simple conceptual model can be adapted for explaining excipient impact by relating finished product quality or performance (satisfaction) to the degree of sufficiency of material attributes [35].

Performance excipients have one or more material attributes which have direct, proportional and immediate impact on finished product quality. These are what would traditionally be regarded as critical excipients.

The attributes of basic excipients exhibit ranges with no impact on product quality but may significantly impact product quality if a threshold is crossed. For this reason, it is not appropriate to describe basic excipients as “non-critical” excipients. The threshold may be dependent on the specific application. Impact on finished product quality is indirect, disproportionate and not immediate.

Rigid categorization of excipients is not as important as awareness of the potential for multiple modes of impact from specific attributes and their interactions. An individual excipient may have both performance and basic attributes, dependent on the application or finished product.

Kano Performance

A Kano performance attribute correlates with the degree of satisfaction, generally the more the better, and vice versa. A performance attribute is generally synonymous with a performance excipient. An excipient falling into this category is typically titrated into the formulation to deliver a specific product performance. An example would be the rate-controlling polymer in a sustained release product, where the lower the rate-controlling polymer concentration the faster the release, and vice versa.

Ignoring interactions, the impact of a performance excipient in a finished product will be a function of its concentration (c), and expression of the relevant excipient attribute (x), i.e. sufficiency, strength or effectiveness. Variability in x can directly impact product performance, and such excipients would traditionally be regarded as critical, with attribute (x) being a potential CMA.

$$\boldsymbol{Performance} = \int(\boldsymbol{c}, \boldsymbol{x}) \qquad \boldsymbol{or}\ \boldsymbol{Performance} = \int \boldsymbol{x}$$ for fixed formulae

Interactions will result in dependency on other formulation or process variables. For Kano performance excipients a range is preferred rather than a single concentration, in order to offset variability in x, in which case x becomes less critical. By using a range, the manufacturer of a

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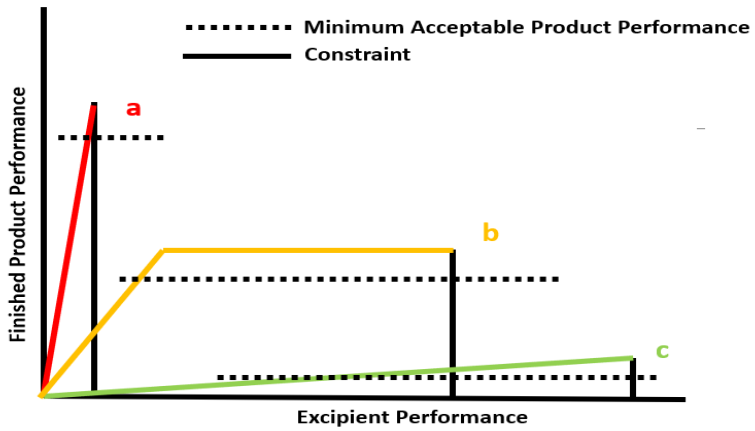
pharmaceutical product can utilize the CMA in an algorithm to determine the concentration to be added. In a fixed formula, if the process does not offer enough compensatory control, the CMA is in the hands of the supplier, in terms of a new specification attribute or tighter limits for pre-existing specifications.

In the Kano model (Figure 2a) a high gradient of the performance line is undesirable. The higher the gradient the greater the magnification of impact from excipient variability, a high coefficient of impact. Conversely, with a low gradient (Fig 2c) it takes much greater excipient variability to significantly impact finished product performance. In excipient ranging studies, if small changes in concentration have significant impact on finished product performance then alternative grades or excipients (or process parameters) should be evaluated to reduce the sensitivity.

In the Kano model (Figure 1) the performance attribute is traditionally shown as a line of proportionality "more is better", but in practice there will be constraints. For example, you cannot keep adding an excipient, no matter how beneficial, without making a tablet too big to swallow, or running into side-effects. Magnesium stearate is an excellent lubricant, but unconstrained addition renders most formulations unfeasible. More realistic profiles are shown in Figure 2, where satisfaction levels are constrained by some other limiting property. Such a constraint is analogous to the therapeutic index of a drug, which is the range between the maximum tolerable dose and the minimum effective dose. A narrow effectiveness index for an excipient in a formulation represents a finished product criticality. The worst case is shown in Figure 2 (a) where there is high concentration dependency and the minimum effective level of the excipient is close to the maximum tolerable level due to a constraint. Any variability in the excipient will result in sub-optimal performance. The plateau in Figure 2 (b) is hence a more attractive operating region, in effect analogous to a Kano basic profile. The wider the formulation concentration range over which a performance excipient is effective, the less susceptible the product will be to variability in that excipient. The benefit of a low concentration dependency is shown in figure 2 (c).

Figure 2 Performance Excipient Profiles



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The logic of Figure 2 can be illustrated by the choice of suspending agent for pourable or sprayable aqueous suspensions. If a soluble thixotropic polymer, such as xanthan, is used, there is a conflict between suspension and viscosity (Fig 2a, constraint), whereas the use of dispersible cellulose[3] gives suspension without viscosity (Fig 2b, plateau). Uncoupling viscosity from suspension frees the designer from the constraint of having to balance viscosity versus suspension. The performance excipient in a plateau operating region becomes less critical, with less dependence on a CMA. Variability in the attributes of a suspending agent in the plateau region will have less impact than those of a constrained suspending agent close to the critical concentration needed to balance competing objectives. A performance excipient in a plateau region is equivalent to a basic excipient, with no impact of variability above a threshold. Categorization of the excipient as performance versus basic is less important than determining whether the excipient response is proportional or threshold.

A CMA is not a predefined property of an excipient, because it is specific to the control of a CQA of a finished product. (see Section 4.3).

Kano Basic attribute

A Kano basic attribute is a minimum requirement without which an excipient is unacceptable. Such excipient attributes are generally taken for granted by users and only result in dissatisfaction if not present or insufficient. As shown in Figure 1, basic excipients exhibit a region of no response above a threshold, below which there may be severe impact on product quality. Excipient attributes included in the basic category fall into two types.

The first are compliance and compatibility. Non-compliance with specification should be detected by the quality system, but lack of GMPs in the manufacture of an excipient can result in the finished product being deemed adulterated. Chemical compatibility with the API is another basic requirement identified during pre-formulation studies. These minimum compliance and compatibility standards are generally independent of specific product design requirements. If chemical incompatibility of the API with an excipient is dependent on the excipient source, then the incompatibility is due to a minor component which should be specified below a no-effect level (CMA).

The second type of excipient attribute in the basic category are those with no correlation to product quality above a minimum threshold. The so-called “non-critical” excipient is a misnomer, as the attributes exhibit a threshold between critical and non-critical ranges. The lack of impact of variability is illustrated by the flat-line response, where variability is well away from the level below which there is dissatisfaction. A good test of “non-criticality” is to range the concentration downwards. If there is no impact on CQAs, it suggests a margin or reserve of performance. Never titrate down to point of failure during development as this guarantees susceptibility to excipient

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variability in production. Variability in a basic excipient close to a minimum level or quality will render the finished product more susceptible to that variability, in which case the excipient becomes critical and the offending attribute becomes a CMA. The operating region with respect to an attribute may shift, especially if pharmaceutical consumption is minor compared to other markets for that excipient.

It should not be assumed that inclusion of so called “non-critical” excipients during development without incident confirms that they are not critical. If there is no reason to expect impact, then absence of impact does not prove absence of potential impact: just that it had not occurred during the experiments. The variability of a basic excipient has no impact as long as the threshold is not crossed.

Ranging studies during development are useful: if you can reduce the level of a basic excipient by 50% and maintain product performance, then the impact of variability of that excipient is generally going to be less than that associated with a more impactful excipient for which only a 5% reduction can be tolerated.

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