AIDCOC Training Academy
Webinar

Critical Role of Excipients in Formulations

By

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DISCLAIMER

The views and opinions expressed in this presentation are *only of the author, and should not be construed to represent IPEC India, IPEC Federation or other IPEC member views or policies.*

Outline

- Introduction to IPEC
- Excipient manufacturing
- Excipient and API differences
- Role of Excipients
- Regulatory framework
- Selection and Use of Excipients
- Total Excipient Control

IPEC Offers Excipient Stakeholders - a Regional Voice with Global Influence

IPEC Federation
- Established in 2009,
- based in Belgium / made up of regional IPECs

IPEC-Americas (initiated IPEC in 1991)
- North, South and Middle Americas
  Partnerships in Brazil, Argentina, Mexico, Canada

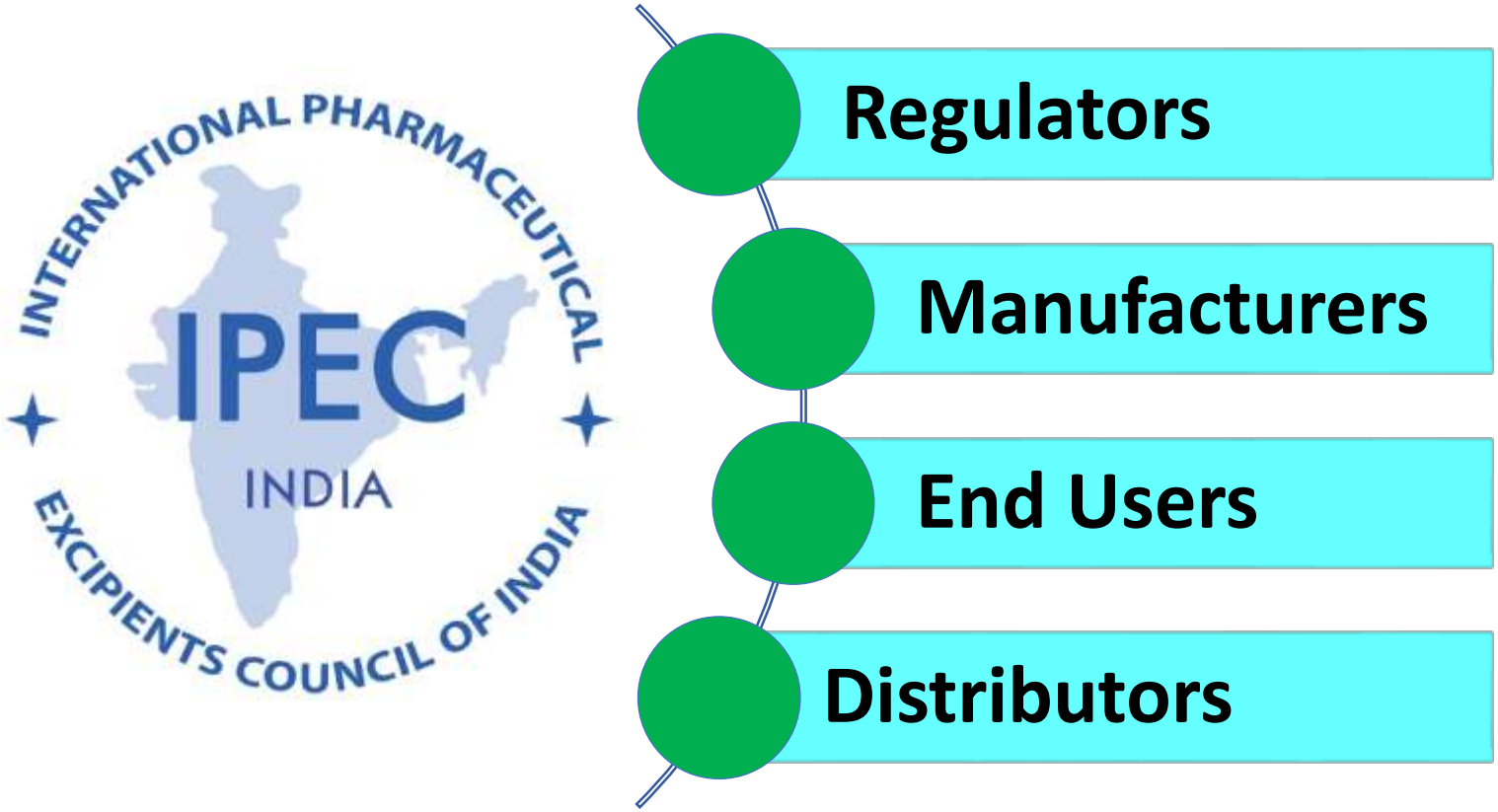
IPEC Europe
- Europe, North Africa, Middle East

IPEC Japan

IPEC China

IPEC India

IPEC India - Stakeholders



IPEC India Vision & Mission

VISION

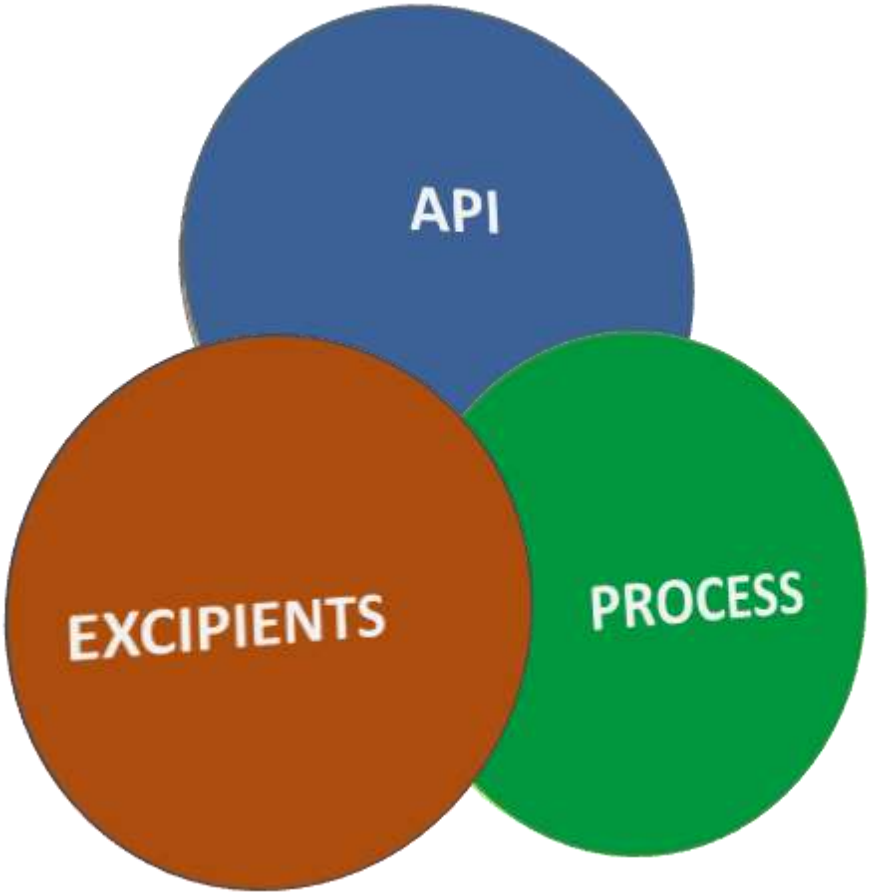
To be recognized as the authoritative Indian body for the promotion of quality, functionality and safety of global pharmaceutical excipients

MISSION

To collaborate with all our stakeholders in order to:

- **Develop and implement Standards and Regulations that are harmonized with global standards throughout the supply chain**
- **Create awareness within our stakeholders on current and future Excipients and their related regulations**

What a Formulation contains ???



Pharmaceutical Excipients - Definitions

What are Excipients

The word *excipient* is derived from the Latin *excipere*, meaning 'to except', which is simply explained as 'other than'. Pharmaceutical excipients are basically everything other than the active pharmaceutical ingredient in a dosage form.

"All other components of a drug formulation other than the active drug."

Lou Blecher (founder of IPEC-Americas), 1991

"Excipients are substances other than the API that are intentionally included in a drug delivery system."

USP-NF General Information Chapter <1078>

"Substances other than the API, which have been appropriately evaluated for safety and are intentionally included in a drug delivery system."

IPEC General Glossary of Terms and Acronyms, 2014

The Common Theme in each definition is that the excipient is differentiated from the API – Reason is because they are VERY different than APIs

What is the Excipient Industry?

Diverse Materials Base

- Chemical synthesis
  (Polymer mixtures, Cellulose derivatives – substances often less defined than low mol wt entities)
- Mining of minerals
- Harvesting of vegetation
- Formulated Products
- Biotechnology & Fermentation
- Genetic Modification
- Animal by-products

Raw Materials in Typical Excipient Mfg.

- Mining operations…
- Agriculture…crops, livestock, forestry, oceans…




Pharmaceutical Excipient Industry – Different than Drugs!

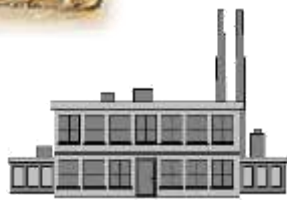
Majority of Pharmaceutical Excipient Suppliers are

Chemical Industry subsidiaries

- **Products targeted at Food, Beverage, Industrial, and Cosmetics**
- **Small fraction of Main Production Volumes for excipient sometimes less than 0.1% of business**
- **Varying degrees of dedicated R&D related to excipient uses**
- **Specifications-driven by main market (usually not Pharma)**
- **Global Market and Manufacturing Base**

Why are Excipients different than APIs?

- **They do not treat the disease or the condition:**
  - Without excipients, the therapeutic revolution of the last 100 years would not have been possible!
  - They are (should be) pharmacologically inactive; but they may not be physiologically inactive.
    - e.g. modified release polymers control drug release
- **Different sources of materials**
  - Harvested (agriculture)
  - Mined
  - Synthetic



Why are Excipients different than APIs?

- Scale of manufacture:
  - Excipient production may be measured as thousands of tonnes per annum
  - APIs are usually manufactured in small batches.
- For many chemicals, production of excipient grades for pharmaceutical usage is only a **small** fraction of the total production
- APIs are typically **ONLY** manufactured for use in drug products
- Many excipients are not simple 'pure' chemicals–and their composition may not be well defined

Typical API Manufacture

Often small scale, dedicated batch processes

Manufacturing of Excipients

The scale of manufacture is usually much larger than for standard APIs and normally only a small portion of the stream is used as an “excipient”

Manufacturing/Storage of Excipients

Excipients are often produced in an industrial chemical facility and packaged/stored in many types of containers typically by chemical companies

The journey from the manufacturing site









Training Academy Webinar 30th October 2021

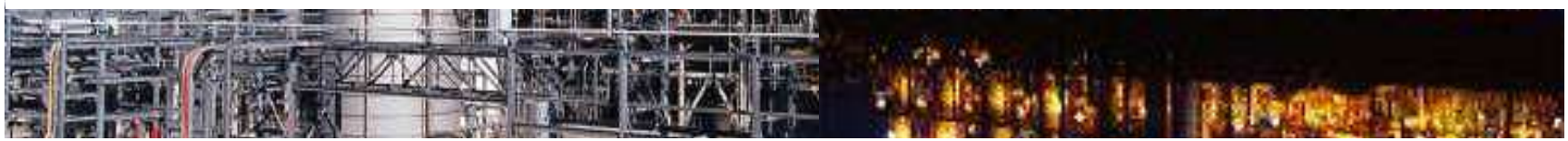
Excipient Industry is significantly different than the Pharma Industry

Excipients CANNOT be regulated like APIs or Drug Products!

Excipient Manufacture – Very different than API / Drug Manufacture

Same excipient and grade may be made in several different plants by the same company

Many different producers of the same excipient as compared to relatively few producers for APIs/Drugs



Appropriate controls for this type of plant are much different than for an API/ Drug plant

Realities of Excipients

KAOLIN

IRON OXIDES

CELLULOSES

TALC

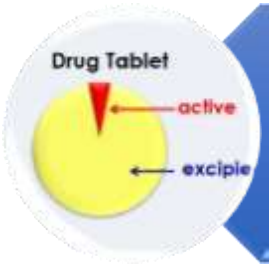
ALGINATES

TiO2

STARCH

OILS

Over 8,000 excipients in use

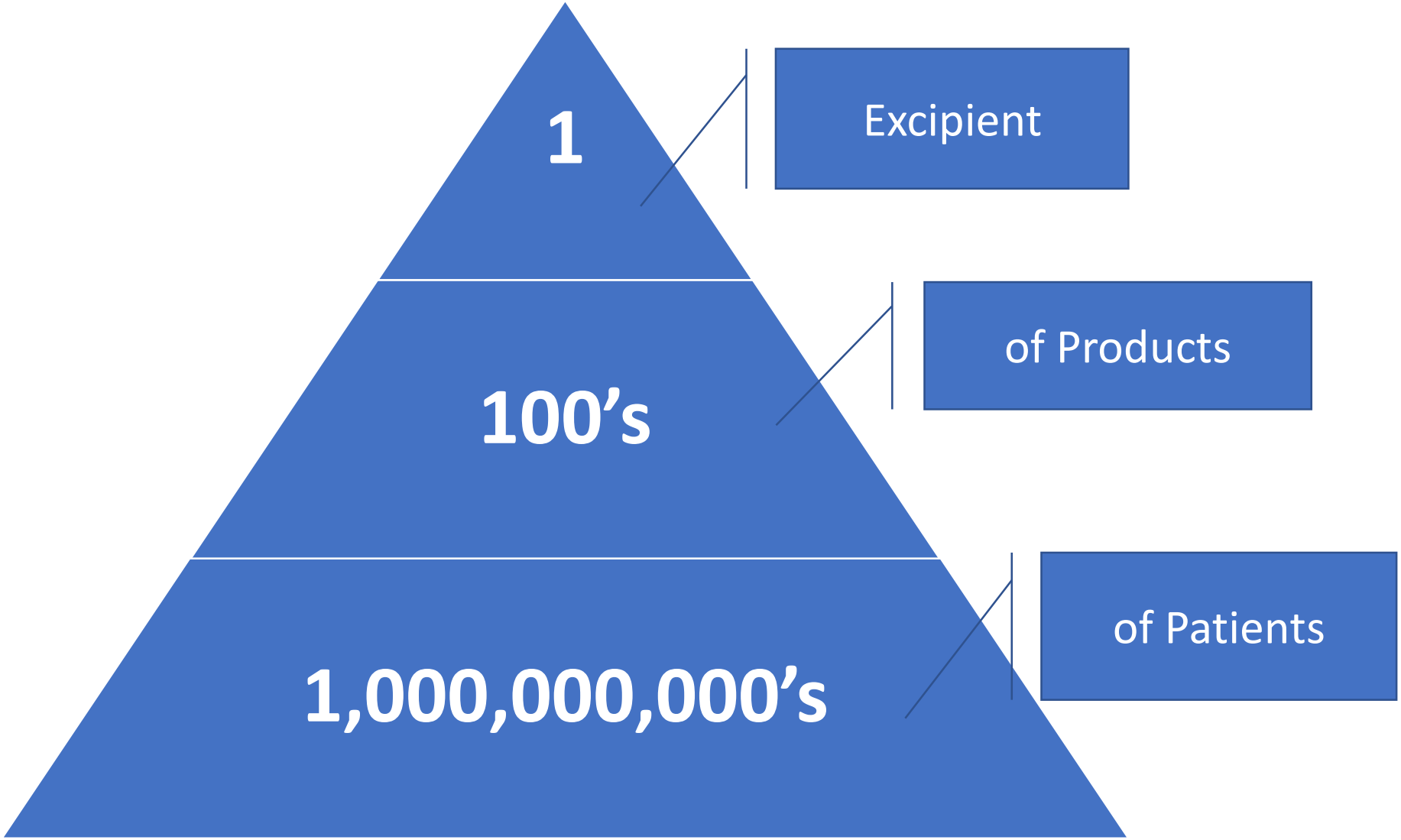


Can represent up up to 95% of the formulation

Patients consume more excipients than active ingredients

Serve important functions in formulations

Impact



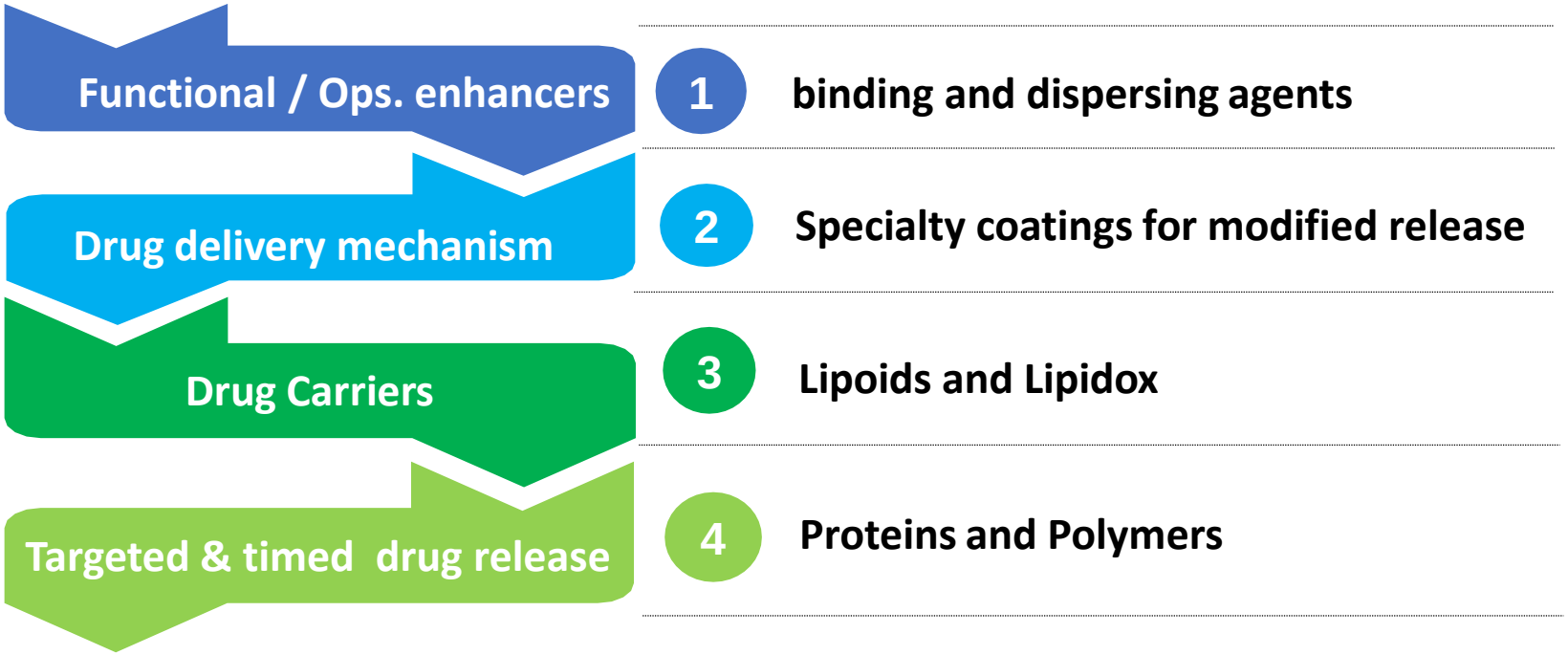
Importance of excipients

“Excipients plays an important role in manufacturing a drug product”

1. Improve process-ability and aesthetics
   - Optimize product performance
2. Act as formulations stabilizers, unit operations enhancers & improve machinability
3. Maintain pH and/or osmolarity of formulations
   - Modulate solubility and bioavailability of APIs
4. Increase stability of APIs in finished formulations

Evolving role of Excipients

The role of excipients has evolved with time and advancements in drug development



ROLE IN PHARMACEUTICALS

- Excipients play a wide variety of functional roles in pharmaceutical dosage forms, including:

  - modulating solubility and bioavailability of APIs,
  - increasing the stability of active ingredients in dosage forms,
  - helping active ingredients maintain preferred polymorphic forms or conformations,
  - maintaining the pH and/or osmolarity of liquid formulations,
  - acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders, and tablet disintegrants,
  - preventing aggregation or dissociation (e.g. of protein and polysaccharide actives),
  - modulating immunogenic responses of active ingredients (e.g., adjuvants), and more.

Commonly used Excipient categories

Acidifying/ Alkalizing agent	Disintegrant	pH Modifier
Antifoaming	Effervescent System	Plasticizer
Antioxidant	Emulsifier	Preservative
Binder	Filler	Solubility Enhancer
Buffering Agent	Film Former	Solubilizer
Bulking Agent	Flavours	Solvent
Carrier	Glidants	Stabilizer
Chelating Agent	Granulation	Surfactant
Coating systems	Humectant	Sweetener
Colors	Lubricant	Taste Masker
Compaction agents	Penetration enhancer	Thickener
Diluent	Permeation Enhancer	Many more

Additives and Processing Aids in Excipients

- **There is a lot of misunderstanding about these:**
  - There are additives (and residual processing aids) that have been present in excipients for many years, but have not been declared – more important with QbD
    - **Excipient manufacturers have historically been unaware that this information was important to users**
    - **Intellectual property issues surrounding additives and processing aids exist and must be considered**
  - Some ‘additives’ are actually ‘processing aids’ carried over from earlier stages in the processing or extraction of the excipient
  - Additives and residual processing aids can be important components and should not be regarded as ‘bad’! – **should not try to reduce or eliminate them**

API (ICH Q7) GMPs vs. other appropriate Excipient GMPs

- **Excipients used in drug products are typically NOT made under ICH Q7 API GMPs**
  - Excipient GMPs (such as IPEC, EXCiPACT™ or ANSI/NSF 363) are typically used when material is marketed as an excipient
  - Food additives and cosmetic ingredients are sometimes used as excipients - food additive and cosmetic *GMPs* are used by manufacturer
    - **User must perform a risk assessment to determine the need to implement additional controls for use of the excipient in a drug product**
- **Significant practical issues with implementing ICH Q7 API GMPs for excipients:**
  - Natural raw materials or products,
  - Large scale (often continuous) manufacturing equipment,
  - Outdoor manufacturing equipment,
  - Bulk shipment, terminals, field tanks, etc.
  - Master batch manufacturing record not available with continuous processing

Excipient Regulatory Framework

- **Regulators in the U.S., Europe and many other countries recognize that excipients CANNOT be regulated the same as APIs / DRUGS**
- **Additional flexibility is needed for excipients** due to the diversity of raw material sourcing, manufacturing processes and facilities
- **Although regulators recognize the importance of excipients, they place responsibility for excipient quality on the drug product manufacturer – Regulators typically perform only limited oversight themselves**
  - Supplier qualification is performed by the drug product manufacturer who is fully responsible for the suppliers they use
- There is no provision of Manufacturing License for Excipients in US, EU and many other countries
- Excipients are reviewed as a part of Drug Application

U.S. / EU GMP Standard Differences

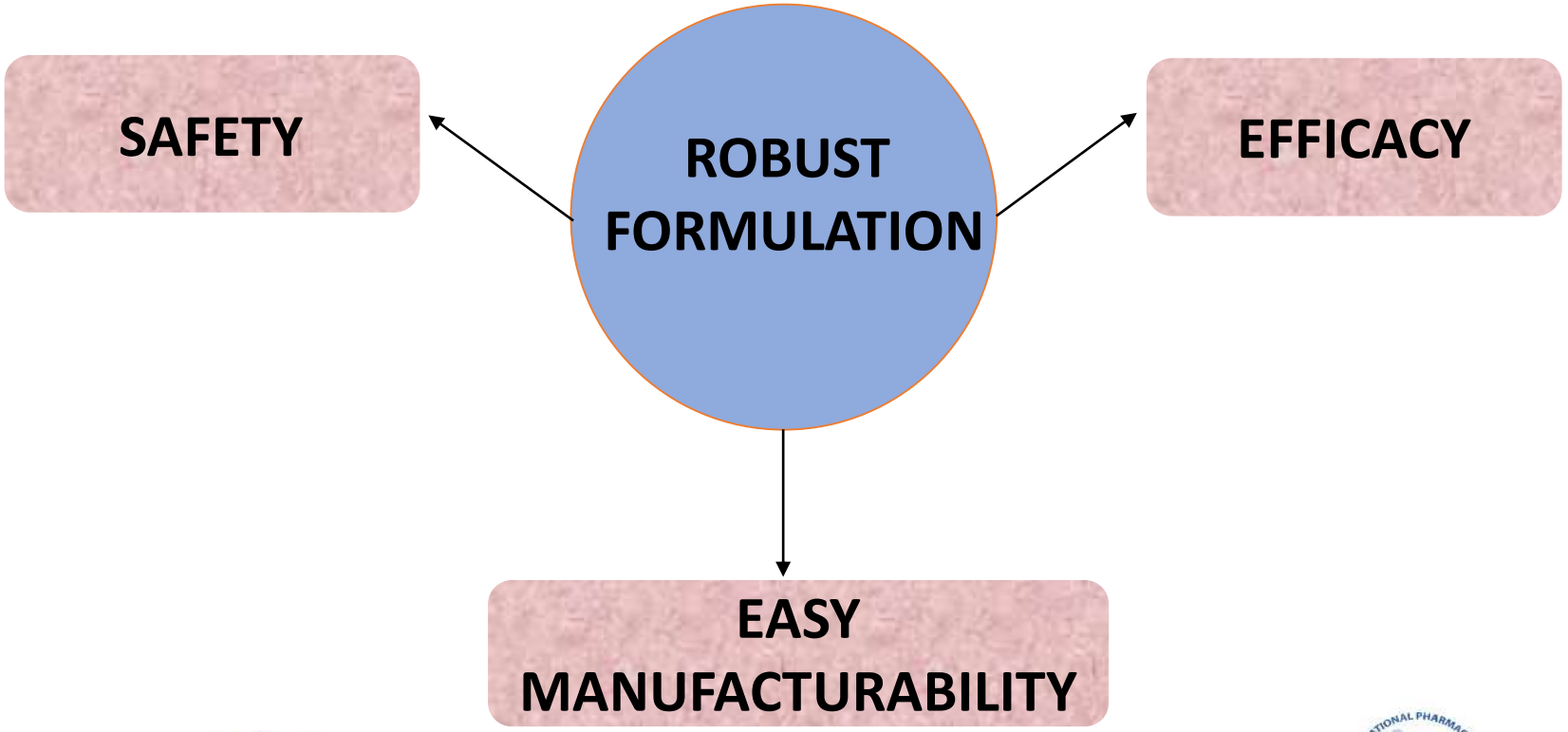
Excipient Manufacturer	API / Drug Manufacturer
No “master” batch record - documentation often created and stored in different systems and locations within the plant	Master batch records exist for each product and batch.
Audited by customers to the ISO 9001 and/or excipient GMPs FDA typically inspects only ‘for cause'	Inspected by regulatory authorities and often audited by customers to comply with ICH Q7 GMPs. 
Process capability and verification studies are more common than formal validation	Formal validation of manufacturing, cleaning and packaging operations
Excipient GMPs Chapter <1078> in USP	

Compendial Status of Excipients

- **USP/NF** includes more than 40 functional categories of excipients in pharmaceuticals, and many more may be added over time to meet the needs of new drug delivery systems and biotechnology-derived products (400+)
- **European Commission** also has its own directives for control of Excipients
- **Japan** has a Japanese Pharmaceutical Excipients (JPE) compendia with individual monographs
- **China** has Chinese Pharmacopoeia and GB standards for excipients and colorants / flavors respectively
- **India** includes Excipient monographs in the Indian Pharmacopoeia (140+)

ROBUST FORMULATION

Robust formulation means that the formulation will not be sensitive to ingredient variability in a manner that would impact the desired characteristics in your finished formulation like safety, efficacy and ease of manufacturability.



Excipient Selection & Use

FACTORS

- Contributes one or more functional attributes to the product characteristics
- Interacts with the active in the final formulated dosage form and/or provides a matrix that affects the critical quality attributes of the actives, including stability and bioavailability
- Quality and its function play critical roles in the effectiveness, safety, potency, purity, and quality of a product
- The lack of understanding of the function of an excipient may lead to a situation in which process control—and hence product quality—may be compromised, particularly when the impact of normal variation of the excipient quality on process control has not been established
- Need for complete characterization of an excipient and understanding its functional role in the formulated product is far greater when the excipient is used in a more complex product, such as a monoclonal antibody, a vaccine, or a gene therapy/cell therapy product, or in a new/novel drug delivery system such as an inhalation product

Excipient Selection & Use – Influence of Excipient on Safety & Effectiveness of Drugs

- depends on the **Route of Administration**, so qualitative and quantitative understanding of the excipient's composition is critically important to the understanding of a dosage form's bioavailability and bio-equivalence.

- **ORALLY ADMINISTERED DOSAGE FORMS**: excipients can affect safety and effectiveness outcomes by promoting or delaying gastrointestinal release

- **INJECTIONS:** The excipients can modify release patterns in much the same way they do for orally administered modified-release dosage forms

- **LOCALLY ACTING PRODUCTS** (topical applications, products for oral inhalation, nasal administrations, otic products, and ophthalmic dosage forms) - excipients modify the effectiveness outcomes by influencing the pharmacodynamic properties of the actives

- **VACCINES :** Adjuvants, which are excipients required for protein and conjugate vaccines, play a critical role in the immunologic characteristics of vaccines

Excipient Selection & Use – Influence of Excipient on Safety & Effectiveness of Drugs

- Manufacturers should understand the functional contributions of the excipients, that is, their "processability"

- Without this knowledge, it is difficult to see how the manufacturers can reliably demonstrate pharmaceutical equivalence among product(s) synthesized or perhaps formulated differently at different manufacturing sites, using excipients that possibly are sourced from different suppliers or vendors

- Such excipients are likely to have been manufactured by different processes, with starting materials whose qualities may be different from and/or sourced differently than those referenced in the original New Drug Application (NDA)

Excipient Selection & Use – Influence of Excipient on Safety & Effectiveness of Drugs

- Quality of the excipients used by different product manufacturers or at different manufacturing sites of the same product manufacturer may be different,
  - particularly if the manufacturer engages in multisourcing
  - interchangeability of excipients cannot necessarily be taken for granted

- Additionally, potential variation in equipment, processing operations, and personnel who may have different backgrounds, training, and levels of expertise, may present a complex multivariate situation that may render very difficult adequate control of the product quality

- Variation could range from minor to significant depending upon the function of the excipient used in the product, excipient interaction with the actives(s), and the characteristics of the product, including its route of administration and other factors

Physical characteristics

Example of Magnesium stearate

In market different hydrates and polymorphic forms of Magnesium Stearate are available

Identification of equivalent material is very critical

- Monohydrate
- Di hydrate
- Mixture Monohydrate and Di hydrate
- Various crystalline form

Magnesium stearate is being used as a Lubricant and its efficiency depends on

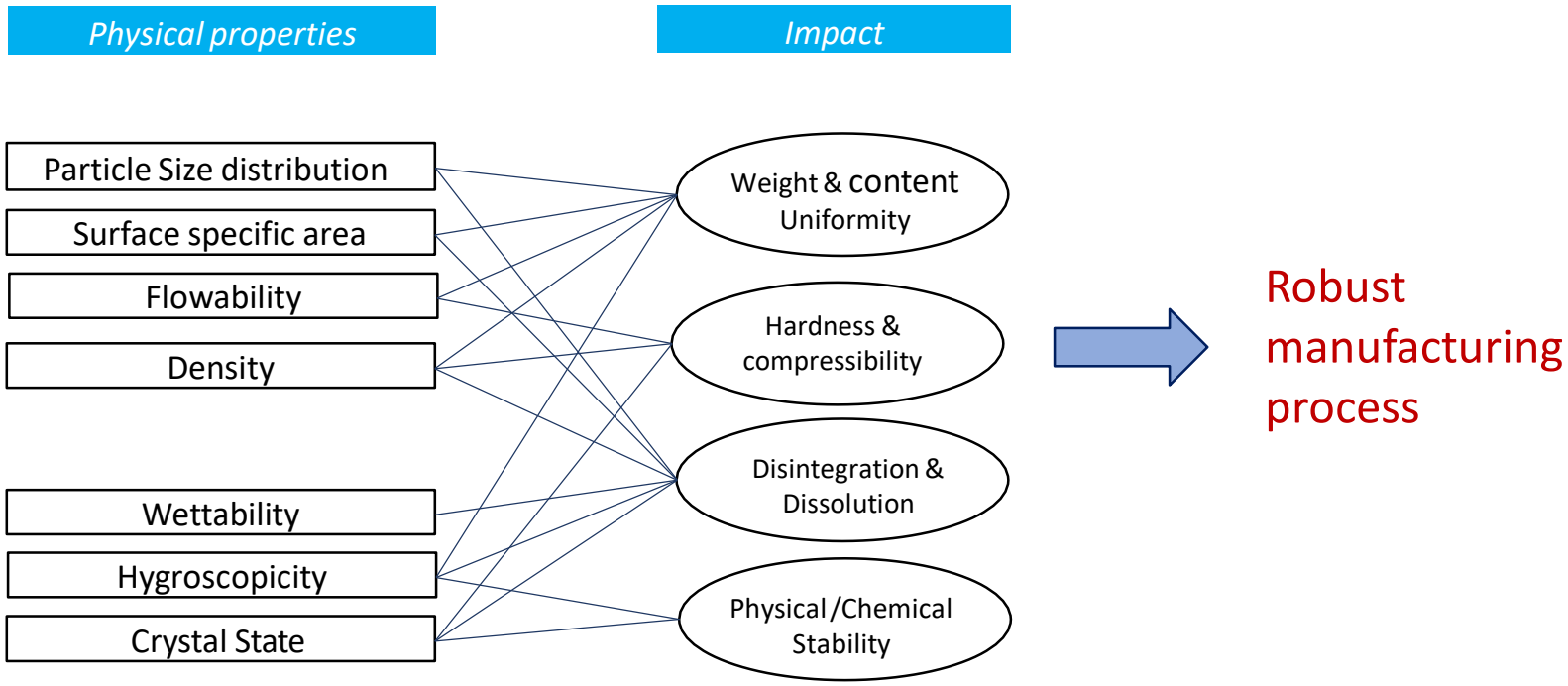
- Particle size
- Specific surface area
- Crystal Structure
- Chemical composition

QbD With Respect to Excipients

Formulation development by the QbD methodology, requires a determination of the Critical Quality Attributes (CQA) of a formulation, as predefined objective, and the knowledge of various physicochemical and performance characteristics of the excipients

Impact of Physical Properties of Excipients on Drug Product

While the analytical properties of excipients are routinely tested and controlled, physical characteristics play an equally important role

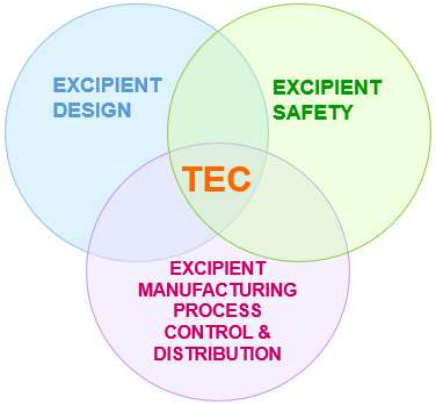


Important Physicochemical Attributes Affecting Excipient Functionality / Performance

Total Excipient Control (TEC)

- **Excipient Design Controls** would include how design criteria are set to meet the requirements for the intended use taking Quality by Design into account
- **Excipient Safety** involves the information which has been developed to support the safe use of the excipient in the intended application at the levels of use expected to be experienced by the patient
- **Excipient Manufacturing Process Control and Distribution** is the area of control traditionally covered by GMPs, Auditing, QC testing, Information Sharing and Supply Chain Security

Total Excipient Control (TEC)



- The concept of TEC utilizes all of the existing IPEC guidelines, programs and proposals to build an overall control system – gaps continue to be identified
- TEC covers the controls needed from the time an excipient manufacturer thinks of marketing a chemical as an excipient for the pharmaceutical industry to the time the patient takes the drug product containing the excipient.

IPEC Guidelines and White Papers

- IPEC-PQG Excipient Good Manufacturing Practices Guide
- IPEC Excipient Good Distribution Practices Guide
- IPEC-PQG Excipient Good Manufacturing Practices Audit Guide
- IPEC Excipient Good Distribution Practices Audit Guide (US & EU)
- IPEC White Paper on Excipient Pedigree
- IPEC Excipient Qualification Guide
- IPEC Excipient Information Protocol Guide
- IPEC Excipient Quality Agreement Guide
- IPEC Excipient Certificate of Analysis Guide
- IPEC Excipient Stability Guide
- IPEC Position Paper on Accelerated Stability
- IPEC Excipient Composition Guide
- IPEC Excipient Significant Change Guide
- IPEC Excipient Master File Guide (US)
- IPEC Risk Assessment Guide (US & EU)
- IPEC Co-Processed Excipients Guide
- IPEC Quality by Design Sampling Guide
- IPEC Technically Unavoidable Particles Profile Guide
- TEC Guidance Document

All guidelines and white papers can be downloaded for FREE at: www.ipecamericas.org

Total Excipient Control (TEC)

EXCIPIENT DESIGN

specifications, stability, validation, etc

- IPEC Qualification of Excipients Used in Pharmaceuticals Guide
- The IPEC Excipient Composition Guide
- IPEC Excipient Information Package (EIP): Template and User Guide
- The IPEC Certificate of Analysis Guide for Pharmaceutical Excipients
- The IPEC Excipient Stability Program Guide
- IPEC Technically Unavoidable Particle Profile (TUPP) Guide

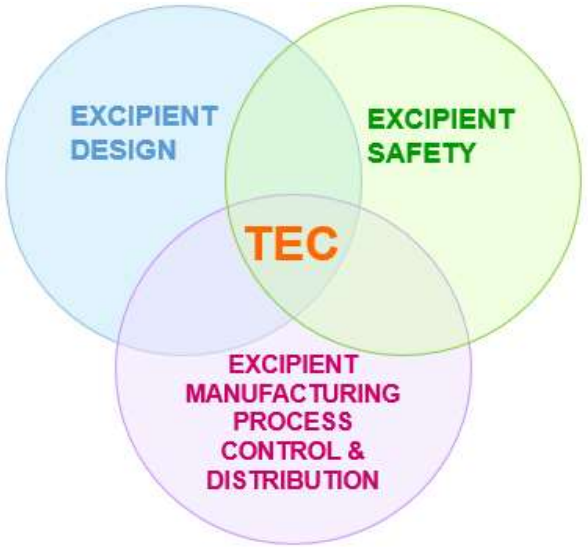
Relevant IPEC Guides

TOTAL EXCIPIENT CONTROL

EXCIPIENT SAFETY

toxicology, precedence of use, etc

- IPEC New Excipient Safety Evaluation Procedure
- IPEC Americas New Excipient Safety Evaluation Procedure



EXCIPIENT MANUFACTURING PROCESS CONTROL AND DISTRIBUTION

GMP, quality agreement, supply chain

- The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients
- The IPEC Quality Agreement Guide and Template
- The IPEC Good Distribution Practices Guide for Pharmaceutical Excipients
- IPEC Significant Change Guide for Pharmaceutical Excipients
- IPEC Americas and Europe Excipient Pedigree Position Paper

Improved Communication is Essential Today!!!!!

- **Users, Makers AND Regulators MUST** take more time to understand each other's needs and controls than done in the past
- **Changing World**
  - Contaminated Excipients from China & Elsewhere
  - Counterfeiting of Drugs & Excipients
  - Bioterrorism
  - BSE/TSE, GMO's, Allergens, Additives
  - Cost Reduction Goals – can drive poor decisions
  - Continuous Quality Improvement – QbD/PAT
- **Increased need for Supply Chain Controls and Traceability as well as Product Consistency!!!**

Conclusion

- Excipients play a critical role in the manufacture of drug formualtions by helping to preserve the efficacy, safety, and stability of APIs and helping to ensure that they deliver their promised benefits to patients.
- Optimal use of excipients provides pharmaceutical manufacturers with drug development cost savings, enhanced functionality capability and can also assist in drug formulation innovation.

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THANK YOU

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