# Excipient usage technical risk assessment for generic solid dose products.

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## ABSTRACT

This paper proposes a methodology for assessing generic solid dose small molecule drug products. It addresses the 'usage of the excipient' portion of the trinomial by utilizing a systematic approach for Risk Identification, Risk Analysis and Risk Evaluation as per ICH Q9 Quality Risk Management outlined for developing risk control strategies. The assessment and maintenance of the excipient risk profile is essential to minimize any potential risk associated with excipients that may impact patients.

**KEY WORDS:** Excipient risk assessment, solid dose, generic

## INTRODUCTION

The European Commission's Guidance for requiring formalized risk assessment for excipients of medicinal products was published in March 2015. According to The European Falsified Medicine (FMD) Directive 2011/62/EU, the manufacturing authorization holder (MAH) is required to ensure that all the excipients are suitable for use in medicinal products (1). The MAH is required to perform a risk assessment with respect to patient safety and document the measures taken to ensure this requirement. The guidance of the International Pharmaceutical Excipients Council of Europe (IPEC Europe) requires a risk rating assigned to the trinomial "excipient + excipient manufacturer + usage of the excipient" based on the outcome of each evaluation (2). This risk rating should not be considered as an evaluation of the performance of the supplier but an attribution of the level of risk of the trinomial.

The purpose of the assessment methodology is to evaluate and establish a risk profile with respect to the function of each excipient used in solid dose generic drug products. The assessment considers pharmaceutical dosage form, the indication of the drug product containing the excipient, function of the excipient in the formulation, proportion of the excipient in the formulation, daily patient intake of the excipient, and known or potential impact of excipient on the critical quality attributes of the drug product. This paper proposes an assessment methodology for solid dose generic

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small molecule drug products. It addresses the 'usage of the excipient' portion of the trinomial by developing risk control strategies utilizing a systematic approach of Risk Identification, Risk Analysis and Risk Evaluation, as outlined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q9 Quality Risk Management guideline (3).

### Risk identification

Generic drug products are developed by establishing and demonstrating bio-equivalency to the innovator product referred to as the Reference Listed Drug (RLD). Generic drugs are required to be equivalent to the RLD by dosage form, safety, strength, route of administration, performance and quality characteristics. Due to these rigorous regulatory requirements, minimal risk is anticipated from the generic drug product, its manufacturing facility and processes, thus not requiring the MAH of generic drug products to conduct full-fledged preclinical and clinical trials. For example, as indicated in the FDA's Quality by Design for Immediate-Release (IR) Generic Drugs, the level provided for each excipient should be consistent with existing drug products and below the levels listed in the inactive ingredient database (IID) for FDA approved oral solid dosage forms (4). Table 1 shows examples of types of information of ingredients provided in the IID Database.

The assessment of the drug product must consider if the same excipient types as was used in the RLD were used in the formulation. In addition the level of the excipients in other similar solid dose formulations will be a factor. Excipient compatibility is important to ensure that there are no interactions or adverse effects of the inactive ingredients to the product quality. The compatibility study will enhance the mechanistic understanding of the drug substance and its impurities, excipients and their impurities, degradation pathway and potential processing conditions for the drug product manufacture. The compatibility of excipients with other excipients must also be established. The concentration and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed in the development report relative to the respective function of each excipient. The report should demonstrate the ability of the excipients to provide their intended functionality and to perform throughout the shelf life of the final product. The levels of excipients should be consistent with the levels in the RLD formulation and for example should agree with the recommendations published in the Handbook of Pharmaceutical Excipients (5). The selection of excipients based on compatibility studies and similarity to the RLD formulation is one of the preliminary steps in product development.

**Table 1** Example of ingredient information provided in the IID Database

| INGREDIENT NAME | ROUTE | DOSAGE FORM | CAS NUMBER | UNII | POTENCY AMOUNT | POTENCY UNIT |
|---|---|---|---|---|---|---|
| Anhydrous Lactose | Oral | Tablet | 63423 | 3SY5LH9PMK | 735.2 | MG |
| Magnesium Stearate | Oral | Tablet | 557040 | 70097M6I30 | 4384 | MG |
| Mannitol | Oral | Tablet | 69658 | 3OWL53L36A | 681.65 | MG |
| Methacrylic Acid Copolymer | Oral | Tablet | NA | NA | 86.7 | MG |
| Starch | Oral | Tablet | 9005258 | NA | 615.6 | MG |

Further formulation development studies should be performed with various levels of excipients in the formulation (6). It should be verified if there was a risk assessment performed on the impact of the formulation variables i.e., selected excipient ratios, to drug product CQA's. This data should be considered while performing the risk review.

Excipients used in generic formulations must be of pharmaceutical grade, meet compendial standards and processed and stored under Good Manufacturing Practice (GMP) conditions. They must also have well-established toxicology data posing minimal effect on the drug product. In addition to submission batches, multiple scale-up (Stage 1) and process validation (Stage 2b) (7) batches are manufactured and tested prior to the commercial product launch. R&D stability data is available for at least 6 months as well as Process Performance Qualification (PPQ) batches are placed on stability. Therefore, there is a substantial body of data to demonstrate minimal impact of excipients on the drug product quality attributes and manufacturability throughout its shelf-life. Critical Quality Attributes (CQAs) of solid oral dosage forms are those aspects affecting product purity, strength, drug release and stability. Controls such as vendor quality management, excipient vendor specification, identification testing of incoming raw materials, drug product manufacturer specification, in process and finished product CQA's, ongoing stability program are all part of the initial product.

A Control Strategy to ensure excipients do not affect the purity, strength and stability of the drug product. Based on the comprehensive information currently available on each drug product, it can be determined if an excipient will adversely impact (high risk) drug product efficacy. This determination should be based on 'usage of the excipient' portion of the trinomial.

## Risk analysis

The functionalities of excipients in solid dose formulations can be used to categorize various levels of risk. Each functionality is evaluated on the basis of the impact on product efficacy to identify low, medium or high risk excipients as shown in Table 2.

**Table 2** Example of some excipient functions in Solid Dosage formulation and Risk Identification

| FUNCTION | RATIONALE | RISK |
|---|---|---|
| Plasticizer | Plasticizers used in film (aesthetic) coating solutions for IR products are added with polymers to make the latter flexible, resilient and easier to handle. No impact on drug product efficacy. | Low Risk |
| Flavor/ Fragrance | Flavor/Fragrance masks taste or odour of API. It has no impact on disintegration/ dissolution or processing based on the Stage 1 characterization studies. Generally they are stable excipients and used in very low % in formulation. No impact on drug product efficacy. | Low Risk |
| Release modifying agent | Release modifying agents are used to control drug release in modified-release formulations. Critical for dissolution. May be present in higher quantities in matrix formulations. Generally stable excipients and hygroscopic. The excipient function may have an impact on drug product efficacy. | High Risk |

## Risk evaluation

After the preliminary risk categorization, the risk evaluation will be based on the identified risk (efficacy/bioavailability) and the impact of each excipient functionality on drug product critical quality attributes. A risk assessment can be performed for each Drug Product manufactured. The categori-zation of low, medium and high should be based on objective data, either from product development studies for new products or product development and commercial product lifecycle data for existing legacy products (Table 3).

For generic solid oral dosage forms, a preliminary decision tree (shown in Figure 1) can be used to assess an excipient's technical risk based on their impact on the bioavailability of the drug substance in the patient. However, this is only a general guideline, special attention should be based on the formulation development as the variability in grades and amounts are mitigated through optimized and fixed control strategies.

**Table 3** Example of Excipient Risk Assessment based on Drug Product CQAs

| | DRUG PRODUCT CQA | | | | |
|---|---|---|---|---|---|
| FORMULATION ATTTRIBUTE | CONTENT UNIFORMITY | ASSAY | DISSOLUTION | DISINTEGRATION | IMPURITIES |
| Diluent | Low | Low | Low | Low | Low |
| Stabilizer | Low | Low | Medium | N/A | Low |
| Binder | Low | Low | Low | Low | Low |
| Disintegrant | Low | Low | Low | Low | Low |
| Lubricant | Low | Low | Low | Low | Low |
| Glidant | Low | Low | Low | Low | Low |

If a risk is identified, a risk mitigation plan is initiated which includes setting acceptable limits based on existing scientific knowledge of the product. A Control Strategy is then defined to ensure that the product be manufactured consistently and to the expected quality. The severity rating (low, medium or high) of the excipient risk will determine the control measures to be applied. All excipient CQAs are controlled by testing and reported on CoA's which are reviewed and approved prior to release of material for use. Changes to any specifications and or tests should be managed through a change management system where technical impacts are assessed and mitigated through trials, process optimizations or post approval changes (as required) to ensure drug product quality is met. With the risk identification, risk analysis, risk evaluation and risk control strategies outlined in this assessment method, risk of excipients used in generic solid dose drug products can be categorized as low, medium and high risk. For excipients that are used for dual functions, the higher risk category may be assigned.

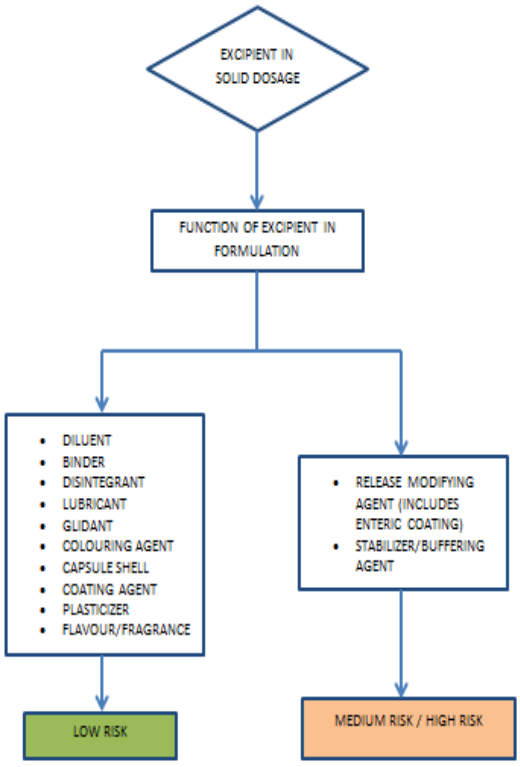


**Figure 1** Decision Tree Based on the Risk Evaluation Strategy

As per the IPEC Europe "How to" document on the formalized risk assessment for ascertaining the proper good manufacturing practice of excipients of medicinal products for human use, the manufacturing authorization holder should consider:

1. pharmaceutical form and use of the medicinal product containing the excipient;
2. the function of the excipient in the formulation;
3. the proportion of the excipient in the medicinal product composition;
4. daily patient intake of the excipient;
5. any known quality defects/fraudulent adulterations, both globally and at a local company level related to the excipient;
6. whether the excipient is a composite;
7. known or potential impact on the critical quality attributes of the medicinal product.

The product development data covers risk elements for numbers 1 to 3 and 7. The excipient IIG database review will address number 4 and an excipient specific review can be performed to address number 5 and 6.

In addition, risks presented to the quality, and safety of excipient from its source has to be assessed and may include:

- presence of transmissible spongiform encephalopathy (TSE)
- viral contamination
- microbiological or endotoxin/pyrogen contamination
- impurity originating from the raw materials
- potential for any impurities carried over from other processes
- environmental control and storage/ transportation conditions including cold chain management
- supply chain complexity
- stability of excipient
- packaging integrity

The excipient manufacturer GMP and supply chain risks are critical factors for which the following are required (verified as part of the site GMP inspection):

- establishment and implementation of an effective pharmaceutical quality system
- availability of competent and appropriately qualified personnel
- defined job descriptions for managerial and supervisory staff responsible for manufacturing and quality activities
- training programs for all staff involved in manufacturing and quality activities
- training programs related to health, hygiene and clothing as identified as necessary to the intended operations
- provision and maintenance of premises and equipment appropriate to the intended operations
- documentation system covering all processes and specifications for the various manufacturing and quality operations
- systems for coding and identifying starting materials, intermediates and excipients to allow full traceability
- qualification program of suppliers
- system for quality control of the excipient and a responsible person independent from production to release the batches
- retention of records for incoming materials and excipients and retention of samples of excipients for the periods required by GMP
- availability of systems to ensure that any activity contracted out is subject to a written contract including effective monitoring program for contracted activities.
- maintenance of an effective system whereby complaints are reviewed and excipients may be recalled
- change management and deviation management system
- self-inspection program has to be reviewed

### Ongoing risk review

An ongoing excipient risk review process is initiated once the excipient and the risk profiles have been created. The ongoing review should include the number of defects connected to batches of excipient received, type/severity of such defects; monitoring and trend analysis of excipient quality; changes made to their quality systems; loss of excipient manufacturer GMP certification; observation of trends in drug product quality attributes which will depend on the nature and role of excipient; observed organisational, procedural or technical/process changes at the excipient manufacturer; audit/re-audit of excipient manufacturer. The review process can be carried out through the company's Ongoing/Continued Process Verification Program (8) and/or Product Quality Review Program that would trend excipient CQA's, CMA's, failures and deviations. The elements as listed above should be reviewed routinely ensure that the risk profile of each excipient is still current.

## CONCLUSION

The final risk profile for each excipient is created with an overall risk rating for each component i.e., excipient, excipient manufacturer, usage of the excipient. If the excipient is used in multiple drug products, a control mechanism to update and maintain the

excipient risk profile must also be established. The review of the excipient risk profile is carried out as a part of the drug product (ANDA) submission process, actively maintained and revised through the change control process. A major contribution to the excipient risk profile comes from its manufacturer. Hence a clear quality agreement (9, 10) and good relationship with the excipient manufacturer's GMP site is critical. The practical methodology explained here helps in effectively maintaining excipient risk profiles using ICH Q9 Quality Risk Management tools. The assessment and maintenance of excipient risk profile is essential to minimise any potential risk associated to excipients impacting patients.

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