

<b>Title: Filing Strategy for Specifications for Raw Materials used in API Manufacturing</b>					
<b>Guidance Number: 128</b>					
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**Introduction:**

This document recommends the strategy for the filing of specifications for raw materials used in the manufacturing of Active Pharmaceutical Ingredients (APIs). A common strategy if used by all affiliate sites, will establish consistency in the API raw materials registered specification and insure that only the minimum appropriate specifications are filed. The strategy is designed primarily for new products filings.

**Practice:**

Review of historical practices for filing API raw material specifications shows that the level of detail is varied across Site, from minimum filing appropriate for the intended use of the material, to large number of specifications of limited value and the related detailed analytical methods.

In order to provide consistency in filing API raw material specifications and regulatory flexibility, this guidance provides recommendations as to the level of specifications required for various categories of raw materials. The categories were defined based on common knowledge of manufacturing process and the level of specifications was established based on the nature of the material and its intended use of each category. Raw materials are categorized in six (6) groups.

**General background**

The major markets (USA, Europe, Canada, Australia, Japan, South Korea, Singapore) regulatory guidances do not provide specific instructions on what specifications to file for API raw materials but indicate that the specifications must be appropriate for their intended use. These major markets guidances are either directly using the ICH M4Q (guidance for the Common Technical Document (CTD)) or a slight modification of the M4Q guidance.

Extract from M4Q, section 3.2.S.2.3: Control of Materials (Drug Substance):

*“Materials used in the manufacturing of the drug substance (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided.*

*Information demonstrating that materials (including biologically-sourced material, e.g. media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate.”*

This strategy addresses only the registered raw material specifications defined as the test technologies and limits provided to “external agencies and are legally binding”. It is expected that PGM API sites will evaluate whether additional internal targets to control the quality of the incoming raw materials are required. Limiting the registered specifications to the minimum requirements allows for future flexibility to adapt to the commodity market for API raw materials, to advances in analytical technology, and to implement improvements without the need for changes in the regulatory filing. Quality of the raw materials will not be compromised, as the sites will use systems and internal targets to control and monitor performance of the suppliers.

**General requirements for filing**

hazardous nature of the material, it will never be sampled and tested by Site and will be accepted on supplier Certificate of Analysis data.

Category 6:

This category includes utilities such as nitrogen and water. Specifications in general should not be filed unless required by prevailing guidances. Specifications for water may be required depending where in the process water is used and how the API will be delivered to the patient. (See reference (2) for example of guidance that requires specification for water under specific conditions)

**Summary of Filing Strategy:**

Category	Minimum specification Filing
1	Identification, potency, purity (include main impurities, if appropriate). Attributes that impact API quality
2	Base specifications (using strategy below). Critical parameters
3	Identification, potency, purity (include main impurities, if appropriate).
4	Identification
5	Basic category requirements but specify that raw material is accepted on supplier COA
6	Preferably should not be filed

**Process flow for development of registered specifications**

In general the primary responsibility for the development of raw materials specifications resides with Analytical Research and Development. The following process flow is recommended:

- R&D identifies the required raw materials for the synthesis of an API and any raw material quality attributes that impact the quality API during process development.
- R&D determines whether registered specifications for the raw materials are already available.
- If specifications are available, R&D evaluates the specification against any know quality attributes required for the process.
- If the specifications are acceptable, they are utilized for the new filing (the underlying assumption is that the existing specifications were established according to the strategy outlined in this document and therefore the specifications are acceptable to all stakeholder groups including the manufacturer. They should be revised if they do not meet the guidelines given in this document.
- If registered specifications do not exist or if quality attributes are required in addition to the current established specifications, R&D, in collaboration with the manufacturing site and the co-development team develops the new specifications based on the above strategy.
- R&D finalizes the specifications and creates the required Material Control Document