TABLE 8.8

Thresholds of Impurities

Maximum Daily Dose[a]	Reporting Threshold[b,c]	Identification Threshold[c]	Qualification Threshold[c]
≤2 g/day	0.05%	0.10% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake (whichever is lower)
>2 g/day	0.03%	0.05%	0.05%

[a] The amount of drug substance administered per day.
[b] Higher reporting thresholds should be scientifically justified.
[c] Lower thresholds can be appropriate if the impurity is unusually toxic.

For example, does known safety data for this impurity or its structural class preclude human exposure at the concentration present?

8.3.1 Good Manufacturing Practice

The term *manufacturing* is defined as one that includes all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, QC, release, storage, and distribution of active pharmaceutical ingredients (APIs) and the related controls. An API starting material is a raw material, an intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. The API starting materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which the production of the API begins. For synthetic processes, this is known as the point at which API starting materials are entered into the process. For other processes (e.g., fermentation, extraction, and purification), this rationale should be established on a case-by-case basis. Table 8.9 gives guidance on the point at which the API starting material is normally introduced into the process.

From this point on, appropriate good manufacturing practice (GMP), as defined in this guidance, should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 8.9. However, all steps shown may not need to be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to the final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating, and physical manipulation of particle size (e.g., milling and micronizing), should be conducted according to this guidance. This GMP guidance does not apply to steps prior to the introduction of the defined API starting material.