Title:	Stability Considerations for Planned or Unplanned API Process Changes				
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Prepared by:		Date:		Supersedes:	
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Approved by:		Date:		Review Date:	

Introduction

This document outlines the considerations site quality organizations should review to assess whether stability data are needed to support planned or unplanned post-approval changes to API or API Intermediate for sale manufacturing processes. This document also recommends customer notification if subsequent intermediate processing or drug product quality may be impacted by the change. This guidance also details considerations for the design of stability studies and the manner in which the resulting data should be used.

ICH Q7A states, "The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program."

If a planned or unplanned process change impacts the registration, validation, or quality attribute(s) of an API, then the impact of this change on API stability should be evaluated for the following issues and documented.

- Significance of Process Change
- Stability Impact Assessment
- Data Analysis
- Stability Study Considerations
- Use of Stability Data

Recommendations & Rationale

1. **Significance of Process Changes**

ICH Q7A states, "Changes can be classified (e.g. as minor or major) depending on the nature and

extent of the changes and the effects these changes may impart on the process." A minor process

change may be defined as a change that has no impact on registration or validation, and little or no impact on product quality. A minor process change should not require major testing or development efforts such as generation of supportive stability data. If stability data are needed, then the change should be categorized as major.

A major process change may be defined as a change that has a potential impact on registration, validation, product quality or GMP compliance. The evaluation of a major process change may require development support, including the collection of stability data.

In addition to determining whether a change is major or minor, the site Validation Team is responsible for determining whether stability data are needed to support a process change.

3. **Data Analysis**

Assessing the impact of change on the stability of API or API Intermediates for Sale may include, but is not limited to, the following steps:

a. **Step 1: Comparison to registered specifications** - Release results for all affected batches should meet registered specifications. In addition, no new impurities should be present in an amount greater than 0.1%. If all release requirements are met, then proceed to the next step where the release data are compared to historical batch release data to check for any atypical trends.

b. **Step 2: Comparison to historical release data** . Historical release data from the most recent batches prepared by the process prior to the change should be used as the "control" for data comparison purposes (lots involved with a previous process deviation may be excluded). It is desirable to have thirty or more batches in the historical data set. Fewer than 10 batches can be used for historical comparison, but the utility of some statistical tools is diminished. Data should be analyzed for any significant changes (i.e. data from affected batches is outside historical maximum, minimum, or average values), unusual trends, or new impurities. If release data for the affected batches still meet registered specification but an unexpected shift in data is noted, supportive stability studies may be needed.

c. **Step 3: Analysis of existing stability data** . Review of existing stability data will identify which chemical or physical attributes of an API or API Intermediate for Sale have been known to change over time. If the planned or unplanned change has potential to affect any of these attributes, then supportive stability studies may be needed.

4. **Stability Study Considerations**

Once it has been determined that a stability study is necessary to support a planned or unplanned change, the purpose of the study should be documented. The stability protocol does not need to be the same as for annual stability lots (e.g. accelerated or long-term conditions, study duration, test intervals, and test methods). The number of lots in the study will also be based upon the extent of the change. Stability data may be used to support a registration change, validation, and/or batch release.

4.1. **Change in Regulatory Process Description**

If a process change results in a revision of the registered process description, supporting stability data may be required. Manufacturing Compliance Team with assistance from Quality Assurance and Regulatory Affairs, is responsible for the regulatory strategy and creation of the regulatory change packages and development of stability protocol.

European Medicines Agency (EMEA) requirements base stability protocol design on the type of process change.

A **Type I Variation** only requires supporting stability data for changes in API retest date or storage conditions. In either of these cases, stability data at label storage conditions are required for two batches covering the duration of the requested retest period.

A **Type II Variation** refers to changes that affect API attributes that have an impact on stability. For changes of this type, accelerated and long-term stability data are required. If the API is known to be unstable (less than 24 month retest interval), six months of data are required for three batches. If the