Final Business Plan
M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
dated 6 May 2010
Endorsed by the ICH Steering Committee on 9 June 2010

1. The issue and its costs

The assessment and qualification of genotoxic impurities has increasingly become a stumbling block in drug development. There are multiple guidances and positions available addressing approaches to identify and qualify genotoxic impurities in pharmaceuticals, however, in several important instances the recommendations differ or provide unclear direction. The current ICH guidance on impurity evaluation (Q3A and Q3B) provides guidance on how to identify genotoxic impurities but give no guidance on acceptable levels. The EMA currently has available a final guidance on genotoxic impurities. The FDA has published a draft guidance. PhRMA has published a whitepaper on the topic, while here is no available guidance from Japan. There are some inconsistencies in the guidances between the EMA, FDA, and the recommendations in the ICH general impurities guidance. Importantly, there is a growing consensus that changes to the existing regional genotoxic impurity are necessary and that remaining points of contentions should be resolved in a new ICH guidance. In this process alignment with and amendments of other existing Q3 guidances should be considered.

2. Planning

The main deliverable is a harmonised guideline for evaluation, qualification and control of genotoxic impurities.

Given the broad impact this guidance may have the ICH six parties are asked to nominate at least two members (minimally 1 chemist, 1 toxicologist), and one member nominated by Health Canada, WHO and EFTA as observers.

A *Step 1* document will be drawn up during the first EWG meeting which is anticipated at the Fukuoka meeting in November 2010. Allowing for the complexity of this issue and the need to create broad support for the proposals the EWG is anticipated to publish a *Step 2* document for consultation in June or November 2012. After collecting and incorporating public comments, a *Step 4* document will be finalised in November 2013.

3. The impacts of the project

The major impacts of this project will be to enumerate acceptable levels and to describe potential approaches to the control of genotoxic impurities in drugs during development (clinical trials) and for marketing. The guideline will clarify when and how a genotoxic impurity should be identified and how it can be qualified and controlled. Identifying, synthesizing and testing impurities is expensive, time consuming and in some cases not technically feasible. The guideline will eliminate inconsistencies between international regulatory agencies help to avoid delays in drug development.