



6 July 2010

## CropLife International Position Paper

### The Use of FAO/WHO Equivalence Assessment in the Registration Process

#### Summary

CropLife International and its regional affiliates strongly support the procedures adopted by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) for determination of equivalence that are described in the “Manual on development and use of FAO and WHO specifications for pesticides”.

CropLife International urges all national crop protection product (CPP) regulatory authorities to incorporate the two tiered approach and the criteria for judging equivalence as a basis for evaluating the safety of secondary product (‘me-too’) or candidate material products, into their regulations or statute and implement those with the rigor and spirit of the FAO/WHO manual. Recognizing that it might take some time to incorporate the two tiered process into national regulations or statute, CropLife International recommends a cascaded approach to equivalence assessment as a basis for “me-too” registrations in the interim.

CropLife International also urges all national CPP regulatory authorities to implement protection of regulatory data (PRD) and use the equivalence procedure for secondary registration only after the period of protection of regulatory data has expired. It is also essential to honor confidentiality, as confidential business information (CBI) is needed to support a Reference Material. CropLife International regards PRD and protection of CBI as pre-requisites for an orderly me-too registration process based on equivalence assessment.

#### FAO/WHO Equivalence Process

The “Manual on development and use of FAO and WHO specifications for pesticides” is the first publication of the joint FAO/WHO programme and was amended in 2009<sup>1</sup>. The Manual provides the standard process, unified requirements and procedures, harmonized definitions and nomenclature, technical guidelines and standards applicable to pesticides for use in agriculture and public health. It also includes a two tiered process on how to determine equivalence and data requirements for

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<sup>1</sup> *Manual on development and use of FAO and WHO specifications for pesticides*, March 2006 revision of the first edition, Rome, with amendments agreed at JMPS in 2009; to be published as revised version in November 2010.

determination of equivalence between a previously assessed CPP and a non-registered CPP with the same active ingredient. That process is followed by the JMPS to determine equivalence and is referred as FAO Equivalence or FAO/WHO equivalence process.

For the purposes of this paper, the following definitions will apply:

**Reference Material:** technical grade active ingredient of an existing registered compound, for which the safety has been demonstrated and complete chemical, manufacturing, and toxicological information has been submitted.

**Candidate Material:** technical grade active ingredient of a product for which registration is sought by relying upon the existing registration of a CCP with alleged equivalent active ingredient (s). The registration of a product based on a Candidate Material is often referred to as secondary registration or “me-too” registration.

### **Establishment of the Reference Material for Equivalence Determination**

A key element of any equivalence procedure is the establishment of the Reference Material. The Reference Material is the technical grade active ingredient of a CPP that has been extensively tested and evaluated to demonstrate that it is safe to use. It needs to be documented with a full data package<sup>2</sup>, which must contain a complete impurity profile (manufacturing impurity limits for all impurities present at  $\geq 1$  g/kg), analyses of active ingredient and all relevant impurities present, taken from at least five typical manufacturing batches, a complete description of the manufacturing process including all reactants, reagents, catalysts, intermediates, and solvents, and a complete toxicology and eco-toxicology profile.

The availability of the complete data package for the Reference Material is of fundamental importance. If there are elements missing from the data package, it will not be possible to conduct a full equivalence determination; accordingly, compounds with incomplete data packages must not be used as Reference Material. The data package contains intellectual property that needs adequate protection<sup>3</sup>.

All FAO/WHO pesticide specifications, and their associated reference profiles, which have been established since 1999, based on data developed using internationally accepted methods of analysis for the active ingredient and on a detailed evaluation of information on physical, chemical, toxicological and eco-toxicological characteristic, can be used as Reference Material by anybody with the required authorization to use the respective data package.

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<sup>2</sup> See Section 3.1 of Manual (ref footnote 1) for ‘minimum data requirements for reference specification.

<sup>3</sup> A data package submitted for registering a CPP typically contains both, CBI (that must remain confidential and must not be shared with any third party at any time) and regulatory data under data protection, such as toxicological study results, which must be protected during the period of “exclusive use” and must only be used for registration of the data owner until expiry of the data protection period, i.e. “exclusive use” period.

Typically the registrant of a CPP with a new active ingredient must have a complete data package on file with the national regulatory authority that holds the basic and, normally, the first registration for use in a given country.

Since the Reference Material will have already been fully evaluated by the national regulatory authorities, it serves as the quality standard against which all other products containing the same active ingredient will be measured.

If the first or primary registrant of a properly established Reference Material has withdrawn its product registration in a given country, the authorities may still rely on the reference profile originally established on the basis of the data originally submitted by the first registrant in order to conduct an equivalence determination. However, in cases where the first registration was withdrawn following concerns about the safety of the product for consumers, workers or the environment, CropLife International strongly discourages registration of a product based on an equivalent material.

#### **First Tier in the FAO/WHO Equivalence Process<sup>4</sup>**

Once it has been ascertained that a Reference Material has been established, and the supporting data mentioned above can legitimately be used by the assessor, it will be possible to conduct an equivalence assessment to determine the suitability of a Candidate Material for product registration from a secondary manufacturer.

The first step in the procedure is to conduct a rigorous comparison of the impurity profile and manufacturing process of the Candidate Material with that of the Reference Material as well as the evaluation of a mutagenicity test (Ames test).

The comparisons required in this step of the procedure are highly demanding, and they must be conducted with extreme care and precision. Once all of the requirements of the Tier 1 of the FAO/WHO equivalence process have been satisfied, the Candidate Material may be assumed to be “equivalent” to the Reference Material, and, if permitted by national regulations or laws, products based on this Candidate Material may be granted a secondary or “me-too” registration.

#### **Second Tier in the FAO/WHO Equivalence Process<sup>3</sup>**

If the requirements in Tier 1 of the Equivalence Determination are not satisfied, then additional data is needed to compare the toxicology profile of the Candidate Material to the Reference Material. These determinations require a detailed evaluation of the acute – and possibly sub-chronic and chronic toxicology data – and, if necessary, the eco-toxicology profile of the Candidate Material in comparison with that of the Reference Material.

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<sup>4</sup> *Manual on development and use of FAO and WHO specifications for pesticides*, March 2006 revision of the first edition, Rome, with amendments agreed at JMPS in 2009; to be published as revised version in November 2010.

In cases where all of the requirements of Tier 2 of the FAO/WHO Equivalence Procedure have been satisfied, the Candidate Material may be assumed to be “equivalent” to the Reference Material, and, if permitted by national regulations or laws, the CPP with the Candidate Material may be granted a secondary or “me-too” registration.

Alternatively, if the Candidate Material in question is not found to be equivalent, the applicant may apply for registration of the CPP supported by a full data package generated on that Candidate Material.

### **Cascaded Approach**

CropLife encourages national registration authorities to follow the FAO/WHO Equivalence Process as described above. In cases, where no profile of a Reference Material is available, we suggest that the authorities consider the following approach:

- a. Where an FAO Specification exists based on the post-1999 procedure, explore the possibility that JMPS conduct the equivalence evaluation process by submitting all required data of the Candidate Material to the FAO or WHO, as appropriate, with a request that JMPS conducts an equivalency determination based on data that supported the establishment of a JMPS specification. This approach is also applicable to compounds for which a JMPS specification has not yet been established. In this latter case, the data for both the Reference Material and the Candidate Material must be submitted to FAO or WHO along with the request for an equivalence determination<sup>5</sup>.
- b. Source a full data package to establish a Reference Material from an applicant. The registration authority may request that the original applicant provides the needed information, or that a secondary/new applicant submit a complete data package for the compound, in order to (re-)establish a Reference Profile for that active ingredient.
- c. Recognize equivalence evaluation results from another country (for the same technical material of the same origin). As a final option, the authorities may accept the results of another country’s equivalence procedure if the applicant wishes to register a CPP with the same technical grade active ingredient (Candidate Material) as has been found equivalent in the other country that determines equivalence with full adherence to the FAO/WHO procedure and another product with the same active ingredient is or has been registered in that country.

### **Conclusion**

CropLife International believes that once the “exclusive use” of data period<sup>6</sup> of an active ingredient expires, other products with the same active ingredient can only be

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<sup>5</sup> FAO and WHO have expressed willingness to provide this service to national authorities on request.

<sup>6</sup> The exclusive use period expires once protection of regulatory data has ended. However, certain data remains confidential (so-called CBI), which means it can only be used by the authorised entity but not shared with any third party without written authorisation from the data owner.

registered without repeating the assessment of the full data package while maintaining an acceptable level of safety, if the following conditions are met:

1. The Candidate Material is equivalent to the Reference Material.
2. The Reference Material has been evaluated and registered based on the complete data package. Any Reference Substance must be supported by a complete data package; otherwise, an equivalence assessment will be meaningless, with the likely possibility that some products based on compounds with toxic, eco-toxic, or otherwise undesirable characteristics, might be granted registration.
3. Where no complete data set for a Reference Material is available, no equivalence evaluation can be carried out.
4. In cases where no complete data set for a Reference Material is available, CropLife International suggests a cascaded approach to equivalence assessment.

CropLife International recognizes that the responsibility to decide, which CPPs are legally sold and used in a country are those of the national registration authority in that country and further believes that the inherent rigor of the FAO/WHO equivalence procedures provides adequate assurance that the properties of a Candidate Material are acceptable with regard to safety to users and the consuming public. CropLife International therefore recommends the rigorous application of these criteria in the evaluation of CPP Candidate Materials for secondary (“me-too”) registrations, where such registration procedure is permitted by national regulations or statutes.

In recognition of the expertise required to conduct equivalence assessments, CropLife International encourages building capacity, where necessary, to evaluate equivalence at national level based on latest FAO/WHO procedures.

Finally, CropLife International reaffirms its commitment to the highest attainable quality standards for CPP’s in global commerce, in order to ensure that all CPP’s have been demonstrated to be safe to users and consumers, when used according to label directions. By applying the FAO/WHO equivalence process to Candidate Material, regulators can be assured that products from each and every manufacturer will meet the demanding global standards and quality requirements that are necessary to protect agricultural workers, consumers, and the environment.