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ECPA considerations: disclosure of studies under Commission initiative on transparency & sustainability of the EU risk assessment model

ECPA supports the objective of increasing public confidence in the risk assessment process, including actions intended to improve transparency. As we consider the possible future disclosure of certain undisclosed safety data, we need to assure that legitimate confidential business information and intellectual property rights will remain protected globally.

Re: possible disclosure of active substances registration dossiers

- Confidential Business Information (CBI) to be exempted from disclosure.
- CBI: justification for non-relevant impurities.
- Timing of disclosure.
- Modalities of disclosure.
- Raw data.

CBI to be protected - summary

- A.I. Manufacturing Process and Route to Manufacture.
- Detailed A.I. specifications including non-relevant impurities profile and non-relevant additives.
    - Justification of the limit (max. concentration) for the impurities in specification.
    - Explanation for the Formation of Impurities, including those theoretically possible.
- Methods of analysis for non-relevant impurities.
- 5-batch analysis.
- Detailed Product Composition and Confidential Statement of Formula.
    - Identity and content of each non-classified co-formulant.
- Personal data for all studies.
- Specific information provided and justified by applicant on a case-by-case basis

Impurities: background

Both industry and regulators across the world consider that the identity and quantity of each non-relevant impurity in a substance are among the most valuable regulatory data in an approval dossier and therefore benefit from a legal presumption of confidentiality under Article 63(2) of Regulation 1107/2009.

The information on the name and the exact quantity (in Certificates of Analysis) or maximum quantity (in the detailed specification) of impurities present in the technical active substance is intended to provide a complete chemical profile of the active substance used for hazard testing purposes. It concerns the minimum purity of the active substance and the identity (i.e. name, CAS number, structural formula) and maximum quantity of each impurity present in the active substance for each manufacturing plant.

The presence of impurities results from the specific substance manufacturing process. In other words, if the manufacturing process changes, the identity and quantity of impurities may also change. This means that the precise manufacturing process of the substance, which is per definition at the heart of the “Confidential Business Information” topic, is revealed in case of disclosure of the identity and concentration levels of all impurities. As a consequence, an experienced chemist would have the capability to then deduce the actual manufacturing process. Therefore, this information must never be disclosed by any authority worldwide.

It is important to note that the identity section of a dossier must provide the regulator with the "realistic worst case" scenario for the active substance in relation to its purity and the presence of impurities (both in terms of identity and content limits for each impurity). This information provided must also include impurities that are not detected but that could theoretically be formed. In reality, the technical material produced has generally higher purity and contains fewer impurities or at lower content levels.

Two types of impurities are distinguished: the so-called "relevant" impurities, i.e. impurities with a toxicological, eco-toxicological or environmental relevance, and all other impurities. An impurity is considered "relevant" if its presence at elevated levels can contribute to the overall hazard which the substance represents for human or animal health or the environment. The relevance of a given impurity is based on assessment of its hazard potential. So, the information on relevant impurities is necessary to allow the regulator to determine the hazard (not the risk) which the use of the substance may have for public health and the environment. As a consequence relevant impurities are not confidential and cannot be treated as such.

The "analytical profile of batches tested", i.e. information concerning the quantity of all impurities present in the various batches and the minimum, median and maximum quantity of each of those impurities reported in a table, is intended to support the detailed specification. The content limits in the specification are calculated from the corresponding data measured in the analytical profile of batches.

At least five representative batches from the industrial scale production site of the active substance must be analysed to confirm the purity of the active substance, impurities, additives and each other component. The batches are taken from 5 different production campaigns selected at random to ensure a more representative coverage.

The results of the analysis are reported in tabular form with quantitative data, in terms of g/kg content, for all components present in quantities of 1 g/kg or more and typically should account in total for at least 980 g/kg of the material analysed. Each component (including each non-relevant impurity) is identified by its chemical name and has its analytical content measured. Accordingly, this document again reveals the precise composition of the substance manufactured, including all non-relevant impurities.

The most representative batch is selected for the eco-toxicological and toxicological testing in order to establish the hazard profile for the substance.
Disclosure of this information raises the same concerns as declared in the previous paragraph because this information is supporting the detailed specification as deduced by calculation of data determined in the analytical profile.

Finally the disclosure of the analytical methods for non-relevant impurities including their validation should be kept confidential as they refer to the identity of the impurity to be analysed and as a consequence they can help to deduce the impurity profile.

Impurities: practicalities and examples

- The disclosure of the complete profile and identity of the impurities including non-relevant impurities, would reveal critical information on how a specific technical material is manufactured.
- Trace levels of impurities from the process can provide a fingerprint as to the technology used. For example the information on the presence of an impurity can provide data on critical manufacturing steps like the catalyst system used for a given reaction. That type of information is a Trade Secret.

- The types of structurally related impurities can be suggestive of process intermediates and the raw materials used to source them. For example, the data might relate to the intermediates used in the recipe of an active where small levels of a specific substitution might suggest specific intermediates and the chemistry by which they are produced.
- The analytical technology to accurately and reliably characterize impurities, primarily because of the large number of structurally-similar impurities, is not easily accomplished and requires significant investment to develop. Similar considerations are valid also in the case of microbially-derived products, the spectrum and level of non-relevant impurities are a fingerprint for the microbial strain lineage used for manufacture. Developing and establishing the safety and reliability of those production strains requires millions of euros of investment. Therefore not only the strains, but also the registered impurity profile is considered CBI.
- The disclosure of information about very distinct non-relevant impurities would make easy to pull out what are the starting materials or intermediates.
- Disclosing the impurity profile and the analytical methods for the full set of relevant and non-relevant impurities would be detrimental to the registrant by giving away open access to information obtained with significant cost and time.
- For the reasons explained above, the detailed composition of the substance must also be considered as CBI.

Timing of disclosure of the complete registration dossier redacted for CBI

For new substances, from the date of first authorization of a formulation in a Member State, following approval of the active substance at EU level.

- Protection of data is at MS level and not at EU level (Article 59) and could be jeopardized if data are disclosed before product is authorized.
- Earlier disclosure would give significant competitive information away to competitors.
- Earlier disclosure would interfere with the decision-making process.
- Consistent with other regulated industries.

A distinction can be made for renewal of substances, where disclosure could occur from the date of renewal of the A.S. approval.

Modalities of disclosure under a controlled disclosure agreement

- Proper modalities have to be in place to guarantee the protection of IP in the EU and globally, including US data compensation rights.
- A standard undertaking must be signed by applicants at the time of submitting an information request. There must be a mandatory “Legal Notice” which applicants have to have “read and accepted”, by ticking a box on a web form, before they can submit their request. In absence of this acceptance, the request cannot be accepted. The Legal Notice includes wording such as, *“You may reuse the document requested and the information in it, free of charge for non-commercial purposes only, provided that the source is acknowledged and that you do not distort the original meaning or message of the document or information.”*
- The standard undertaking needs to be backed up by the availability of legal remedies and injunctive relief. For example, data accessor expressly consents the jurisdiction of a specified court or tribunal, agreeing to an anti-misuse provision with wording such as *“The data accessor consents to the data submitter pursuing effective remedies before a national court in order to seek recourse for misuse of information, including but not limited to injunctive relief and/or damages to the full extent provided by law”*. An additional consideration could be the imposition of criminal penalties if the undertaking is not respected.

- The standard undertaking must be backed up by a system for accurately identifying the applicant. Otherwise, “phantom” requests could be made and enforceability of the undertaking becomes practically impossible. This can be achieved by requiring that a scan of a valid ID card (for those countries with ID card) or passport be submitted. A control is needed to prevent identity theft. IP addresses of computers used to make submissions can also be recorded and this fact can be indicated. Controlled disclosure should prevent access to competitors and to entities who have pending litigation with the data owner, with wording such as: *“Applicants certify that they do not compete and/or that there are not engaged in any legal litigation with the data owner”.*
- Redaction/Removal of other Non-Safety Data elements of relevant studies. This should include the redaction or removal of Good Laboratory Practice (“GLP”) Certificates and Certificates of Analysis. The details of this certification are not required to understand and engage with the regulatory risk assessment process. However, regulatory authorities in several jurisdictions require that submitted studies are demonstrated to be GLP compliant.
- Include watermarks on each page, clearly forbidding use for regulatory purposes and showing the identity of the applicant.
- Include conspicuous copyright notices and warnings within the documents.
- A request should be made for each individual study of a particular dossier.
- The IT system should be developed in a way which facilitates the controlled disclosure and minimizes the risk of misuse:
    - The study to be disclosed could be virtually downloaded within the system but not physically transferred to the applicant’s computer, like the streaming facility typical in the music industry.
    - The disclosed study should not be printable.
    - The disclosed study should be available in the system for a limited period of time.

Raw Data

The expression “Raw Data” is often used inaccurately, and raw data wrongly confused with information already existing in study reports, which it is not. The definition from OECD is given below - ref. ENV/MC/CHEM(98)17. Access to raw data is defined by GLP/GEP procedures. Raw data as defined below should never be part of the disclosure.

7. *Raw data* means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognised as capable of providing secure storage of information for a time period as stated in section 10, below.