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Quality data: what are they?

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Summary. - Nowadays, quality has become a very important factor in almost all areas of endeavour. The data generated from tests for the assessment of potentially toxic chemicals is obviously no exception. It is necessary, therefore, that quality systems be developed to ensure that the data generated to support these tests are of good quality. An acceptable quality system should require that, where applicable, the tests be performed according to defined guidelines. Once defined guidelines have been identified for the type of test to be performed, it is then necessary to design a plan which describes how, when, where and by whom the data will be generated. If at all possible, the data should be generated according to written standard procedures which provide for the production of data to the same quality standard. The data should be generated and collected by properly trained staff using data collection systems (paper or electronic media) which ensure the accuracy, reliability and integrity of the data recorded. The data must then be recorded in such a way as to ensure that they are reported completely clearly and accurately. The report, whether it be in the form of scientific article, monograph or formal study report, should present the data in a consistent manner and allow for adequate reconstruction of the events which took place during the test. Finally, the report and the data supporting it should be verified to ensure that the test was carried out according to the relevant guidelines (if used), that the study plan was correctly followed and finally that all data were properly generated and accurately reported in the report. Adherence to a quality system of this sort should guarantee the achievement of quality data.

Key words: quality control, good laboratory practice, databases, toxicology.

Riassunto *(Dati di qualità: cosa sono?).* - La qualità, al giorno d'oggi, è diventata un fattore molto importante in quasi tutti i campi di attività. I dati che provengono da prove per la valutazione di sostanze chimiche potenzialmente tossiche, ovviamente, non fanno eccezione. Pertanto è necessario sviluppare sistemi di qualità al fine di assicurare che i dati generati a sostegno di queste prove siano di buona qualità. Un sistema di qualità accettabile, dovrebbe richiedere, ove pertinente, che le prove vengano eseguite in base a quelle linee guida ben definite. Una volta identificate le linee guida adeguate per un determinato tipo di prova, diventa poi necessario elaborare un piano che descriva come, quando, dove e da chi i dati saranno generati. Ove possibile, i dati dovrebbero essere generati in base a procedure standardizzate scritte, al fine di fornire dei dati aventi lo stesso standard di qualità. I dati dovrebbero essere prodotti da personale adeguatamente addestrato usando sistemi di raccolta dati (cartacei o elettronici) che assicurino la precisione, l'affidabilità e l'integrità dei dati registrati. E' necessario poi registrare i dati in modo tale da assicurare che vengano relazionati con chiarezza, completezza e precisione. La relazione, a prescindere che sia sotto forma di pubblicazione scientifica, monografia o rapporto formale, dovrebbe rappresentare i dati in maniera coerente e consentire una adeguata ricostruzione degli eventi che hanno avuto luogo durante la prova. In fine, la relazione ed i dati generati a suo sostegno dovrebbero essere sottoposti a verifica. Tale verifica dovrebbe assicurare che la prova è stata eseguita in conformità con delle linee guida (se utilizzate). Si dovrebbe verificare inoltre che il piano o programma delle prove sia stato eseguito correttamente e che i dati siano stati accuratamente riportati nella relazione. Seguire un sistema di qualità di questo tipo dovrebbe garantire la produzione di dati di qualità.

Parole chiave: controllo di qualità, buone pratiche di laboratorio, basi di dati, tossicologia.

Introduction

A good data bank for the control of toxic hazard of chemicals, whether for drugs, pesticides, household products or industrial chemicals depends on the quality of the studies performed which in turn depends on the quality of the data generated to support such studies.

The recognition of the need for quality data has led to the development of test guidelines issued by regulatory agencies throughout the world. The primary aim of these guidelines is to provide a standard by which the studies should be conducted as well as to harmonize the criteria for acceptance of the data generated in these studies.

Another step taken by the regulatory agencies was to establish a code of principles, better known as good laboratory practice (GLP). The purpose of these regulations, which are now implemented in many countries worldwide, is to assure the quality and integrity of the data obtained; to assure that the study can be reconstructed at any point in time and that valid conclu-

sions can be reached about the results of the studies. Last, but by no means least, GLP serves also to assure that the data generated will contribute to and improve the protection of public health and the environment.

Today there are national and/or international guidelines for the conduct of almost all types of studies. This paper deals primarily with data generated regarding the information and control of potentially toxic chemicals in international trade.

Guidelines and regulations

The international body most directly involved with the testing of chemicals is the Organisation for Economic Co-operation and Development (OECD) [1]. Since 1977, the OECD has been involved in extensive international consultations covering harmonization of chemical programs. In 1977 the OECD established an expert group with the aim of harmonizing GLP requirements and laboratory monitoring programs among member countries.

The result of this effort was the development of guidelines for the testing of chemicals and the principles of good laboratory practice. However, these guidelines and principles were seen in the broader context of the concept of mutual acceptance of data (the "MAD" decision). Both these documents for ensuring the harmonization of data generation and data quality were incorporated into the Council decision on MAD in 1981. All 24 member countries agreed to implement this decision which states that "data generated in the testing of chemicals in an OECD member country in accordance with OECD test guidelines and OECD principles of good laboratory practice shall be accepted in other member countries for purposes of assessment and other uses relating to the protection of man and the environment".

The adoption of the test guidelines and principles of GLP laid the foundation for harmonized standards.

Implementation of the test guidelines in member countries was very simple. However, verification that the data were generated in compliance with GLP called for a further set of procedures. To this end, the OECD in 1983 adopted a Council recommendation on mutual recognition of compliance with the principles of GLP. This "recommendation" was replaced by a decision in 1989 which called for the implementation of harmonized national GLP compliance monitoring procedures and made provisions for the mutual recognition of compliance among member countries. There are activities ongoing to bring this harmonization process forward.

Beyond the regulations

There is no question that GLP has brought an improvement in the overall quality of toxicological testing. However, it is quite obvious that GLP cannot assure also "good safety evaluation practices". Good safety evaluation includes not only quality studies and identification of hazard, but also evaluation of all data permitting the safe use of beneficial products. Where GLP assures the quality of the studies, good safety evaluation practices assure the quality of hazard and risk assessments necessary for the continued use of existing products. For all these factors to fall into place, the production of quality data has to be properly planned, correctly generated, collected and accurately reported.

Good laboratory practice: how does it apply?

It is a known fact that the principles of GLP were established primarily for non-clinical laboratory studies, especially toxicology studies. However, the basic concepts guiding these regulations can be applied to almost any type of data collection system.

In the case of the assessment of health risk of potentially toxic chemicals the applicability of GLP concepts is easily described.

First of all we should look at the processes used to generate health risk assessment for a designated site.

These are primarily: data collection, exposure assessment, toxicity assessment and risk characterization [2].

Data collection

Data collection and evaluation entail gathering and analyzing site data and quantitatively identifying potential chemical substances and hazards found to be present in on-site media (soil, surface water, ground water, air, biota). The types of data needed for a baseline risk assessment usually include identification of contaminants and their concentrations in key sources and media of interest, some characteristics, especially information related to release potential and the characteristics of the environmental factors that may affect the fate, transport and persistence of the contaminants. In this phase, procedures which could be brought under the GLP umbrella might include: a protocol for the sampling procedures, proper use of the sampling devices, use of references samples, collection procedures, preservation precautions, chain of custody and chemical analyses.

Exposure assessment

Exposure assessment estimates the magnitudes of actual or potential human exposure to chemicals at a site, or migrating from a site, the frequencies and durations of these exposures and the pathways by which all potential human receptors may be exposed. Results of this assessment are pathway-specific intakes for current and future exposures to individual substances. They should

consist of a discussion, analysis and conclusions that synthesize the results from the earlier portions of the baseline risk assessment document, and give a balanced representation of the available data and its relevancy to the health effects of concern. This document should reflect an accurate representation of the data collected and the results derived therefrom.

Toxicity assessment

Toxicity assessment takes into consideration the types of adverse health effects associated with chemical and radiation exposures and the relationships between the magnitudes of these exposures and adverse effects. The purpose of toxicity assessment is to weigh available evidence regarding the potential for particular contaminants to cause adverse effects in exposed individuals and to provide, if possible, an estimate of the relationship between the extent of increased likelihood and/or severity of adverse effects.

This is usually accomplished in two steps, hazard identification and dose response evaluation. Hazard identification involves characterizing the nature and strength of the evidence for causation. Dose response evaluation is the process of quantitatively evaluating the toxicity information and characterizing the relationship between the dose of the contaminant administered or received and the incidence of adverse health effects in the exposed population. From this quantitative dose response relationship, toxicity values are derived. These toxicity values are used to estimate the incidence of potential for adverse effects as a function of human exposure to the agent. In this instance applicability of GLP principles for data collection and interpretation is quite straightforward.

Risk characterization

Risk characterization combines the results of exposure and toxicity assessments to characterize baseline risks. Toxicity information specific to the chemical is compared against both measured contaminant exposure levels and those levels predicted through fate and transport modeling to determine whether current or future levels at or near the site are of potential concern.

It stands to reason that most of these processes would benefit from the application the principles of GLP. In fact, they need written statements which obliges the management of an organization involved in the generation of risk assessment data to establish a formal program to ensure the quality of the documentation produced. It is also possible to make reference to specific sections of GLP. These may include, but may not be limited to study plan, staff qualifications, standard operating procedures, data generation, validation, maintenance and calibration of equipment, data retention and storage and last, but not least, quality assurance.

Data generation. The plan

Most of the data generated regarding potentially toxic chemicals usually become part of scientific articles, reports of individual case studies and reports of toxicology experiments.

How the data are recorded, collected, interpreted and finally inserted into these documents are all very important steps in determining the quality of the data to be used.

Therefore, it is important that studies are designed properly in order that the findings, determinations and observations obtained are reliable, accurate and unbiased.

For this reason study plans, experimental protocols and research programs need to be adequately discussed and properly implemented in order to permit the generation of the right kind of data at the right time and in the right way.

The study plan should inform the user what, when, where, how and sometimes why the data are generated.

A very important factor is the experience and level of competence of the individuals actually involved in producing the data.

Personnel are a vital part of any quality program. They must obviously be sufficient in number and have the expertise to carryout their assigned tasks. In addition, they must be fully aware of the study plan and the purpose of the study.

There are many standard protocol designs and regulatory requirements that have been published or that are available. Oftentimes these protocols are followed in a noncritical fashion. Many times information from previous studies on the substance under investigation or on a substance structurally related to the one under test may suggest that a different investigative approach would provide better information for evaluation of health risk. This information should be used for the sake of good safety evaluation practices.

The importance of standard procedures

The use of standard operating procedures (SOPs) are in most cases a benefit and a valuable tool for good safety evaluation practices, but there is also a risk that they may represent a danger to these "good practices".

In order to be beneficial SOPs must be kept current and used. This method of utilizing SOPs enhances the conduct of the study as well as the quality of the data obtained and the interpretation of the results.

However, if SOPs are allowed to become obsolete, not critically used or staff members are not made aware of important changes, then the quality of the data may be seriously affected. There are cases where more appropriate procedures should be used in place of the current SOP. In this case either the study plan may be amended to include

this new procedure or the current SOP may be changed to allow proper changes to be made in due time. In this latter case it is vitally important that personnel involved in the generation and collection of the data be informed and sometimes trained regarding this change to standard procedure.

Collection of data

The gathering of the data relevant to the parameters required by the study plan and especially the observations made of the effects of the test substance on the test system (subjects) represent the most critical information obtained from safety evaluation studies.

Therefore the accuracy and reliability of the numerical data produced and the description of non-numerical data (observations) can significantly influence the interpretation of the effects during the evaluation phase of the study. To this end it essential to have properly trained technicians/observers. Poorly trained technicians and/or observers may generate unrealiable data or inadequate observations.

The data generated by these studies can either be collected on paper or by a computer system.

Under GLP, any computer system which captures data directly on line (no paper back-up) should be properly validated.

The validation process should ensure that the computer system (hardware and software) is functioning according to specifications. Obviously, there should be adequate documentation to demonstrate that the validation process was carried out correctly.

Reporting the data

Once the data have been collected, it is necessary to present them in an acceptable form. Data may be presented in a variety of ways: scientific articles, monographs, expert reports, etc. Regardless of the form or format in which the data are presented, it is very important to follow certain rules to ensure that what is reported in the final document is a clear and accurate reflection of all those data which have been collected and selected for presentation in the final report. Another important factor is to ensure that the data presented are complete and consistent throughout the report. In some cases it may be useful to produce a SOP to serve as a guide in preparing the report.

It is usually standard procedure to present scientific reports with sections such as: Introduction, Materials and methods, Results and Conclusions.

The "Introduction" should give a brief description of the purpose or objective of the study, where, why and when it was performed and by whom the data were collected, assembled and interpreted.

The "Methods and materials" section should state how the study or experiment was actually carried out.

If a study plan was used and followed, the methods section should describe how the study plan was implemented.

That is to say, if all actions and measurements required in the study plan were carried out completely, at the proper time and using the required instruments, equipment or other necessary materials.

If any deviations or modifications to the original study plan occurred these should be mentioned and an indication given as to whether these unforeseen events or changes in the study plan have affected the validity and/or integrity of the data collected or even the outcome of the study.

It is obvious that the "Materials and methods" section should be followed by a "Results" section which indicates the findings and observations obtained.

It is important that the findings be presented according to severity or importance, mentioning especially those findings which were found to be statistically significant or highly relevant to the purpose of the study. It is usually advisable to present the results following the same pattern used in discussing the methods. Finally, the "Conclusions" should very briefly but accurately state what the outcome of the study was and if the purpose and objective of study was satisfied. It is also useful to mention whether the report will be used to support other data or documentation and to what end.

Appended to these sections of the "text" or discussion of the report, it is sometimes useful or necessary to present the actual data collected.

If this is done, also the data section should be divided into sub-sections which present: the individual values obtained; the tabulation (means, incidence tables and statistical evaluation) of the individual data and any diagrams or figures representing an overall view of the values obtained.

Verifying the data

The key to obtaining quality data is to institute a system of data verification.

This system should be planned in such a way as to establish verification checkpoints at all stages of data generation; from the planning stage to the reporting stage. At the planning stage, verification should consist of ensuring that the study plan or program describes the type of data that are going to be generated and the data collection timetable, which states when the data are to be collected. From the timetable checkpoints can be established to ensure that the relevant data are collected at the times foreseen by the study plan. This stage of verification should also check that the data are generated in accordance with the requirements of the study plan or standard written procedures (if they exist). In addition, this phase of verification should also ensure that the data are recorded properly regardless of whether this occurs electronically or on paper.

It is advisable, in all data verification stages taking place during the course of the study or experiment, to gather all the data collected up to that point in time and perform the relevant verification procedures as mentioned above. This type of check, although apparently time-consuming, is an extremely important quality tool. It avoids unpleasant surprises at the end of the study and it permits correcting errors or problems in a timely fashion rather than at study termination when it is usually too late to take remedial action. Therefore, rather than being time-consuming, in reality this type of data check actually saves time because when the scientist prepares his/her report, he/she knows that the data are of good quality and reliable.

Once the study plan has been completed and the timetable followed in all stages, the data must be gathered and presented in report form, as mentioned earlier. If the data checks, carried out during the study, have been conducted properly and any remedial action required has been taken, this can be a relatively quick excercise.

However, all the data generated in the course of the study are gathered and checked against what is presented in the report. In the case where the data are presented also with individual and tabulated values, as well as the text, these sections should also be checked to ensure that all data requirements established in the study plan have been met. This serves also to ensure that the reported data are complete, accurate and in agreement with the requirements of the study plan and relevant standard procedures.

Storage of data

All data generated during the course of a study should be properly retained in order to permit an accurate reconstruction of the events of the study at any point in time. Data may be stored either on paper or on computer readable media. If data are stored only on magnetic media with no paper support, it is advisable to have two copies of the magnetic medium made and to store one copy in a different location. Care should be taken when changing hardware systems, because it is necessary to ensure that there is always a hardware system available which can read the data stored on the magnetic medium. Should the latter not be possible, it is then advisable to print all the data stored on the magnetic medium in order to ensure that a hard copy is available at all times.

All the documentation and specimens (if required) relevant to the studies performed should be stored in a safe place with access allowed only to authorized personnel. There should be measures taken to prevent loss of data in case of fire, vandalism or other possible means of loss or destruction of data. The data, however they are stored, should be classified in such a way as to allow quick and easy retrieval of any piece of data.

All movements of data whether they are being received into or withdrawn from the storage area should be properly documented.

Conclusions

This paper has discussed what constitutes quality data. The discussion was directed primarly at the data produced in the evaluation of potentially toxic chemicals, but the concepts presented are applicable to any data collection system.

Therefore any data collection system should foresee a planning stage which should follow formal guidelines (if they exist) and possibly contemplate written operating procedures for the phases indicated in the study design. A system of data verification should also exist, with checkpoints before, during and at the end of the study. Many of the concepts expressed in this paper bear a striking resemblance to several of the guiding concepts of GLP. This, in the present day and age should not be very surprising due to the fact that quality systems are being implemented throughout the world in all areas of endeavor.

Therefore it would seem a necessity, rather than an option, that all the data which are used to assess the toxic potential or risk of existing chemicals (a serious threat to human health and the environment) be of the best quality.

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