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EDITORIAL

GMP—three letters with many interpretations

Protection of patients or killing the clinical and research applications of PET?

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The purpose of good manufacturing practise (GMP) is not to place patients at risk due to inadequate safety and efficacy (and to hamper fraud) (Eudralex IV). These principles taken as long back as to Aristotle's "not to do harm to patients" are non-inevitable and non-disputable. But, which is the best way to fulfil this in the production of radiopharmaceuticals particularly for those evolving to become the molecular tools for positron emission tomography (PET)?

PET as a molecular imaging technology in clinical research was originally developed by teams of devoted clinical scientists, nuclear medicine physicians, physicists, data analysts and chemists. The short half-life of the radionuclides demanded and still demands production close to the patients. The authorities were satisfied and accepted that these first attempts could be regarded as an extempore (magistral) production with demands on identity, purity and sterility and always considering a careful risk assessment.

The enormous clinical perspectives of PET as an "experimental medicine" tool for clinical research, to support the development of new treatments and for patient management have now been seen together with the general development of GMP for pharmaceutical preparations.

It is important to recall that GMP in the context of preparing radiopharmaceuticals or in vivo diagnostic tracers is wider than sterility and apyrogenicity, but it also includes the production chain from producing the short-lived radionuclides and processing these into molecular entities at sub-pharmacological doses for use as diagnostics or research tools in man.

The regulations have with time increased and the authorities demanded and recommended proper organisation and management, competence of personnel, hygiene, premises, equipment, production, quality control, documentation, withdrawals and inspections.

This extended Site Master File was accepted by the producers and users. However, in hospital routines with few strict regulations, the new technique was pin-pointed as not just being expensive but also extra-regulatory demanding, which hindered the growth of molecular imaging as an important clinical diagnostic and research tool. This became even more obvious in the work to produce the few existing single monographs. In the extended Site Master File, the demands and the requirements were detailed, voluminous, exaggerated, confusing and have surely hampered further development. The introduction of PET as an important tool for drug development has also contributed by the addition of the demands from a thoroughly regulated pharmaceutical industry. Teams of quality persons from the industry, but with little knowledge of the PET technique, made clinical trials with PET all-through regulated and bureaucratic and with a full-scale administration and management. Any risk identification should be met by cautionary handling and documentation.

The compliance to all regulations concerning the development of pharmaceuticals in general has broken the clinical success of PET, which has not reached the bright perspectives outlined earlier. Fluorodeoxyglucose (FDG) is in fact the only widely accepted clinical tool used for numerous diagnoses available worldwide. There has been no lack of radiotracers with good characteristics, there has

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been no lack of applications, there has been no lack of evaluation methods, there has been no lack of resources to build new centres and there has been no lack of patients that would benefit from PET investigations. But, the expanded regulatory demands not balancing the risk assessment has been slowing down the development due to the lack of a reasonable safety assessment considering the risk benefit perspective.

To some extent, the slow development of appropriate synthesis technology to be used in small and developing PET sites has hampered the clinical characterisation and validation of new tracers and easy clear-cut evaluation tools for the clinical diagnoses of different diseases. There has not been any general agreement on the evaluation and interpretation of results from PET investigations and there is a continuous competition of what is the best radiotracer, the best model and discussions on the adequate clinical use.

However, the most hampering factor in our opinion is the requirements related to GMP. With the quality requirements, the number of quality people increased. Each one is a specialist in his own field but unable to communicate with others due to lack of general competence of the whole PET technology. PET is a tracer technology working with very small amounts, small administered volumes and, due to the short half-life, planned to be used within a short time frame (low CVT (concentration, volume and time) risks) The early development of PET was made on realistic risk analysis, but the trend of today's development is increasingly losing control of the risk benefit aspects. The time to supply quality documentation and quality control development has risen from hours or days to weeks and even months. The situation is that developed radiotracers do not reach clinical investigations even with successful animal experiments due to the imbalance of this burden.

There would also be a new definition of a closed system for the production of sterile pharmaceuticals. An ampoule with a membrane penetrated only by a needle is still a closed system. This opens for production ideas in closed on-line systems and isolator thinking in facilities where the ventilation process using air locks is not necessarily mandatory. The technicians operating the process are no longer in a closed system, only the process. Focus is no more on the filtration of radiopharmaceuticals through sterile membranes than on the whole process. The procedures may be general and supplement documentation for a new radiotracer minimal. It is important in this perspective to consider the safety assessment which may be handled differently in early clinical research or if the applications is a part of the diagnostic protocols. There is still a need in the latter case for full clinical trials with validated tracer production, investigation protocols considering data handling and evaluation. From our experience, we feel that the on-going trend is loosing the safety risk assessment perspective and may make it very difficult to progress the PET tool as a molecular imaging technology applied in clinical and clinical research beyond FDG. We believe that there is a need for a change in the communication among all the players/professions involved in this development.

We thus need a new type of quality person (QP). The QP is responsible for and report to the management on the production quality of radiopharmaceuticals. They should not only have knowledge in laws, regulations and in hygiene. A QP for PET must have an insight on the whole process and, therefore, must have a much broader competence including organic synthetic chemistry, trace analysis, toxicology, bacteriology, pharmacology, biochemistry and clinical medicine. He should take part in the early stages in the development process, give advice on how to "build in quality thinking in the process", assess risks continuously and support the colleagues in their improvements. His competence must be constructive, practical and responsible in order not to delay the process but instead to support and participate. The quality process must already be established based on risk assessments, when the development process is ready to go to humans.

A challenge is to perform appropriate risk analysis. Risk analysis has been used in many other circumstances and with great success. It came late to the pharmaceutical industry. In the last few years, the increasing acceptance of micro-dosing in PET is related to risk assessment analysis. However, it is now demanded by the Pharmaceutical Inspectors Convention that risk analysis, assessment, management and handling should be included in all steps in drug production Many procedures are easily assessed, general principles can be adopted and much time can be gained by agreements on how to reach an adequate risk management.

It is time to re-think about GMP for PET given the low risk factors associated with the PET tracer technology: (1) low concentrations (microgram) of the tracers, (2) small volumes (typically a few millilitres) administered and (3) the short time between tracer production and QC and administration to the human (minutes to hours and hence little time for culturing microbes). GMP must be integrated into the whole process, therefore, requiring a new competence of the QP and cautious inclusions of the new regulation possibilities. The QP function might be the most exciting position in future PET if used as an adviser and not mainly for control. GMP is in fact common sense including risk analysis thinking in a structured manner. GMP must be present in all procedures in radiopharmaceutical production for PET without being seen or noticed. GMP must be a safety guarantee to the patients and an advantage to PET, not an obstacle. Upfront discussions with country medicine inspectors on the issues/risks that are particular to PET and not avoiding the basic implementing GMP within the *true spirit* of its definition will surely be the way to resolve the existing issues and move forward.