European Medicines Agency
Inspections

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Notes on a seminar involving EFPIA and the EMEA PAT team in Ireland, 31 March- 2 April 2008

The Seminar was arranged as an initiative of EFPIA's PAT group following earlier dialogue with the EMEA PAT team in which it was agreed that site visits to discuss real life applications of the principles of Quality by Design, Design Space and PAT would be useful for both industry and regulators. The seminar involved several site visits followed by a plenary meeting to discuss the outcome of the visits, engage in an open discussion and identify priority actions for follow up.

The following summarises the main discussion points arising from each of the site visit topics. It should be noted that some of the issues identified arose in parallel in some of the other topic sessions but are only reported once in the report below to avoid duplication.

Mock inspections

One of the "inspections" was at a development site and therefore enabled an insight to be gained into what a pre-authorisation inspection might entail. It is unlikely that inspections of such sites would become routine. The need for such an inspection would depend on the complexity of the application and is likely to be driven by questions from the assessor where the opportunity could be taken, if necessary, to review data supporting an application. It might therefore be appropriate for an assessor to accompany the inspector for this. The amount and type of data that should be available on site during the inspection was often raised by industry as an issue that needs clarification. The inspector could focus on the reliability of data generated on site by looking at the quality system. It was recognised that full GMP standards are not expected.

The other site visit was of an active substance manufacturing site and the key issues for inspection here were the transfer of knowledge from the development site to the manufacturing site and in particular how the Design Space is translated into the routine manufacturing environment. Relevant staff in manufacturing need to know whether the process is within the Design Space or not and the quality system (as required by GMP) needs to enable "failures" to be identified and to facilitate assessment of the impact on the Design Space.

There was some discussion on scale-independent Design Spaces and at the time of this seminar the regulators were of the opinion that data at full scale to verify/validate this aspect would need to be submitted for assessment, particularly for biologicals.

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Implementation of ICH Q8, Q9 and Q10

From the regulators side it was made clear that Quality by Design does not automatically mean there will be a Design Space or Real Time Release. Furthermore there are differences in understanding of what a Design Space is and some confusion with Proven Acceptable Ranges. The former is concerned with multivariate interactions between parameters and product attributes. There is also confusion between the term "Control Strategy" and PAT.

Specifications should take process capability into account as well as safety and efficacy.

There is a need to communicate risk strategy to regulators.

Regulatory Experiences

The increased interaction between applicants and FDA in the pilot programme has led to a decreased number of questions arising from the ensuing assessments. It is encouraging to note that there is some consistency in the questions raised by FDA and those raised by EU regulators. One area of concern is that experience with the EU work-sharing pilot for "PAT-related" variations has revealed a potential disconnection between QWP and assessors at Member State level. There is a desire for access to advice pre-submission and it seems not many companies are aware of what is available at present.

Criticality

There are differences in approach and the main discussion was on whether it was necessary to establish a common approach and agree on a common understanding of terms used. Some argue that this is not needed provided companies provide full explanations in their dossiers.

There is concern on the regulators side that if risk is not assessed correctly that invalid conclusions could be reached. Furthermore it was agreed that attributes or parameters identified as critical should remain critical, even if mitigated, otherwise confusion could ensue. In this regard, besides classifying variables as critical or non-critical some companies have introduced a category often called "key". These are usually critical variables where risk to the safety and efficacy of the product has been mitigated.

Risk should be revisited periodically based on experience. It has to be recognised that risk management processes are not perfect since there will always be unknowns; however this also applies in conventional approaches to pharmaceutical development. We should not lose sight of the fact that a structured risk-based approach is an improvement.

It has also to be recognised that companies may take aspects other than quality, safety and efficacy into account in defining what is critical e.g. efficiency.

There was an interesting discussion about what should happen if problems occur in routine manufacture as this could undermine confidence in the Design Space concept. Has something new been learned about the Design Space? How should this be dealt with? Are further experiments needed?

Role of the Qualified Person

This was a new specific topic added to the seminar day as a result of experience from the site visits.

It was agreed that the QP is responsible for ensuring that the GMP quality system accurately translates the dossier contents into manufacturing instructions and control methods. For the QP to make appropriate decisions he must be familiar with the product and process and know where to go to for detailed information and advice. This is no different from the conventional situation.

It was confirmed at an earlier session by the regulators that the use of PAT for information gathering purposes only, does not need to be filed in a regulatory submission nevertheless the QP should be aware of the information being gathered and take appropriate action if the additional information challenges the validity of the existing approach.

Conclusions

The event was very useful in terms of taking stock of where current thinking is on both the industry and regulatory side. Discussion on real life examples was particularly useful for the regulatory side and furthermore a range of issues that require further reflection have been identified. Each topic session threw up issues for discussion and in many cases common issues arose. Some of the issues are for the regulators to work on, others for industry and some jointly between industry and regulators. Time is needed to reflect on these before coming together with industry to take things forward.