accordingly; for example, the particle size distribution of lactose used as a carrier in an inhalation dosage form is usually smaller (for improved lung penetration) than lactose used as a filler in tablets manufactured using direct compression (in which powder flow and compaction properties are important functional properties). Such properties, which may be critical to the quality and the performance of the finished drug product, need to be monitored and controlled in accordance with their functionalities.

The selection of a particular excipient is based not only on the chemical compatibility, but also the intended manufacturing process, the final dosage form, and the unique functionalities of available grades of excipients. New types of excipients intended for unique functionalities have been developed by coprocessing or modifying the particulate properties of existing excipients. For example, bigger or more spherical particles exhibiting enhanced flowability may be more suitable for direct compression than finer grades of otherwise chemically identical excipients, provided powder segregation is not a problem. Where chemical compatibility is not an issue, this approach could be effective in addressing the difficulty in commercial introduction of chemically novel functional pharmaceutical excipients because of the high costs associated with establishing their safety profiles.

Quality risk management

As part of the drug product development process, the concentration and functional performance of the API and excipients, which impacts the drug product's Critical Quality Attributes (CQAs), must be documented in the ICH M4 Common Technical Document (CTD)[9] and be assessed during the Quality Risk Management (QRM) process. These are respectively described in the ICH guidance documents: *ICH guidance Q8 (R2), Pharmaceutical Development*,[10] and *ICH guidance Q9, Quality Risk Management*.[11] This evaluation is crucial to the development of a drug product, with the guidance documents highlighting the specific understanding of the impact of the API and excipients on the quality of final product.[10,11] Key to both guidance documents is the identification of the CQAs of the final drug product, and *ICH Q9* details the process for assessing the risks associated not only with the drug product manufacture but also with its components. The CTD should also include an evaluation of the compatibility of the API with the excipients, and requires that 'the excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient.'[10] Therefore, identification of the respective key excipient attributes, which impact the drug product CQAs, is an integral part of the drug product development and the QRM assessment conducted includes both the paper exercise and resultant development batch manufacture.

The Certificate of Analysis (CoA) for a given excipient lists specifications, but may not cover all the attributes relevant to the drug product CQAs. Additionally, the ranges may be too wide to be useful, even with compendial materials. While chemical attributes (e.g., purity) may be sufficiently explicit for the purposes of determining impact on the drug product CQA, physical attributes may be lacking. For example, a single sieve specification (e.g., 99% passing through a given mesh size) may be listed on the CoA, when a more detailed particle size distribution may be desired for properly assessing impact on drug product CQA. In the QRM process, the inherent risk related to the intended functionalities of excipients must be evaluated to reduce the risks of varying excipient attributes on the drug product CQAs. These risks are integrated into the process of developing a control strategy for the drug product under development. Such information may be obtained by measurements on multiple lots of excipients representing the whole range of variability, which may not be easily available otherwise. On the other hand, an overly tight specification based on certain physical attributes may risk rejection of excipients batches that are suitable for delivering desired CQAs to the drug product. It is advisable for the drug product manufacturer to discuss with excipient suppliers before setting tighter limits for an excipient specification.

Conclusion

By comparing the functional categorization in *Pharmaceutical Excipients* with that in the compendial literature and highlighting the impact of the excipient attributes in their respective functional roles on the drug product, consideration of the diversity of functionalities of excipients as well as the crucial role they play in the overall quality of the drug product dosage form is encouraged.

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Date of Revision

5 December 2016.