MAN_04 - Application of Quality by design approach in the development of biosimilars monoclonal antibodies Nivolumab and Pembrolizumab

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Introduction: Biosimilars are complex biological products with a high degree of similarity in terms of the structural, functional, biological, and clinical attributes, to reflect the safety and efficacy of reference products (RP). Biosimilars could lead to more affordable treatments and increase patient access to expensive therapies. In this sense, Quality by design (QbD) plays an important role as a modern approach based on scientific data and risk management aiming to attend the quality pattern of an end-product. For biosimilars, QbD assumes an information-driven process that uses all available knowledge on the RP, mitigating potential risks and guiding to a more assertive process development.

Objective: Develop and validate the use of the QbD approach in biosimilar development projects, applying this method in the development process of the biosimilar monoclonal antibodies (mAbs) nivolumab and pembrolizumab.

Methodology: QbD process began with the determination of quality target product profile (QTTP) and critical quality attributes (CQAs). The establishment of these parameters were defined using information of the RP Keytruda and Opdivo and other registered mAbs. After the QTTP definition, the potential CQAs were assessed using a risk ranking and a filtering (RRF) approach developed by Roche/Genentech®. The RRF method evaluated each attribute according to impact score based on bioactivity, pharmacokinetics/pharmacodynamics, immunogenicity or safety, and the uncertainty of the impact, to identify final CQAs.

Results: QTTP for the biosimilars were assessed based on RP characteristics, considering their own production process. The CQAs were divided in structure, physicochemical and biological activity. Orthogonal methods were determined to measure similarity between biosimilar and RP, according to the Bio-Manguinhos reality. As described for other mAbs, some CQAs were obligatory due to regulatory requirements, as sterility and API concentration. As expected, the absence of detailed information in clinical trials studies increased the uncertainty score, leading to a high score impact of most CQAs. Structural parameters that have a higher impact in product quality provided us more information to a better assessment of the risks, leading to smaller scores. A final multidisciplinary brainstorm meeting shall validate these results.

Conclusion: QbD is an important approach to guide biosimilars development at Bio-Manguinhos, as it helped to a strategic preparation at the very beginning of the projects. More information will be acquired along the biosimilars' development to assure a continuous evaluation and risk prioritization of CQAs.

Keywords: Quality by design; Biosimilars; Risk Ranking Filtering