VAC_25 - *In vitro* transcription of mRNA vaccine synthesis step: a risk assessment which became a Control Strategy documentation at Bio-Manguinhos

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Introduction: The mRNA synthesis is one of the most important steps in the mRNA vaccines production. And if you could improve your vaccine production processes starting at the development phase? Believe in your research means believe in its development. Literally. Using a risk assessment approach and elaborating a Control Strategy, it is possible to implement a document which could lead to control of the process and the best quality of the product. The Control Strategy is designed to ensure that products are of the desired quality, both in process and final form. The development of a Control Strategy is possible due to an integrated approach, considering aspects described in the International Harmonization documents ICH Q7, Q8, and Q10 Guides, Quality Risk Management described in ICH Q9, ICH Q13, and applicable current guidelines.

Objectives: To evaluate the risks in *in vitro* transcription of mRNA COVID-19 vaccine production processes at experimental development stage, leading to a map and classification of parameters and their criticality. This assessment will enable Bio-Manguinhos to have their own Control Strategy document in this stage of mRNA vaccine production.

Methodology: The *in vitro* mRNA synthesis process was mapped and meetings between the technical-scientific team of the Molecular Biology Platform and Quality Assurance were held to define the criticality of each process parameter. Aspects such as Material Attributes, Process Monitoring and Control, Holding Time, and Critical Process Parameters were evaluated in this Control Strategy. Team members defined criticality based on prior experience with in vitro mRNA processing.

Results: A total of 40 parameters were classified according to their criticality in the process. Of these 40 parameters, 2 were classified as critical and 38 as non-critical. This risk assessment and classification were able to identify in which step the mRNA strand can be degraded at the IVT. Mitigation of this impact was described to ensure the quality of the RNA drug product. As a Key Process Attributes, we could identify 3 outputs which are measured and assure the purity and integrity of the RNA strand.

Conclusion: We established a Control Strategy based on risk assessment to guarantee the Drug Product quality, even within the development stage. This document will be necessary to allow technological transfer for pilot plant area and to submit a vaccine registration at the regulatory agency in Brazil. Furthermore, the mRNA drug product can follow to the next mRNA process step with its quality assured: the nanoencapsulation.

Keywords: Messenger RNA; Vaccines; Control strategy