**Cover letter**

**To the Journal Hemijska Industrija Editors,**

Thank you for considering the original research article: **Machine Learning Modeling of Wet Granulation Scale-Up Using Compressibility, Compactibility and Manufacturability Parameters** for publishing.

Studies utilizing the QbD approach and machine learning modelling for scale-up of the wet granulation process focused on either process parameters or a formulation approach with responses being observed usually relating to granule properties (e.g. particle size distribution, porosity, and bulk density). These studies either did not utilize machine learning techniques or the machine learning modelling involved testing of the prediction of developed methods using mostly laboratory scale runs. This unprecedented study tests the developed models using large data obtained from both pilot and commercial scale runs with formulation and process parameter input variables analysed in a complex system of wet granulation process scale-up, examining the compressibility, compactibility and manufacturability of granulate samples. Multiple machine learning techniques (regression, regularization, decision tree and ensemble algorithms) are compared in order to provide extensive examples of how different machine learning techniques can be utilized to determine significant variables (both categorical and numerical) together with the magnitude of their influence.

This work presents findings which are particularly useful to pharmaceutical manufacturing industry and wet granulation scale-up as the observations and conclusions have practical and commercial value.

Nada Millen conceived, designed and performed the experiments. Commercial scale runs were conducted by operators at Probiotec Ltd. as part of regular production. Aleksandar Kovacević and Lalit Kehra performed machine learning modeling. Nada Millen wrote the paper. Jelena Djuriš and Svetlana Ibrić reviewed the paper.

Authors claim that the submitted manuscript is original, has not been published elsewhere and has been written and approved by all the stated authors as well as by the responsible authorities where the work was carried out (Probiotec Ltd.). Also, the manuscript is currently not being considered for publication by any other journal and will not be submitted for publication elsewhere while in the reviewing process in the journal Hemijska industrija. If accepted, it will not be published elsewhere including electronically, in the same form, in English or in any other language, without the written consent of the copyright-holder. Authors declare no conflict of interest.

**A**leksandar Kovačević was partially supported by the Grant No. III-47003 provided by the Ministry of Education and Science of the Republic of Serbia.

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Yours sincerely,

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