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Simulation and development of cleaning processes for pharmaceutical equipment

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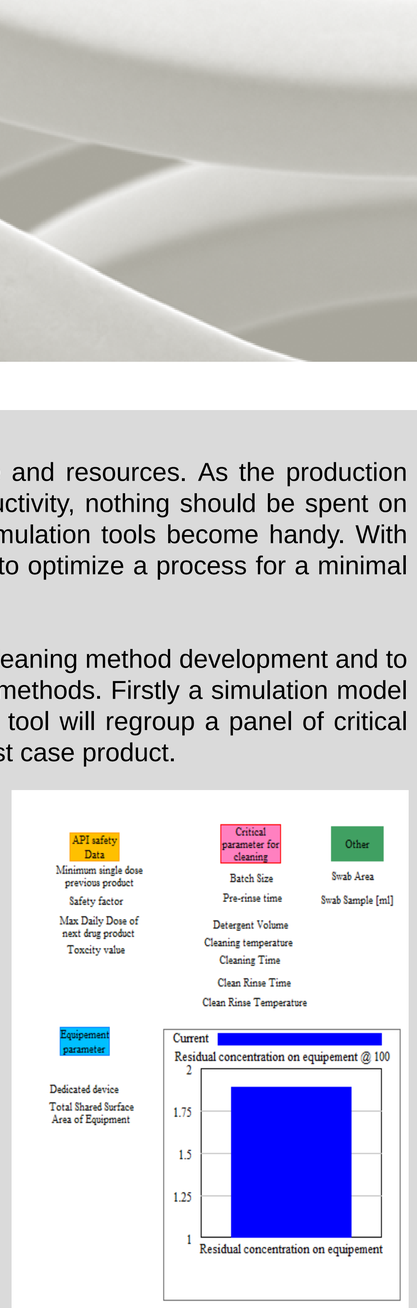
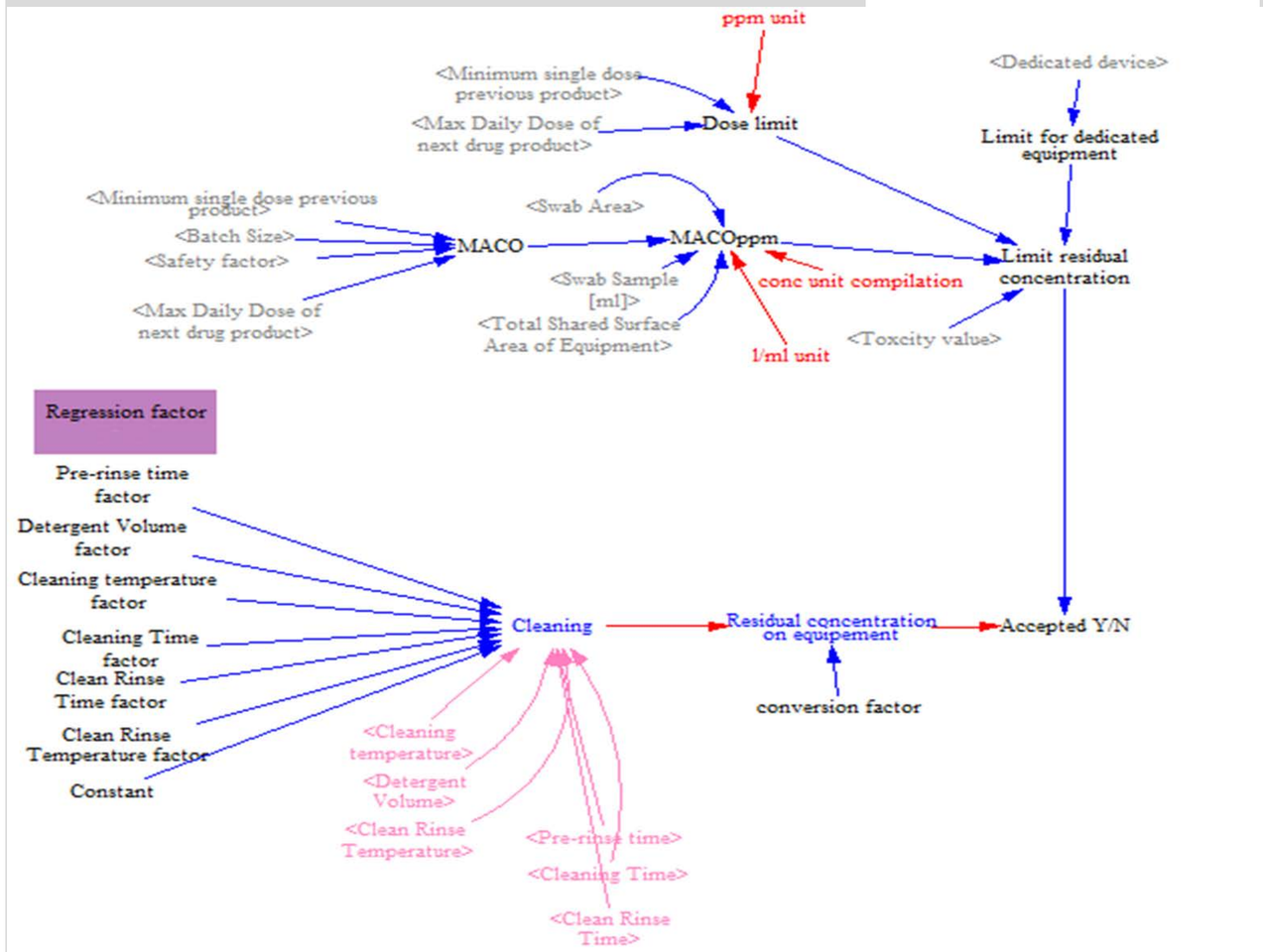
Development of a Quality by Design systematic

Method development is currently a costly process in terms of both time and resources. As the production world thrives for more time and resources in order to increase the productivity, nothing should be spent on dead-end investigations. This is where the laboratory-scale trials and simulation tools become handy. With them, it is possible to investigate many parameter combinations in order to optimize a process for a minimal cost.

The purpose of this work will be the development of a systematic for the cleaning method development and to challenge it with current SOPs. It will combine two different investigation methods. Firstly a simulation model will developed on Vensim®, a system dynamics modeling program. This tool will regroup a panel of critical parameters and will show their influence on the cleaning process of a worst case product.

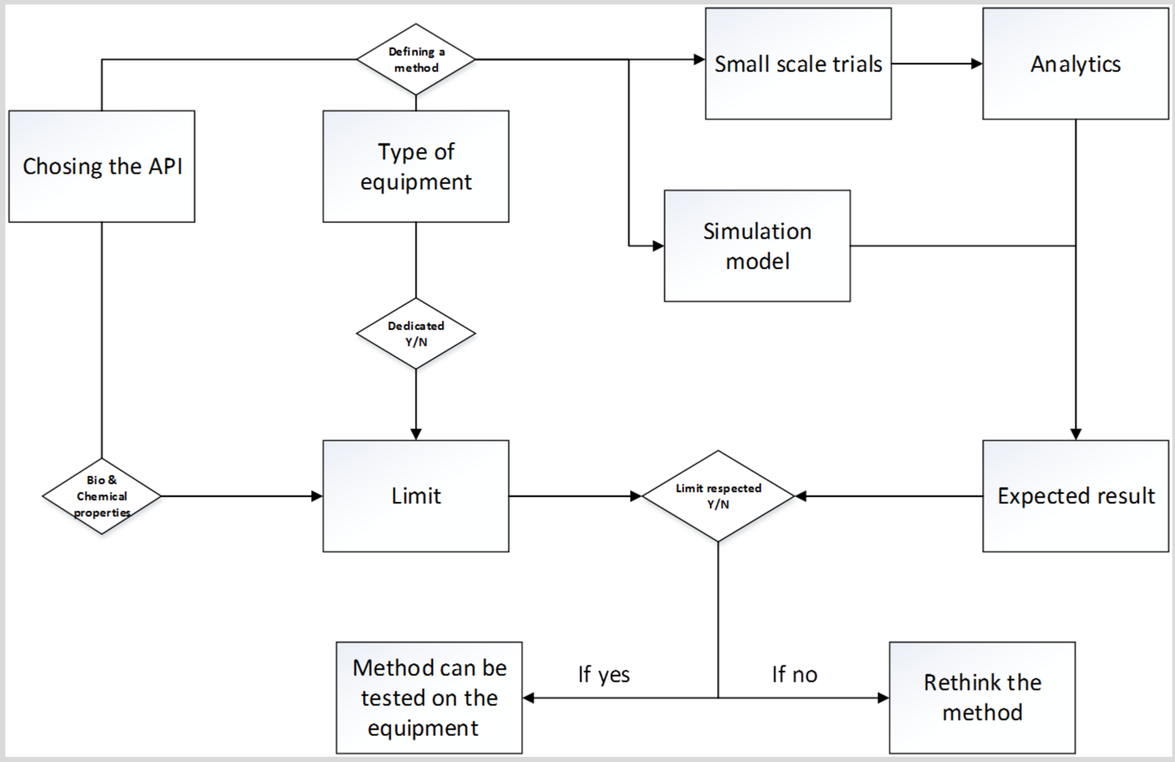
Then, a laboratory-scale procedure conducted on 10 x 2 cm plates will then be verifying results found on the simulation tool. The tested product will be the same worst case material as in the software. They will allow the user to screen possible conditions and chose the optimal method. The method could then be used and confirmed with practical results from the continued cleaning process verification.





Model building

The model will focus on the prediction of the residual concentration of API after the cleaning process and compare this value to the allowed contamination limit. It will serve as a first step in the method development and/or a tool for the optimization of a current method.
The biggest challenge of model building is to obtain a system that is as close as possible to the reality. In this case, the model will focus on automated cleaning method (washing machine). It could be represented in a model but there parameter such as the washing machine in itself are a source of variation.
The determination of critical parameters was made after statistical analysis of technical investigation conducted on two differents washing machine.



Small scale study, concept

The idea is to develop an experimental procedure that will allow a quick and easy confirmation of some of the critical parameters for both manual and automated cleaning. New products will be able to be tested on surface material that will not endanger the production with cross contamination risks.

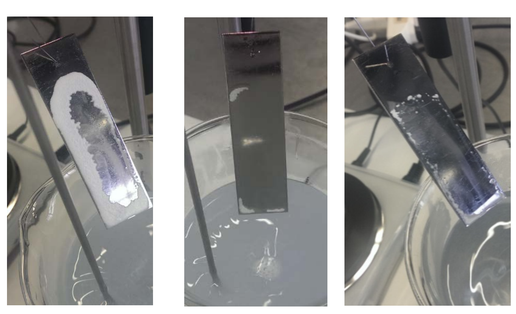
Small scale study, results

During the small scale trials, three parameters of the cleaning process were tested on a worst case product. These parameters were: cleaning temperature, detergent concentration of detergent and surface material.

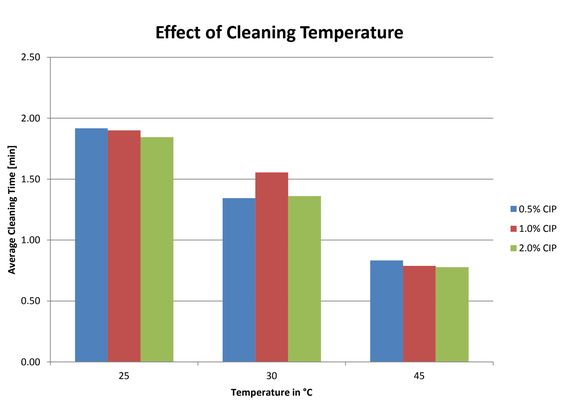
Firstly, the effect of the cleaning temperature has shown a direct impact of the cleaning time. With higher temperature, the cleaning process becomes more efficient.

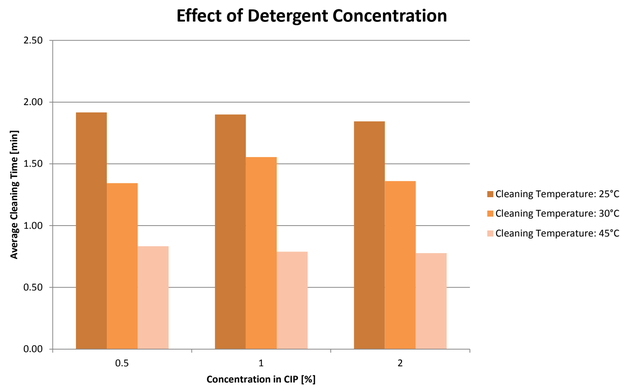
Secondly, no trend was found when comparing runs with identical cleaning temperature. This means that the concentration in detergent has little to no effect on the tested temperature range and worst case product.

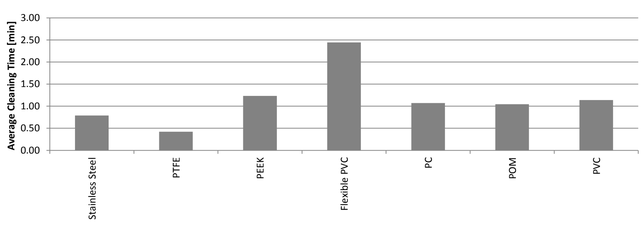
Finally, a panel of surface material was tested. Results have interesting consequences for the evaluation of a cleaning SOP. As tests on stainless steel plate is a good “all-around” material, it could be possible to consider other material as testing references. It is the case of PEEK, PC, POM and PVC. They plastics with low porosity and similar surface structure. Cleaning tests confirmed this clean with equivalent cleaning times. On the other hand, the extreme for easy of poor cleanability are not good testing materials for method development. They should be considered as best cased and worst case to be eventually investigated later, in trials inside an optimized washing machine



Progression of the cleaning process from 50 % removed material to 95 %







Conclusion

A systematic for cleaning method development was formulated. A simulation model and a SOP for laboratory-scale trials were developed and the later confirmed the efficiency of current cleaning SOPs for real-scale equipment.

The first version of a simulation model has been developed but this version remains a beta version that will need improvements. Once these modifications are implemented, the model will be able to simulate a reliable outcome and can be used later for method confirmation or improvement, especially for automated cleaning procedure. Its design could be rethought in order to also consider manual cleaning methods.

In complement to the simulation tool, the laboratory-scale trails could be coupled with analytical methods. This will back up the results obtained on the computer and add value to them. Once both laboratory-scale and computer-based tests are fully operational, method transfer and new products will be easily tested. For new products, a few simple runs on laboratory-scale trials will give a glimpse of the product behavior. Based on this knowledge, fitting coefficient could be applied to the model and give reliable output after simulation.

The addition of a model will be useful to gain even more time in the screening process. It will also give the user a powerful tool for further transfer to automated cleaning and/or optimization of current washing machine programs. The next step to this thesis will be firstly to obtain a reliable data set and then transfer it into the model, making it more reliable. Laboratory-scale testing method could be improved with the development of a robotic washer that could simulate the mechanical stress of the operator.

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