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RESEARCH ARTICLE

# Adding a Factor in the Course of a Design Space Characterization

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**Abstract**
*Introduction* An early decision on the design space of a pharmaceutical could imply that some process parameter is to be held fixed during production. Therefore, the effect of such a parameter is not studied in the exploration of the design space with statistically designed experiments. Later decisions may necessitate a changed setting of the parameter.
*Purpose and Methods* In this paper we discuss a statistical design strategy that permit inclusion of a new parameter in the course of a design space characterization and the risks one could run in adopting the strategy. The main tool used is computer simulation based on an initial design of 48 runs and 12 factors, which may or may not have been completed before introduction of a 13d factor.
*Results and Conclusions* If the original statistical design has a particular structure, new settings of the parameter can be introduced halfway the originally intended experimentation without having to start a completely new exploration of the design space.

**Keywords** Design of experiments · D-optimal designs · Design augmentation · False-negative results · False-positive results · Model selection

## Introduction

One of the key issues in the late stage development of pharmaceutical products is the establishment of the design space [5]. This is a collection of all combinations of process settings and attributes of the starting material that lead to the desired product. Very often, the design space is explored using a statistical design of experiments (DOE). The process parameters and starting material attributes thought to be relevant are included as factors in a DOE. The DOE specifies for each experimental run the required settings of the factors such that their effects can be optimally estimated.

Typically, there are many factors to be studied. Due to the late stage in the product development, one expects that a substantial number of these factors will be active. In addition to main effects of the factors, there may be two-factor interactions (2FIs); the presence of a 2FI means that the effect of a factor may depend on the setting of another factor. This situation calls for intensive screening using two-level fractional factorial designs. The designs recommended by Schoen and Mee [8] can identify all the main effects of the factors and a moderate number of 2FIs. When the results are complete, a formula can be calculated to quantify the effect of the factors on the product properties. This formula, on its turn, is used to define the design space.

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