the pressure difference between the center and the edges of the shelf is quite small; in this case it is more influenced by the position of the duct (not shown). On the contrary, when the shelf-to-shelf distance is quite small, or the size of the shelf increases, as in the industrial apparatus, the pressure difference between different points of the chamber becomes significant, but it is weakly affected by the position of the duct (as proven by the fact that pressure profiles are in this case slightly asymmetric). As it has been already reported, this significantly impacts the sublimation rate, and we will come back to this aspect later on.

Another important factor to consider when designing freeze-drying equipments is the presence of composition gradients in the vapor inside the chamber, due to spatially heterogeneous partial pressure of solvent (water or organic). In fact, according to the geometry of the chamber and condenser, and depending on the operating conditions, not only the total absolute pressure in every point of the chamber can vary, but also the composition in different points may be substantially different, and both these effects potentially lead to batch heterogeneities. This latter one is strongly determined by the number and position of the inert gas nozzles, very often used to manipulate and control the overall chamber pressure. These have to be positioned to guarantee as much as possible uniform inert gas distributions inside the chamber.

Vapor and inert gas distribution and vapor pathways can strongly influence efficiency and performance of the condenser; the inert mass fraction increases in the condenser approaching the outlet. Of course, optimal design of the condenser should guarantee the best performances in terms of both heat and mass transfer. An example of how CFD allows to estimate the local variation of water mass fraction is shown in Figure 2 (lower right).

A proper design is important in pilot-scale equipments where the geometry is generally much simpler, but most of these issues become even more important when considering an industrial-scale apparatus. In particular, the design of the condenser can largely benefit from the knowledge of the real fluid dynamics inside the condenser itself and from the evaluation of the ice deposition rate on coils and surfaces: computations can become extremely heavy in this case, especially in the complex geometry of an industrial apparatus, due to the necessity of modeling the vapor disappearance (and the ice formation) with a realistic mechanism that takes into account the proper kinetics.

Regarding the fluid dynamics of the vapor in the drying chamber, in Figure 3 the typical absolute pressure profiles encountered on the shelves of a laboratory-scale and on an industrial-scale apparatus are reported and compared.

As it is seen, under similar operating conditions the pressure values and the pressure differences (in different points of the same shelf or in different shelves) may significantly differ in the two apparatuses. As already reported, this has a huge impact on the final drying history of each vial, since the local water vapor pressure determines the interface equilibrium temperature of the drying product and, as a consequence, the sublimation rate. This can be estimated by resorting to a two-scale approach, where the evolution of the product in each vial is linked to the mathematical description of the entire chamber. Different strategies can be used and a very brief discussion is reported in what follows; however, readers interested in the details are remanded to the work of Rasetto (20). In many practical cases it is very interesting to construct the two-scale model within an online framework, by resorting for example to user-defined scalars and subroutines available in many commercial and open source