needed at the beginning of the process (i.e., number of containers, product area in each container, filling volume, amount of solids, etc.) and logging the calculated soft variables (i.e., sublimation interface temperature, sublimation mass flux, diffusivity of the dry phase, heat transfer coefficient, etc) and events (i.e., end of primary drying, mass transfer control situation, etc.).

Interaction with the freeze-dryer is also needed: periodical closing/opening the valve between chamber and condenser at prespecified intervals, actuating (closing) the leak valve used for pressure control during the PRT, acquiring the PRT data at high speed (generally 10 Hz is sufficient), and the shelf fluid temperature at the beginning of each PRT.

SCADA software must communicate in real time with the DPE and/or the control software (namely LyoDriver) without compromising 21CFR Part11 requirements about electronic records and electronic signatures (33).

THE UNKNOWN: REGULATORY APPROACH

No matter the advantages and importance of the perceived benefits of all these presented technological tools, there is, nowadays, still a lot of uncertainty about the regulatory approach to implement tools like them.

In November 2008 the FDA issued a new document "FDA Draft Guidance—Process Validation General Principles and Practices" (34). In the chapter IV—B "Specific Stages and Activities of Process Validation in the Product Lifecycle" specifically states:

> More advanced strategies, such as process analytical technology (PAT), use timely analysis and control loops to adjust the processing conditions so that the output remains constant. Manufacturing systems of this type can provide a higher degree of process control. In the case of PAT strategy, the approach to process qualification will be different from that for other process designs.

Each pharmaceutical industry planning to implement these tools need, therefore, to start since the early beginning a joint work with the Regulatory Authorities to establish the roadmap of the specific process validation.

CONCLUSIONS

It is possible to design a process with a consistent output, despite a very variable input, and with a mechanistic model; it is possible to perform powerful analysis of the correlation between the process parameters and the process output. These simulations allow identifying key parameters and spend the limited resources where it is gained the most.

The associated complexity and hardware associated to the implementation of these mechanistic models are much more modest than other accepted practices when implementing typical PAT tools (as for example, modern process analyzers or process analytical chemistry tools and multivariate data acquisition and analysis software, generally requiring high processing power and high investment).

The pharmaceutical industry should benefit from the implementation of QbD as it

- ensures better design of products with an expectation of fewer problems in manufacturing;