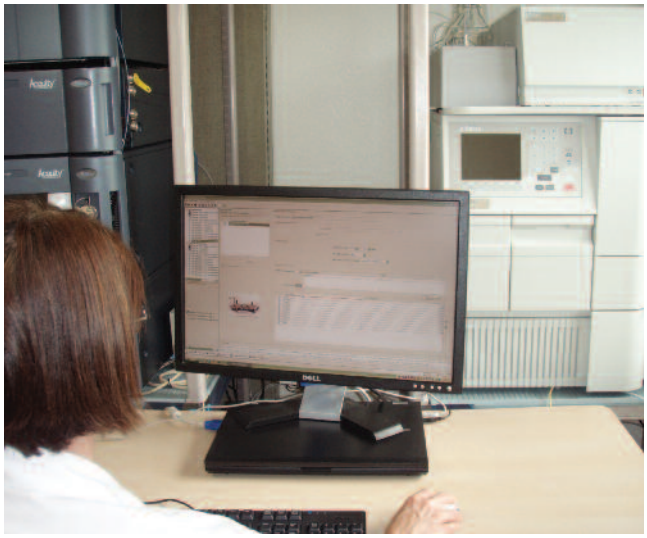
Parameters to consider in software for respiratory drug and device testing

Application-specific software can integrate with a liquid chromatography testing platform to facilitate automation of inhaler testing



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S-Matrix and CI Informatics

Ensuring that an inhaled drug reaches the required parts of the lung is essential for achieving a good clinical response. Characterization of the aerodynamic particle size distribution of such an inhalable drug substance is therefore important during product formulation, inhaler device design and thereafter during stability trials. Aerodynamic particle size distribution testing requires complex and lengthy initial device/sampling plan setup procedures. Such testing generates large numbers of samples for liquid chromatographic (LC) analysis. These analyses, in turn, generate even larger results data sets that require transcription, collation, calculation and reporting in accordance with USP Chapter 601 or Ph.Eur. Chapter 2.9.18 guidelines.

Many laboratories rely on Microsoft Excel to calculate and report particle size distributions. However, application-specific software tools for inhaler testing, such as Fusion Inhaler Testing from S-Matrix and CITDAS from Copley Scientific, offer an alternative. Such tools can be categorized as either "automated" or "off-line," depending on the level of integration with the Chromatography Data System (CDS) controlling the LC and, in some cases, integration with Laboratory Information Management Systems (LIMS) software.

Given today's competing requirements for increased regulatory compliance and improved laboratory efficiency, several parameters for respiratory drug and device testing software may be desirable from both utilitarian and regulatory compliance points of view. These software parameters include:

- automation and integration
- workflow management
- data import, results calculation and reporting
- regulatory compliance

Figure 1 provides an example of workflow and a feature set in application-specific software for automated respiratory device testing.

Automation and Integration

Eliminating the potential for error is an important goal of any respiratory drug testing procedure. Automation and system integration are crucial support tools for achieving this goal. Companies make significant investments in installing and implementing regulatory compliant LIMS and CDS software. Therefore, when inhaler testing is done within the framework of a 21 CFR Part 11 compliant environment using electronic records, it is desirable for res-

piratory drug testing software to integrate with and fully support these systems.

Respiratory drug testing software can be designed to exchange respiratory drug testing plans (sampling plans) and chromatographic results data. This is done via compliant, file-less and electronically-auditable mechanisms utilizing the software-addressable interface tools available with most LIMS and CDS systems. Therefore, the ability to automatically reconstruct a product testing configuration and protocol within the CDS as ready-to-run methods and sequences in native data and file formats is also desirable. A second integration element could be closing the electronic data exchange loop by automatically importing and collating the CDS-generated results. The data could then be automatically analyzed and the results reported in the required formats with the relevant content.

Workflow Management

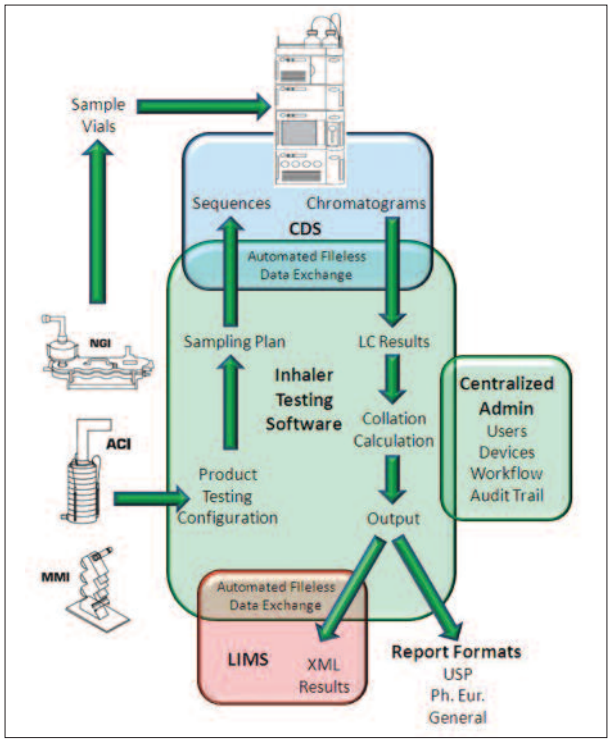
A fully-featured inhaler testing software system can allow system administrators to set up and securely store an unlimited number of product testing configurations. These can specify and enforce all relevant apparatus types, configurations and testing protocols for a given testing effort. A system may also allow an unlimited number of testing apparatuses to be specified and may maintain records of all relevant apparatus data, such as nominal effective cut-off diameters (ECDs). Administrators can also create user role templates with specific user permission and authority settings. These can be assigned to a system user, which can enforce the required testing protocol and include review/approve e-signature control loops. Elements of the workflow control that user role templates could enforce may include:

- selecting a product testing configuration
- generating a sampling plan (testing protocol)
- adding calibration and control standards to the sampling plan
- exporting the sampling plan to the CDS as ready-to-run sequences
- importing LC results from the CDS and mapping these back to the sampling plan
- data analysis and reporting

To obtain meaningful data for mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), fine particle dose (FPD) and fine particle fraction (FPF), as well as stage grouping data, many factors come into play. Impactor configuration, effective cut-off diameters, flow-rate and calculation methodology can be elements of a pre-defined product testing configuration. Therefore, the ability to make relevant respiratory drug testing information available to the user in a pre-configured workflow can eliminate the need to specify multiple options on a software setup interface each time the software is used. Such a templated approach can help ensure, or even enforce, adherence to business rules and maintain a high level of data quality. An example is shown in Figure 2.

Figure 1

An example of workflow and a feature set in application-specific software for automated respiratory device testing.

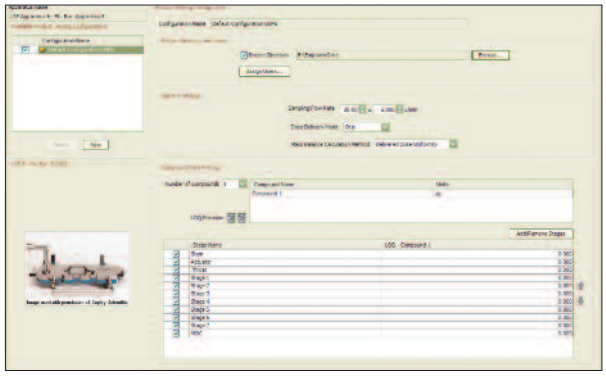


Data Import, Results Calculation and Reporting

The ability to electronically import chromatographic

Figure 2

A product testing setup template can let an administrator define testing configuration elements.



results data directly from a CDS into inhaler testing software can be advantageous. No intermediate files (.csv, .txt) need to be created and manual transcription errors cannot occur, thereby eliminating the need to check these imported data. However, even when such a high degree of automation exists, the complexity of the required cascade impaction result calculations and subsequent reporting remains challenging. Therefore, the availability of a role-based data analysis wizard, which allows users to be guided through the calculation options and restricts access to a pre-defined calculation approach, can be an important consideration.

To avoid the requirement for final report compilation occurring outside of a compliant and traceable software environment, final reporting output should be made comprehensive. In addition, inhaler testing software must be capable of generating reports in USP and Ph. Eur. formats. Having a "LIMS-friendly" XML report output option can provide additional flexibility regarding data that can be automatically transferred to LIMS. This can further reduce effort and the risk of transcription errors. Final results data should also be traceable to the original chromatographic results data, sampling plan, product testing configuration and analyst associated with each individual test. Such traceability can be achieved via comprehensive audit trails.

Regulatory Compliance

Regulatory standard 21 CFR Part 11 includes a description of the elements that must be included if one chooses to have electronic records within product testing software. In this instance, the following software parameters are required:

- User identification and password controls that are unique, protected and administered
- Adequate user-role based security controls to prevent unauthorized access to certain software features and functions
- System audit trails, which must be independently generated and all changes made to records within a Part 11-compliant system, should include time and date-stamps with the stated intent being to deter record and signature falsification
- The system must maintain an irrefutable link between documents, metadata and the electronic signature
- Clear electronic signature manifestations must be established for all electronic records and any record signed must include the following components:
  - Printed name of the signer
  - Date and time of signature execution
  - Meaning of signature (review, approval, responsibility or authorship)
- The system must be fully validatable by the customer to ensure accuracy, reliability and consistent intended performance; it must allow auditors to discern invalid or altered records; all internal calculations must be verifiable, either manually or with other software tools, using standardized data sets

Potential Advantages to Consider

Respiratory drug testing can be highly automated by using application-specific software integrated with an associated liquid chromatographic (LC) testing platform. Such automation may offer important advantages to the user. These can include increased efficiency, elimination of error prone manual operations and a high degree of assurance that the final reported results are both correct and defensible.

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