Introduction: Aerosol Delivery of Orally Inhaled Agents

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Abstract

Deposition scintigraphy methods have been used extensively to provide qualitative and quantitative data on aerosol drug deposition in the lungs. However, differences in methodology among the different centers performing these studies have limited the application of these techniques, especially in regulatory roles. As an introduction to the standardized techniques developed by the International Society for Aerosols in Medicine (ISAM) Regulatory Affairs Networking Group, we present potential advantages of the use of standard techniques for deposition scintigraphy. Specifically, we propose that standardized techniques would allow for better comparisons between labs and would facilitate multicenter studies. They would allow for improved methods of establishing equivalence and could be better utilized to establish dosing for new medications. They would allow for the performance of more accurate dose ranging or multidose studies and complement pharmacokinetic studies of new inhaled medications. Standardized techniques could help to establish the relationship between the deposition of drug in the lungs and clinical effect, and may also facilitate clinical measurements of deposited dose for medications with narrow therapeutic indices. In the sections that follow, we discuss the best techniques used to perform deposition scintigraphy through planar, single-photon emission computed tomography, and positron emission tomography modalities and propose a detailed set of standardized methods for each. These include methods for radiolabel validation, radiolabel accountability and mass balance, and imaging acquisition and analysis.

Key words: aerosol deposition, scintigraphy, PET, SPECT

DEPOSITION SCINTIGRAPHY includes two-dimensional (2D) planar scintigraphy, three-dimensional (3D) single-photon emission computed tomography (SPECT), and 3D positron emission tomography (PET). These imaging modalities have been used for many years to derive qualitative and quantitative data on the delivery of aerosol medications to the lungs and to develop new inhaled medications and delivery systems. Some measurements that can be obtained with these imaging modalities and their application are shown in Table 1.

Despite the valuable developmental contributions of these methods, their application in a regulatory role has been limited largely due to the differences in technique that have evolved among different investigators. Although these various techniques have been published and widely discussed and consensus recommendations have been made on how these techniques should be developed to enhance their utility,^(1,2) there has never been a successful comprehensive attempt to standardize the methods used to perform deposition scintigraphy. As part of an initiative by the Pro-

duct Quality Research Institute (PQRI) and the International Society for Aerosols in Medicine (ISAM), a committee of experienced investigators in the field was convened for the purpose of developing standardized protocols for the performance of deposition scintigraphy studies. These methods were further discussed and refined at a consensus workshop held in December 2011 in Edinburgh, Scotland, as part of *Drug Delivery to the Lungs 22* (DDL 22).

Regardless of methodology, the outcome of deposition scintigraphy studies is a measurement of deposited aerosol dose. The importance of the technique derives from the difficulty associated with predicting deposited dose through *in vitro* methods and the dosing variability exhibited within and between subject populations.^(3–6) Although the need to understand deposited dose seems intuitive, some trial failures have been attributed to poor aerosol dosing that was not directly assessed ahead of performance.^(7,8) A few direct correlations between scintigraphy-measured deposited dose and clinical effect

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TABLE 1. DEPOSITION SCINTIGRAPHY MEASUREMENTS AND APPLICATIONS

Measurement	Application
Total amount of radiotracer in the lungs (compared with, <i>e.g.</i> , the oropharynx and upper respiratory tract)	Efficiency of deposition for an inhaler
Regional deposition of inhaled radioaerosol within the lungs	Effect of particle size and flow parameters on drug deposition
Relative or absolute amount of radiotracer in each lung	Relative lung function prior to pneumonectomy (<i>e.g.</i> , in lung cancer); uptake by a radioligand to a target such as neoplasia, infection, etc.
Relative or absolute amount of radiotracer in each lobe of the lungs	Relative lung function prior to lobectomy

are found in the literature.^(9–12) Other studies have related deposited dose to systemic or local drug concentrations.^(5,13–16) However, to move this field forward and enhance its usefulness from a regulatory point of view, a collaborative approach based on standardized techniques is needed. The techniques presented here provide the best standards for designing deposition scintigraphy studies for scientific and regulatory purposes. Application of these techniques by multiple investigators will facilitate the accumulation of evidence needed for these techniques to be applied in more critical regulatory roles in the future. Other potential advantages of incorporating a standardized methodology are discussed below.

Standardized techniques would allow better comparisons between labs and would facilitate multicenter studies

The large variety of testing methodologies currently in place makes it difficult to compare or combine deposition scintigraphy data from different centers. A standardized method would allow for seamless comparisons and facilitate the performance of multicenter studies, allowing for improved drug dosing characterization.

Standardized techniques would allow for improved methods of establishing equivalence

The determination of equivalence for inhaled drug products often includes studies of pharmacodynamics (dose to response) and/or pharmacokinetics.^(17–19) Deposition scintigraphy studies provide information on drug distribution that could be additive to current methods for determining bioequivalence. Previous consensus documents have described a need for standardized methods if deposition scintigraphy is to play a role in establishing bioequivalence.⁽¹⁹⁾ Deposition imaging is mentioned as a possible method within procedures for establishing bioequivalence in current European Medicine Agency (EMA) guidance.⁽²⁰⁾ The development of standardized techniques would allow this regulatory role to be expanded.

Standardized techniques could be better utilized to establish dosing for new medications

The determination of proper dosing is an essential developmental step for new medications that will affect safety and efficacy in clinical trials. Precise deposition scintigraphy techniques would allow for better comparisons with pre-clinical toxicology, thereby allowing for the design of safer studies. These techniques would also allow for proper scal-

ing from preclinical dosing established in animal or other efficacy models, thereby increasing the likelihood of success in clinical studies. Accumulated evidence with a standardized method would facilitate the transfer of such techniques to new applications.

Standardized techniques would allow for the performance of more accurate dose ranging or multidose studies

Dose ranging studies can play a powerful role in drug development by allowing small numbers of subjects to demonstrate dose-to-effect correlations that provide key evidence of drug efficacy. Dose determinations based on deposition scintigraphy are more likely to correlate to response than dose determinations based on *in vitro* testing, and dosing regimens established through standardized imaging techniques would allow for more precise comparisons. The doses associated with individual inhalations in multidose studies could also be independently resolved using proper techniques providing important interpretative information on delivered dose versus time.

Studies with standardized deposition scintigraphy techniques would complement pharmacokinetic studies of new inhaled medications

An understanding of pulmonary and systemic drug concentrations is important to establishing safety and efficacy. Deposition scintigraphy could provide a bridge between accepted *in vitro* methods for assessing delivered dose and *in vivo* methods for assessing systemic dose. In many cases, deposition studies can be performed simultaneous to pharmacokinetic studies, providing local deposition information that complements systemic dosing results from individual subjects. However, to play this role and be accepted by regulatory agencies, deposition scintigraphy must be standardized.

Standardized techniques could help to establish the relationship between deposition of drug in the lungs and clinical effect

It is not clear why the clinical utility of deposition scintigraphy measurements has not been more thoroughly established, but inaccuracies in the application of the technique may play a role. These inaccuracies could have resulted from improper drug labeling, image collection, image interpretation, or analysis. A standardized method for deposition scintigraphy that incorporates best practices from prior experience would allow for more precise measurements and

the best opportunity to test the relationship between deposited dose and clinical effect for individual medications.

Standardized techniques may facilitate clinical measurements of deposited dose for medications with narrow therapeutic indices

As more complex entities are developed in inhaled forms, the potential exists for the development of drugs that will require dose adjustment in order to attain therapeutic outcomes. If these medications are deployed on a large scale, a standardized technique might facilitate dose adjustment through deposition scintigraphy studies performed by clinical centers.

In the following sections, we discuss the best techniques used to perform deposition scintigraphy through planar, SPECT, and PET modalities and propose a detailed set of standardized methods for each. These include methods for radiolabel validation, radiolabel accountability and mass balance, and imaging acquisition and analysis.

Author Disclosure Statement

The authors declare that no financial conflicts of interest exist.

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