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A lesser known use of imaging studies in drug development is to determine the patterns of deposition, biodistribution, and regional kinetics of drugs in the body. This kind of study is of most interest when the drug is intended for local action following topical administration by inhalation. Imaging provides a convenient noninvasive method for observing initial deposition patterns and their variations caused by variables of the drug's formulation and delivery method. Though planar gamma imaging is the method that has most often been used, recent years have seen promising demonstrations of SPECT and PET imaging to provide three-dimensional and quantitative measurements of drug deposition. When the goal of a drug is direct local treatment of diseased tissue, delivery of that drug is an important therapeutic variable. Imaging studies allow the drug delivery to be measured and optimized before a drug formulation is committed to clinical trials.

KEY WORDS: imaging, inhalation, SPECT, PET, drug development.

INTRODUCTION

MEASUREMENT OF REGIONAL distribution and kinetics is fundamental to all tracer studies. Tracer kinetic data is often used to calculate biological parameters such as organ function, metabolic rate, and receptor concentration. With regard to drug development work, such measurements show the effects of the drug on biological processes. However, the drug's biodistribution remains unknown and, in most cases, of relatively little interest because it is beyond our control.

With local drug administration, there is control over distribution that is not available from systemic administration. Application of a high concentration of drug to the site of needed action while systemic concentration remains low has obvious advantages, as opposed to the reverse that occurs following systemic administration. Local drug administration offers control over effectiveness and safety.[1] It also removes the correlation between effectiveness and traditionally measured pharmacokinetics, making regional drug distribution an important variable in design of the formulation and the delivery method. External topical application generally does not require imaging, though imaging might provide some useful information. However, when a topical drug is distributed internally, the drug is not accessible to traditional means of measurement. The quantity of drug deposited remains im-portant, and there is little option but to use imaging methods to measure it. This is the case when drugs are administered by nasal or oral inhalation.

Assessment of nasal and oral drug inhalation forms the largest body of scientific literature with regard to the imaging of drug biodistribu-

Author to whom correspondence should be addressed: Marc S. Berridge, PhD, Department of Radiology, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106; Associate Professor, Department of Radiology and Chemistry, Case Western Reserve University, School of Medicine, 10900 Euclid Avenue, Cleveland OH 44106. E-mail: msb5@po.cwru.edu

Zhenghong Lee, PhD, Assistant Professor, Department of Radiology, Case Western Reserve University, School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106.

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tion and kinetics. Inhaled drugs are used to treat allergic rhinitis, asthma, respiratory infections, and cystic fibrosis. Drugs that the gastrointestinal (GI) tract does not absorb, or that it destroys, may be inhaled in order to achieve systemic delivery via pulmonary absorption. Insulin is a prominent example of ongoing work in this area.[2-5] The distribution of these drugs may be evaluated by traditional pharmacokinetics; however, the use of imaging protocols can be very useful when designing and evaluating formulations and devices for effective, reproducible drug delivery. Other somewhat related studies have been performed to evaluate oral drug preparations and suppositories in order to determine the relationship between local distribution and systemic delivery.

For all imaging studies involving inhaled drugs, the goal is to determine the regional distribution of the drug in the airways following inhalation. An underlying assumption is that delivery of some amount of drug directly to the airway surface is necessary for therapeutic effect on each portion of the tissue. It follows that clinical effectiveness should require sufficient distribution of drug to all relevant portions of the airway. As an example of the use of imaging distribution studies, consider a drug that is intended to treat lung disease but, upon inhalation, distributes only into the mouth, possibly because of an ineffective delivery device. The drug would not have the desired effect because none of it reached the lungs. However, if the cause of the poor clinical result is not known, a good drug could be abandoned when all that may have been needed was a small adjustment. Sound measurement of the drug's distribution leads to proper assessment and allows the formulation and inhalation method to be modified in ways that will permit the desired delivery outcomes. Imaging can reduce the cost and time of drug development by allowing the best formulation and delivery device combinations to be selected before clinical trials begin. After clinical trials, imaging can be used to compare the distribution of different drugs, formulations, and delivery methods. It can evaluate whether those distributions are similar when the goal is to match some previous achievement, and can define correlations between distribution and clinically measured parameters.

The goal is to determine the regional distribution of the drug in the airways.

This type of work touches on areas of pharmacy practice that deal with the use of radiotracers. For an inhaled drug, the goal is always to measure the regional deposition of the drug, being as quantitative and spatially accurate as possible. Naturally, no drugs are radioactive in their normal form. A radioactive form of the drug must be synthesized in order to follow its distribution in the body. A radiolabeled drug must be formulated so it accurately represents the distribution of the nonradioactive form of the drug in its intended commercial formulation. Alternatively, a radioactive tracer that is itself not a drug may be added to a given drug formulation. Such tracer methodology can measure the initial deposition of the drug formulation, provided this approach assures the same initial distribution of the active drug component. The production and formulation of suitable tracers falls under radiochemistry and radiopharmacy. Reviews that are more comprehensive than this introduction to the field have been published, and the interested reader is encouraged to refer to them. [2,6-10]

TYPES OF STUDIES

Before addressing chemistry, formulation, and compounding issues in drug development, it would be useful to examine the goals that these steps are meant to achieve. There are a few general types of distribution studies. The largest group of these involves inhaled drugs

that can be further subdivided into nasal and oral inhalation formulations. Some distribution studies have also been done to trace the passage of solid dosage forms through the GI tract,[11–15] and a very limited number of studies have been done to measure the distribution of materials after their administration in suppository formulations.[16,17]

Nasal studies are performed in order to determine a drug's distribution in the nasal region including the sinuses. The object is to determine how far distribution extends over the nasal turbinates, or into the sinuses, and how much of the drug is deposited there. Nasal administration of a drug is commonly used when treating allergic rhinitis. The nasal structures are optimized for removal of particulate matter from inhaled air, so the majority of inhaled material collects in the nose and turbinates, while only the smallest aerosol particles are able to pass into the lungs.[18] Therefore, the goal of any nasal preparation is to have enough penetration to cover the turbinates and possibly the sinuses, but not to penetrate the lungs. Another consideration may be to increase the retention time of the drug on the nasal tissues beyond that which would normally result from the rapid mucociliary clearance on the nasal tissues.[19] Planar imaging studies give an indication of how far posterior and superior the drug distribution extends. Three-dimensional methods are able to distinguish lateral distribution and possibly quantitate any deposition that occurs in the sinuses.

In order to deliver medication to the lungs, an oral inhalation is often used. Even so, there is a tendency for drug collection to occur on the surface linings of the mouth and trachea, as well as at the bifurcations of the bronchi. Some of these locations may also be target areas depending on the drug. Penetration of drug into the deeper lung tissue cannot be assumed, though smaller particles tend to reach deep into the lung structures. Some drug formulations may be required to reach the small, deeper airway generations, while other formulations may be directed more towards the larger airways. The absorption or clearance rate of the drug also varies on a regional basis.[20] Therefore, a variety of drug formulations and devices are used. The most common are pressurized metered dose inhalers (MDI), dry powder inhalers (DPI), and fluid nebulizers. Spacer devices are chambers of various designs that are inserted between the inhaler and the patient's mouth. Their surfaces collect the largest particles and aggregates which would otherwise deposit in the mouth. Additionally, their volume and airflow characteristics serve to channel the particles in a controlled way into the inspired air flow, thus giving those particles that are inspired a better chance to penetrate reproducibly into the lung. The effectiveness of a spacer in achieving the goals of improved drug delivery and more favorable deposition pattern can also be evaluated using an imaging study.[21–23] In some cases, the spacer can affect biodistribution significantly.[20] In each case, an imaging study measures the distribution of deposited tracer in the mouth, airway, and lung, possibly as a function of time. The optimum distribution depends upon the intended action of the drug.

The other type of study is illustrated by use of the example of a swallowed tablet. Most tablets are dissolved and absorbed into systemic circulation through the stomach. Imaging studies of these formulations provide little useful information.[14,24,25] However, the design of tablets that are meant to provide time-release of a drug or have enteric coatings to permit the release of a drug in the lower GI tract sometime poses questions that can be answered by imaging. Radiolabeling a tablet simply for tracing its bulk distribution is relatively easy to do. Imaging studies show the location of the tablet, while pharmacokinetic measurements provide the drug release information. The performance of an enteric coating can be similarly evaluated with respect to the design goals and may help to ascertain the cause of unexpected pharmacokinetic or clinical results.[13,15,26–29] Reports of this type of drug imaging study are not numerous in the scientific literature, though they provide valuable information for evaluation and design of such drug formulations.

IMAGING METHODS

From a drug formulation standpoint, the methods used for imaging drug biodistribution can be conveniently divided into "single photon" techniques and the "dual photon" technique of positron emission tomography (PET). These two types of imaging techniques produce different data and employ different radiotracers. The obtained images and measurements they produce also have different characteristics. Conceptually, however, they are similar in that both methods acquire scan images that show distribution inside the body after inhalation of a radiolabeled formulation of the drug.[19,20,30–34] The experimental questions behind any given drug study will impact the choice of imaging method, since the extent and complexity of obtainable information from each varies greatly according to the choice of imaging method and ancillary techniques that may be used.

Single photon techniques include single photon emission computed tomography (SPECT), which produces three-dimensional images (analogous to computed tomography or CT scans) of the tracer distribution in the body, as well as planar imaging which produces two-dimensional images (analogous to conventional X-rays). All imaging methods use techniques and imaging cameras that were developed for routine diagnostic nuclear medicine applications commonly found in a majority of hospital settings today. These camera systems contain detectors that most commonly use sodium iodide (NaI) crystals arranged in specific configurations that permit the detection of emitted radiation coming from the subject's body. Lead collimators are placed in front of the NaI crystals to remove radiation that is not moving in a nearly straight line normal to the crystal's surface. This allows the position-sensitive detectors to produce an image in two dimensions of the intensity of the radioactive material placed in front of them. In planar imaging, this is typically the final image produced by the study, and often, two images are obtained in order to enhance one's ability to interpret the data. In SPECT imaging, there are commonly numerous intermediate images that are never actually displayed. These intermediate images, which are taken at various angles to the body, are used to produce a three-dimensional (3D) image of the radiotracer distribution inside the subject's body. A wide variety of radionuclides in different chemical forms is used with these cameras.[35–46] The most common nuclide is ^{99m}Tc (technetium, 140-keV gamma emissions); however, there are other nuclides that can also be used: ^{201}Tl (thallium), ^{131}I (iodine), ^{123}I, ^{111}In (indium), ^{169}Yb (ytterbium), ^{59}Co (cobalt), and ^{51}Cr (chromium), among others. Most of these nuclides are metallic elements with a resultant chem-istry that is similar from a drug formulation perspective. The iodine radionuclides provide some additional interesting capabilities for radiolabeling organic molecules, which could have some effects upon drug formulation issues.

These images produce a three-dimensional (3D) image of the radiotracer distribution.

Planar imaging is technically the simplest technique. Planar images look much like X-rays, although the image shows drug distribution in the airway or the location of a tablet in the GI tract. In planar imaging, emitted radiation from the imaging agent(s) used is both absorbed and scattered as it passes through the body. Therefore, tracer that is farthest away and behind more dense tissue appears less intense and more diffuse if all other factors are equal. Figure 1 illustrates the anterior and posterior views of a single subject after inhalation of a drug formulation radiolabeled with ^{99m}Tc. The difference between the two views is a result of their different spatial orientation relative to the detector. Because the actual distance of the tracer from the imaging detector is generally

unknown, quantitative estimations of drug deposition from planar images are usually not appropriate. Experience in viewing the data contained in such images is necessary for accurate qualitative interpretation. Often, a geometric mean of the anterior and posterior images is used to partially correct for these effects. The planar imaging technique is most accurate when the distribution of radioactivity and tissue density are uniform throughout the observed body region.[47] Other methods of correction for attenuation and scatter have been used.[48–53] The better the corrections become in data processing, the more accurate are quantitative estimates of tracer deposition. However, the lack of depth information from planar imaging makes it difficult to produce reliable quantitative deposition estimates, even when the most rigorous correction methods are employed. A study of qualitative drug distribution does not require rigorous correction. Planar imaging is therefore best considered only for qualitative deposition observations.

SPECT images are calculated using 3D reconstruction algorithms and data gathered from many directions around the body. The 3D images can be presented as rendered volumes, or more commonly as a series of planar slices through any desired axis. Figure 2 shows a volume rendering (summed projection) in the center, with two orthogonal slices through the data on either side. Note the good delineation of central deposition in the slices in comparison to the projection. Intensity scaling of each image relative only to itself produces the seeming mismatch in intensity, but this is normal. The 3D distribution data and higher resolution of SPECT allow for a better qualitative distribution interpretation. Distribution variations in the depth dimension are easily seen.[54–56] The depth information also provides a theoretical possibility of accurate attenuation and scatter correction in order to get accurate quantitative deposition data.[51,53,57,58] In practice, it is difficult, though certainly more reliable, than planar imaging and possibly sufficient for many purposes.[35,46,59] SPECT however, generally requires more time (5 to 30 minutes) to acquire an image, and sometimes that amount of time delay is problematic because significant absorption or redistribution of the tracer can occur. ^{99m}Tc-Pertechnetate, for example, has an average absorption half-time in the whole lung on the order of 10 minutes. But other tracers such as labeled albumin exhibit very slow absorption and thus permit longer imaging times to be used.[60] Because the majority of imaging centers include SPECT scanners and because technical improvements to shorten the time needed for scanning are being reported,

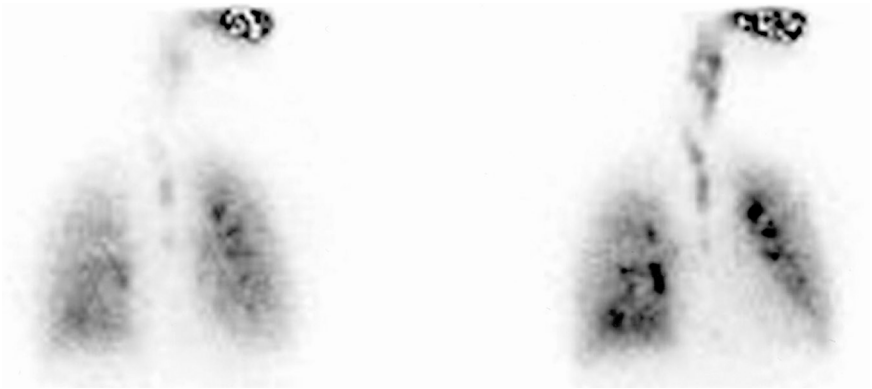

Figure 1. Planar Images: Posterior (left) and anterior (right) views taken by a planar gamma camera of a subject with head turned over left shoulder, after inhalation from an anti-inflammatory corticosteroid MDI formulation containing ^{99m}Tc-pertechnetate. Views are adjusted to place the subject's left side to the right of the image in both cases.

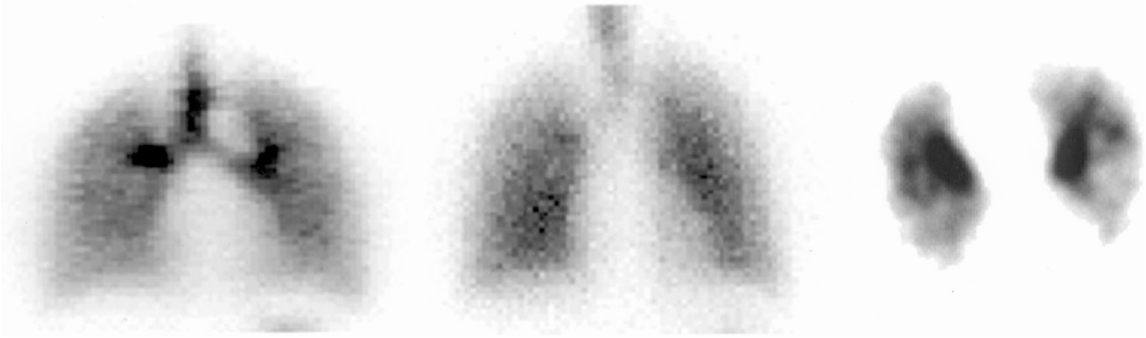

Figure 2. SPECT Images: A pulmonary aerosol SPECT study. At left is a view of a single coronal slice through approximately the center of the body showing distribution along height and width of the body. In the center is a projection of the sum of the entire depth of the body into a single plane. At right is a transaxial slice at a level below the bronchial bifurcations to show depth and width distribution. Each image is scaled to its own maximum. Courtesy of Dr. Stefan Eberl, Royal Prince Alfred Hospital and Dept. of Pharmacy, University of Sydney, Sydney, Australia.

this is likely to be the method of choice to image single photon radionuclides in the future.[46,54,61]

PET scanning produces images that are like SPECT, three dimensional and provide detailed distribution information. PET image resolution of about 5 mm is better than seen with either SPECT or planar imaging. Additionally, PET image reconstruction techniques are similar to those used for SPECT. A PET scanner detects the dual photons (511-keV) that are emitted simultaneously and in opposite directions (180 degrees to each other) when emitted positrons undergo an annihilation reaction. This means the PET scanner uses detectors that are more dense than single photon instruments and must use only positron-emitting nuclides, such as ^{11}C (carbon), ^{13}N (nitrogen), ^{15}O (oxygen), ^{18}F (fluorine), ^{64}Cu (copper), ^{68}Ga (gallium), ^{77}Br (bromine), and ^{134}I. The first four of these examples are the most readily available, with carbon-11 and fluorine-18 being the most common positron-emitting radionuclides used for drug studies. These nuclides offer organic in addition to inorganic chemistry for the production of PET radiotracers. Organic chemistry for labeling PET radiotracers is well developed and provides a general potential to radiolabel the active ingredient of a drug formulation. The physics of dual-photon detection also allows for relatively easy and accurate correction of radiation attenuation and scatter, while the higher energy of the annihilation photons reduces the magnitude of these corrections relative to single photon imaging. The result is that PET images are readily used to provide regionally quantitative drug distribution measurements.[62,63] The ability to produce individual quantitative images in time periods as short as a few seconds further provides the ability to make quantitative kinetic measurements. Figure 3 shows a PET image of the same drug that is illustrated in the planar images presented in Figure 1. The difference in resolution and depth sensitivity of the two methods is apparent. On the right, an overlaid CT image of the same person provides anatomic reference. Figure 4 is an example of 3D rendering that is possible with PET and SPECT. Again, a CT overlay provides anatomic reference. Rendering techniques such as this are most illustrative of the 3D drug distribution when several viewing angles or a rotating image volume is displayed.

TRACERS AND FORMULATIONS

In drug development work, ^{99m}Tc is nearly always the tracer that is used for single photon applications. Most drugs do not contain any of the available single-photon-emitting elements, so labeling the drug is usually not an option. Therefore, it is necessary to label the formulation in a way that allows the tracer to be distrib-

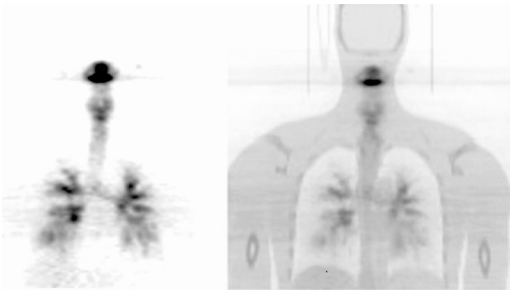

Figure 3. PET Images: PET images of a labeled anti-inflammatory steroid, front projection of the full body thickness. The particular drug shows noticeable central airway deposition. On the left is the PET data showing the resolution of the technique and well defined airways. This is the same formulation and deposition pattern as shown in Figure 1. On the right is the same drug deposition shown with an overlay of a CT scan of the same individual to provide anatomic reference.

uted in the same way as the active drug ingredient for the purposes of the measurement. Any nuclide will do, yet ^{99m}Tc is readily available and inexpensive. However, using such elements does not allow one to measure the kinetics of drug absorption, because any kinetics would be those of only the labeled technetium compound. Nevertheless, there can be estimation of initial distribution when the tracer is not rapidly absorbed from the deposition site. If the intended drug formulation under investigation is a solution, then the tracer need only be dissolved in it. If the drug formulation involves a suspension, then the tracer must be distributed throughout the particles and the solution in the same way as the drug is distributed.[64] For all drug distribution studies, it is customary to measure the distribution among particle sizes of both the drug and the formulated tracer using a cascade impactor. This helps to ensure that the tracer is distributed in the same way as the drug. It should be remembered that any factor that causes the drug to behave differently from the tracer could invalidate the measurements. ^{99m}Tc is produced by a ^{99}Mo/^{99m}Tc radionuclide generator in the chemical form of pertechnetate. Pertechnetate can often be formulated satisfactorily with the desired drug. Generally, it is extracted into organic solution in order to leave other salts behind, and then the solution is evaporated. The evaporation can be accomplished leaving the tracer directly on a powder for use in either solid or suspended drug formulations, or as a residue that can be taken into solution. Depending on the solubility, lipophilicity, ionic character and other aspects of the drug, it is possible that pertechnetate will distribute differently from the drug. For example, it may be soluble, while the drug under study is a suspension. When situations such as this occur, other compounds radiolabeled with ^{99m}Tc can be used.[39,65] There are a number of different ^{99m}Tc-labeled radiopharmaceuticals used routinely in nuclear medicine or produced for research purposes. Some of these agents include chelation complexes with various sizes and properties, labeled proteins, and other macromolecules. This usually allows the chemical properties of the ^{99m}Tc tracer to be altered sufficiently so as to eventually achieve a bulk behavior that is similar to that of the drug under study, at least until it is deposited into the airways.

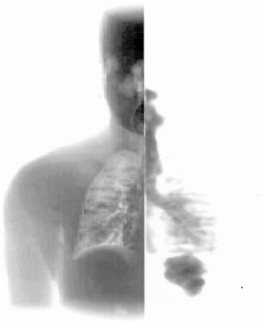

Figure 4. 3D Rendering: Three-dimensional rendering of drug distribution data from PET shown with a similar rendering of the CT data, using half of the body to allow better perception of the drug distribution.

Positron emitting radionuclides can be formulated using the same strategies as those used in the preparation of single photon emitters. There is a large variety of chemical entities that have been labeled with ^{11}C and ^{18}F, from very simple organic compounds to all types of biochemical and drug molecules, including macromolecules. Even ^{15}O-water has been proposed as being a reasonable tracer for an aque-

ous solution. In PET imaging, ^{18}F-fludeoxyglucose (FDG) is analogous to ^{99m}Tc-pertechnetate as the most commonly used and available radiopharmaceutical and has been used as a radiotracer for inhaled biodistributions.[66–68] Other common PET radiopharmaceuticals such as ^{15}O-water, ^{13}N-ammonia, and ^{11}C labeled acetate, palmitate, or amino acids could also easily be used as nondrug tracers in this way. However, carbon, and to some extent fluorine, can also be used to label the actual ingredients of a drug preparation.[62,69–72] In this way, not only can the initial deposition of the radiolabeled drug be ascertained, but mea-surements can also be acquired of the drug's subsequent redistribution and absorption kinetics.[19,20] Although nondrug tracers can be used in PET, in the majority of the studies reported to date the tracer has been a labeled drug of interest. When the tracer is not an active ingredient, the methods used are identical to those described above for single photon imaging. When the tracer is a labeled drug, then the methods remain similar. In fact, it is generally easier to match a drug's physical properties and to obtain an accurate distribution of the tracer among the various particle sizes and phases present in a given formulation when the tracer is the same chemical entity as the drug under investigation.

PET radionuclides have short physical half-lives.

PET radionuclides have short physical half-lives (T½). Those of ^{11}C and ^{18}F are 20 and 110 minutes, respectively. However, large enough quantities of either of these PET radionuclides can be produced so that there is a sufficient amount of material available for study at the end of a one- or two-hour period. That is generally enough time to allow the nuclide to perform what is usually a single chemical reaction to synthesize the drug from a closely related precursor, and formulate it into the desired form. It is then possible to collect distribution kinetic data from one to four hours postadministration. This is not too short a time interval relative to many dosing schedules. It allows one to estimate regional absorption rates ranging from minutes to many hours, which is sufficient for most drugs. This is certainly more data than is available from an initial deposition measurement using a non-drug tracer.

CONCLUSION

In contrast to planar imaging, the use of SPECT and of PET for drug development is still in relative infancy. Even so, PET and SPECT imaging have been shown to have significant importance in terms of the quality of the information that can be obtained in the assessment of drug behavior. PET has already been used to study the biodistribution of several labeled drugs and to produce regional distribution and kinetic data that has explained observed clinical data and supported applications for regulatory approval. Additionally, PET techniques have enabled quantitative measurements of the effects of different delivery devices for inhaled drug administration and to show evidence of safety of excipient ingredients. It is likely that the field of 3D imaging of drug biodistribution and its application in terms of drug development or postmarketing surveillance will continue to find widespread interest among investigators and scientists for many years to come.

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