CROSS-INDUSTRY Organizations

Drugs in the Lungs: Recent workshops and events

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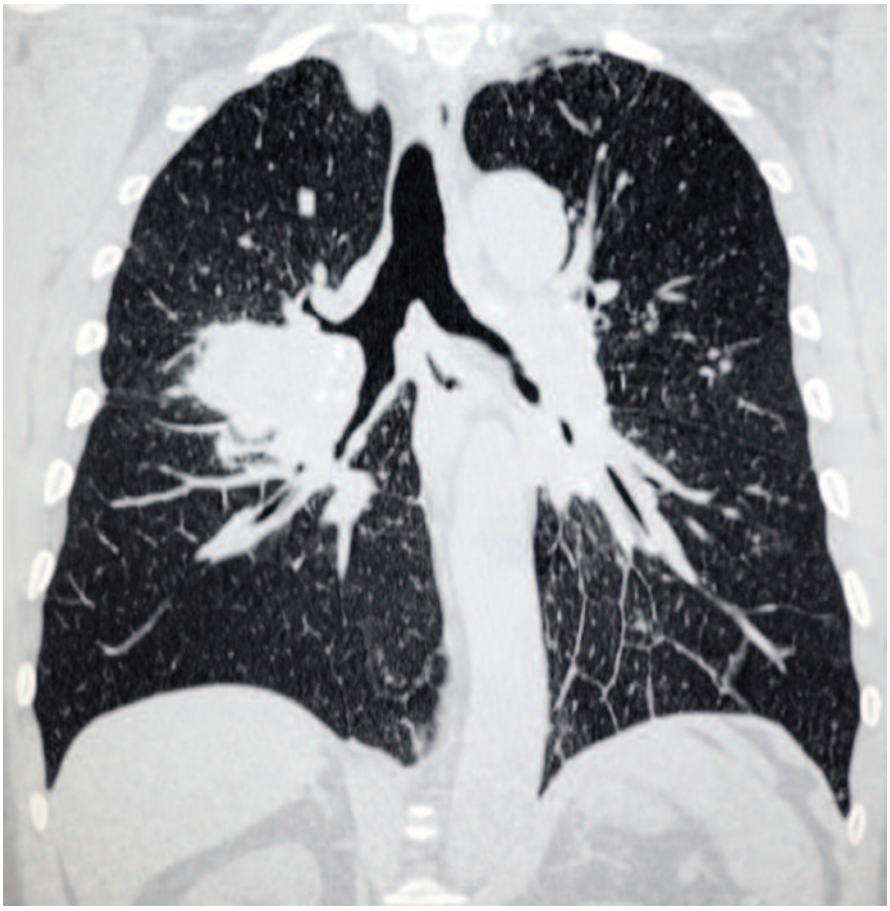
On behalf of the Drugs in the Lungs Network

The Drugs in the Lungs Network of the Academy of Pharmaceutical Scientists (APS) of Great Britain recently ran two workshops on very different aspects of respiratory medicines. A one-day meeting on November 5, 2015 addressed the issue of why and how the pharmacokinetics (PK) of inhaled drugs can be modified. A two-day meeting on January 21-22, 2016 looked at established and emerging techniques for clinical imaging and asked how these can help the development of inhaled medicines. Both workshops were structured according to the operating principles of the Drugs in the Lungs Network, which stipulate: (a) each meeting should address a defined, current issue related to the action or fate of drugs in the lungs, (b) meetings should be low cost but high value, making participation open to all, (c) meetings should be interactive, data-rich and expert-led, and (d) the state-of-the-art at the meeting should be captured and disseminated via an opinion-leading publication and consensus for research priorities should be agreed upon, e.g., pre-competitive initiatives in data or protocol sharing, gaps in knowledge or technology.



An illustrative image from a cancer patient, generated by quantitative computed tomography, the most established method for structural lung imaging. X-ray attenuation is linearly proportional to tissue density and the technique utilizes the inherent tissue contrast of aerated lung to generate high spatial resolution.

Modulating the pharmacokinetics of inhaled drugs

This workshop featured short talks, followed by facilitated small group breakout sessions. The major themes considered were:

- Why do we want to modify lung PK?
- Do we understand and can we measure lung targeting?
- What are the advantages of different PK-modifying approaches?
- What are the barriers to developing PK-modifying formulations?
- Are there opportunities for PK-modulation?
- What are the next steps in developing optimized inhaled formulations?

A brief summary of some of the workshop's major conclusions follows.

Modifying lung pharmacokinetics. Improvement in pharmacodynamics (PD) is the main driver for modifying PK, assuming systemic toxicity is not a problem. Novel PK-modifying formulations would only be developed if there were a clear value versus risk; improving molecular properties of drugs to alter their disposition is generally preferred to post hoc formulation approaches to optimize PK. Although there is non-clinical evidence that formulations can modulate lung PK and that this leads to changes in PD, this is still to be verified clinically. The properties of a drug candidate that favor inhalation as a delivery route include low oral bioavailability, high systemic clearance and retention of inhaled drug in the lungs. A barrier to developing PK-

modulation is that measurement capabilities for determining pulmonary fate (PK) and effects (PD) are not sufficiently developed to guide development or evaluate outcomes. It was apparent that methods for indirectly estimating lung PK in humans are evolving rapidly. Modeling approaches using plasma and urine data include empirical and physiologically-based pharmacokinetic (PBPK)/mechanistic modeling. These techniques can derive the amount of drug in lung and its net/apparent absorption rate(s) into the blood. However, to date, it is not possible to directly measure drug locally in lung tissue. Access to lung samples (bronchoalveolar lavage, induced sputum, etc.) to measure drug concentration may help in measuring lung PK, especially for targets located in the lumen of the airways. However, most experimental approaches do not differentiate between drug in the lungs that is solid versus dissolved, free versus bound or localized at the target. Thus, estimating lung concentration can be useful, but may also be misleading. It may be necessary to consider lung PK in different compartments within the lungs.

Development of formulation approaches. Formulation approaches are limited by: (a) the lack of approved excipients for the inhaled route, (b) toxicity concerns, (c) compliance with device platforms, and (d) the amount of material that can be delivered to the lungs by aerosol. There may be scenarios where formulation approaches become imperative, e.g., protection of biologics, cell targeting of nucleic acids or enhancing mucus penetration. A limitation in formulation approaches is that few generally recognized as safe (GRAS) excipients or materials listed on the US Food and Drug Administration Inactive Ingredient Guide are approved for pulmonary administration. This therefore largely confines PK-modulating strategies to manipulation of a molecule and its salt form. There may be an opportunity for pre-competitive collaboration (by academia and industry) to foster approval for novel excipients (similar to the IPAC-RS model used for HFAs). Other agreed-upon research priorities include the development of better techniques to measure lung PK, optimization of mechanistic models, identification of biomarkers and improvement of disease models. The Innovative Medicines Initiative Orbito Project (Innovative Tools for Oral Biopharmaceutics) hierarchy of work packages (understanding the API, the formulation and the *in vivo* environment) could be applied in a useful manner to understanding the PK of drugs delivered by inhalation.

Developing new drugs for respiratory diseases—How can clinical imaging help?

This workshop brought together clinical imaging groups to analyze opportunities to address areas of unmet need in the pharmaceutical industry: The workshop aims were to:

- Identify, from a pharma perspective, the key gaps in inhaled medicines development that clinical imaging could help fill
- Bring imaging groups closer together and start to define the imaging techniques best suited for given clinical endpoints and, therefore, which techniques could tackle different mechanisms of drug action
- Provide a source of reference for justifying any particular imaging modality in future drug development studies
- Publish a summary of the way that clinical imaging is used today and what it needs to do for the future

This meeting consensus is currently being collated.

Presentations from all Drugs in the Lungs events are freely available on the website: http://www.apsgb.org/drugsinthelungs. Any suggestions for future symposia or initiatives for open innovation in the area of inhalation biopharmaceutics are welcome. Please contact Ben Forbes for further information.

The APS Inhalation Focus Group

The Inhalation Focus Group which hosts the Drugs in the Lungs Network presented three other events in 2015. These were a meeting on "Bioequivalence of Orally Inhaled Products," the training event "Product Development Workshop: Inhalation Science: The Science and Strategy to Develop an Aerosolized Medicine" (which is envisaged to run biennially) and inhalation sessions at the annual APS PharmSci Conference.

The next meeting of the Inhalation Focus Group will be held towards the end of 2016, on the topic "Delivering High Doses to the Lungs." Details will be announced soon.

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