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Research focus on nasal biopharmaceutics: A workshop by the Biopharmaceutics Focus Group of the APS

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The Biopharmaceutics Focus Group of The Academy of Pharmaceutical Sciences (APS) of Great Britain presented a workshop on nasal biopharmaceutics at the 2022 Drug Delivery to the Lungs Conference (DDL2022) in December 2022 in Edinburgh, UK. The aim was to bring together the scientific community to discuss challenges in the development of nasally administered therapies. The workshop featured thought-provoking talks on topics ranging from research and development through clinical studies. The speakers summarized how biopharmaceutics and performance of nasal products are currently evaluated and shared their thoughts on new developments and unmet needs. The workshop concluded with a facilitated panel discussion that explored opportunities and challenges in these areas. A summary of workshop content is provided below.

Nasal drug product characterization

Regina Scherließ, Kiel University (Germany), summarized current guidance from the European Pharmacopoeia (Ph.Eur), United States Food and Drug Agency (FDA) [1] and European Medicines Agency (EMA) [2] including the Ph.Eur monograph "Nasal Preparations" (Ph.Eur. 11.0/0676), which stipulates tests for the uniformity of delivered dose. The FDA has guidance on the general characteristics such as pH, osmolarity and viscosity, plus guidance on nasal spray product performance: plume geometry, dose uniformity and spray pattern.

Both the FDA and EMA emphasize the need to determine the proportion of nasal spray droplets below 10 µm, a safety consideration to control lower respiratory tract exposure. However, different apparatus and configurations for impactor methods to measure mass fraction below 10 µm result in significantly different outcomes. In response, Regina's group has developed a new "realistic" nasal inlet for use with impactors.

Physiologically-based biopharmaceutics modeling (PBBM)

Claire Patterson, SEDA (UK), discussed potential applications and the status of physiologically based biopharmaceutics modeling (PBBM) for nasal delivery. PBBM combines drug metabolism and physiologically-based pharmacokinetic (PBPK) software with models of dissolution and other dynamic processes relevant to nasal drug delivery. Mathematical descriptors linked by differential equations are used to predict concentration-time profiles at a target site, whether it be drug concentration locally within the nasal cavity, in the systemic circulation or in the brain. Such simulations can guide formulation and device development and inform dose selection.

PBBM is well established for oral drug delivery and has potential for similar impact in nasal delivery. The commercial software platform GastroPlus® (Simulations Plus, Lancaster, CA) contains a pulmonary/intranasal absorption model in its Additional Dosage Routes Module, although there is little reported regarding its use or efficacy. Building a PBBM model for nasal drug delivery relies on identification of input parameters and generation of datasets (perhaps requiring new methodology) required to build and validate the models. This requires more advanced mechanistic understanding of processes involved, particularly in nose-to-brain delivery, and a cycle of continuous improvement to challenge prototype models with data to understand their strengths and limitations.

Modeling deposition in the nasal cavity

Andrew Martin, University of Alberta (Canada), focused on *in silico* and experimental modeling

of drug deposition in the nasal cavity. Nasal product quality is currently controlled by assuring reproducible delivery of emitted doses with consistent spray pattern, plume geometry and droplet size distributions, assuming this provides consistent deposition profiles within the nasal airways. However, newer methods aim to estimate regional delivery in different patient and product use scenarios.

Research into nasal drug product deposition in realistic nasal geometries was discussed, including complementary *in vitro* and *in silico* approaches. For example, an idealized nasal geometry was evaluated by conducting *in silico* simulations over a wide-ranging parameter space [3]. In addition, *in vitro* experiments conducted using the Alberta Idealised Nasal Inlet (AINI) were in good agreement with previously published *in vivo* data [4]. It was noted that these tests have been developed for nasal sprays and their applicability to other nasal dosage forms, such as nasal powders, remain to be investigated.

In vitro biological characterization

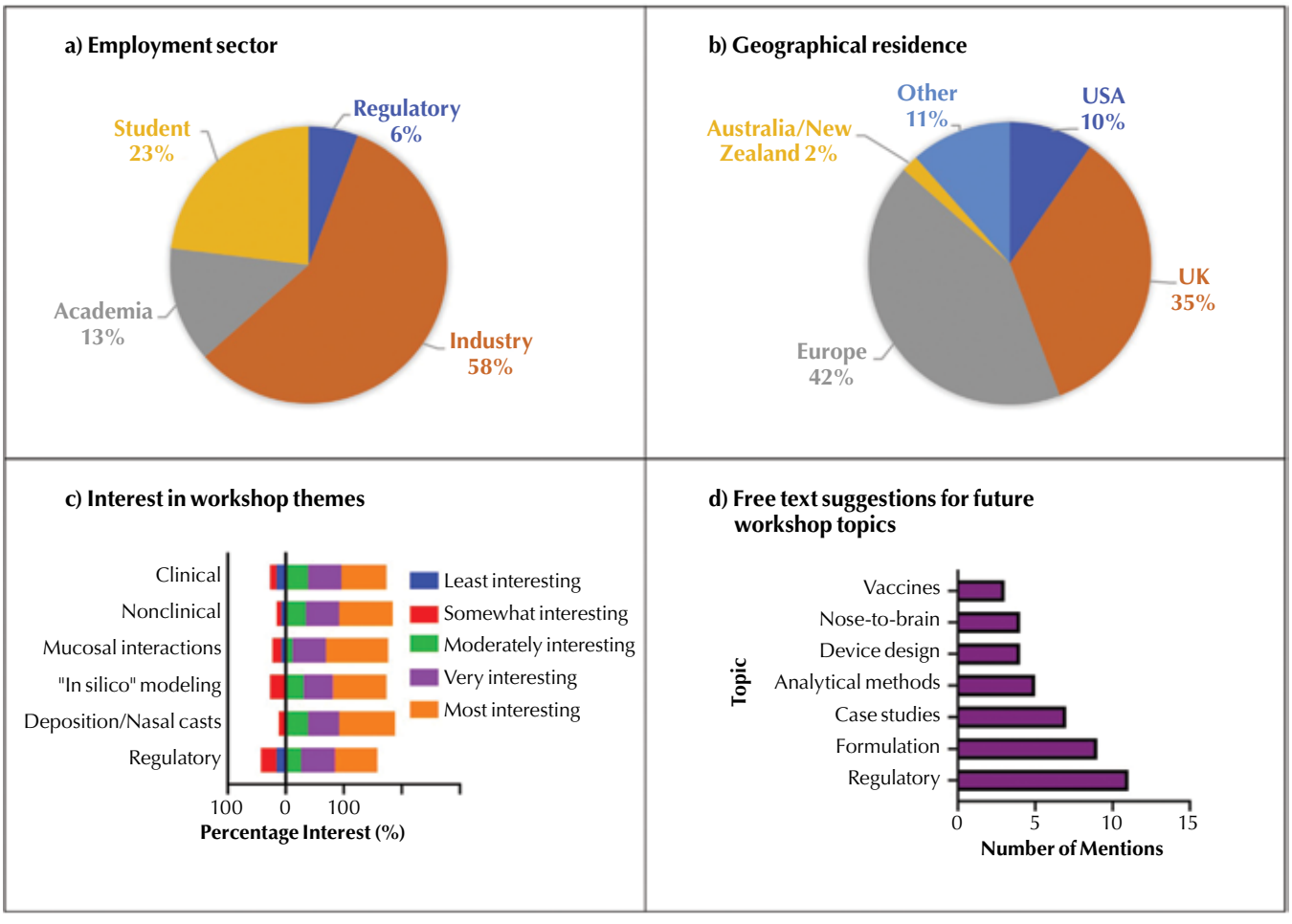
Alison Lansley, University of Brighton (UK), discussed the role of mucus and mucociliary clearance in nasal drug delivery. A nasally administered formulation deposits onto the mucus that lines the nasal cavity, followed by dissolution (for suspensions and powders) and diffusion of drug, concurrent with mucociliary clearance—all of which may be affected by the properties of mucus itself and interactions with drug or formulation. Mucus-secreting respiratory cell lines of human origin (Calu-3, UNCN3T, NuLi-1, RPMI 2560) and rat origin (SPOC-1) have been used to model the mucus of respiratory mucosa typical of the turbinates. In contrast, there are fewer examples of cell models of the olfactory mucosa and nasopharynx. Importantly, cell models need well-defined culturing conditions and experimental protocols to study mucus interactions and drug permeation.

Nonclinical studies

Helen Palmer, Labcorp (UK), discussed the practicalities of

Figure 1

Responses to a survey of attendees at the Nasal Biopharmaceutics Workshop (152 registrants) to gauge interest in topics related to nasal biopharmaceutics. The survey had a 33% response rate and collected data from the respondents on the following topics: (a) sector of work or study, (b) location, (c) interest in workshop themes (positive interest shown to right of line) and (d) topics suggested for inclusion in future events, categorized and ranked according to number of times mentioned.



nonclinical studies of nasal formulations and considerations in study design and methodology. The nasal architecture of a rat or dog is far more complex than that of a human, with different dimensions and convolutions that impact greatly on administration, whether by instillation (placing of liquid into the nose) or insufflation (blowing or aerosolization of liquid or powder into the nasal cavity). As such, nonclinical regulatory expectations are primarily around safety. The use of nasal devices is not necessary, provided the formulation remains in contact with the nose and (if intended for a systemic indication) the drug reaches the circulation. Translation of nonclinical findings to humans would benefit from more discerning methods for intranasal dosing of rodents, better understanding of drug distribution *in vivo* and techniques to provide greater insight into brain exposure.

Clinical development

Chris Roe, Quotient Sciences (UK), discussed clinical evaluation of nasally administered drug product performance by scintigraphy/magnetic resonance imaging (MRI). Gamma scintigraphy quantifies deposition and clearance of formulations in the nasal cavity, which is demarcated by MRI. If oral absorption is minimal, imaging data can be combined with pharmacokinetic (PK) and/or biomarker data obtained from the same study subject to provide greater insight into product performance. A limitation is that radiolabels typically label the formulation rather than the drug. Clinical case studies included (i) comparison of nasal delivery by a pump spray, which was superior to a nebulizer and (ii) multi-day dosing of a chitosan formulation demonstrating retention in the nasal cavity with negligible delivery to the lungs.

The challenge in sampling nasal fluid in clinical studies was also discussed, exemplified by a study comparing nasal wicks with nasal washes for sampling cytokine levels as markers of inflammation after nasal administration of novel and reference formulations.

Feedback from workshop delegates

A survey of workshop registrants obtained 51 responses (a 33% response rate). Most respondents (58%) worked in the pharmaceutical industry, with academia, research students and medicines regulators also represented (Figure 1a). Geographically, most respondents resided in the United Kingdom or Continental Europe, with 23% offering a wider global perspective (Figure 1b). There was interest in the full range of topics covered, with scores in the 79-94% range for positive interest, i.e., "moderately interesting" to "'most interesting" categories, with respondents having a slight preference for biopharmaceutics *(in silico)* modeling, *in vitro* experimental methods and nonclinical studies compared to clinical and regulatory aspects (Figure 1c).

There was general enthusiasm for further events on nasal biopharmaceutics, with similar proportions of respondents (approximately two-thirds) indicating they would attend an in-person workshop, online conference or webinar. Free text responses to the question "Was there anything you felt we missed or would like to see next time?" were coded and broadly fell into seven categories (Figure 1d).

"Regulatory" was most popular with interest in US versus EU requirements, bioequivalence, regulatory-industry interaction and development of critical quality attributes. Interest in "formulation" included excipients, liquids versus powders and formulations tailored for regional deposition or molecular drug class. "Case studies" were requested from key opinion leaders or nasal product development companies based on optimization for local or systemic delivery or new molecules/products. Interest in "analytical methods" included nasal casts, dissolution methods, spray characterization and emitted dose. There was interest in how to target "nose to brain" delivery and *in vitro/in vivo* correlation for this route, "devices" with an emphasis on innovation, device/formulation matching and device switching, and "vaccines" including mucosal biology.

Next steps

The content of the workshop is being supplemented by reference to the literature and will be published shortly as a detailed review article titled, "Nasal biopharmaceutics: Fit for current and future drug delivery needs?" In addition, the focus group is using the feedback above to plan follow-up events and will announce details soon.

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