Expert Opinion

Respiratory Drug Delivery X

Boca Raton, FL, USA, 24 – 27 April 2006

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There were ~ 700 delegates who attended Respiratory Drug Delivery X (RDD-X) at the Boca Raton Resort and Club in Boca Raton, Florida, between the 24th and 27th April 2006. Participants from North America, Europe and many other parts of the world came together to hear a series of invited podium presentations covering the latest scientific developments in pulmonary and nasal drug delivery, along with regulatory and quality control issues. A total of 150 proffered posters were also presented, and a Technology Exhibition involved the products of 78 companies. The conference also provided unparalleled networking opportunities. The proceedings of RDD-X will prove to be an invaluable resource for years to come.

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1. Introduction

Respiratory Drug Delivery X (RDD-X) took place at the Boca Raton Resort and Club in Boca Raton, Florida, between the 24th and 27th April 2006. The RDD conference series is run by a team headed by Peter Byron of Virginia Commonwealth University School of Pharmacy in Richmond, Virginia, and has become established as the pre-eminent gathering of scientists in this expanding field. The emphasis in these conferences is on pulmonary drug delivery, but nasal drug delivery also features significantly.

The conference was attended by ~ 700 delegates, the majority of whom were from North America, but there were > 240 delegates who were from Europe, and there was also representation from other parts of the world including India, Japan and Australia. The majority of attendees were from the pharmaceutical industry with only around 10% from academia, and these were predominantly scientists with only a few physicians. The regulatory authorities in both the US and Canada were represented. The meeting received generous sponsorship from a total of 34 pharmaceutical companies and device manufacturers.

The meeting repeated the tried and tested format of previous RDD meetings, and comprised 36 invited podium presentations over 4 days in a single auditorium. In addition, 150 posters that were submitted by delegates from 70 organisations could be viewed over the first 2 days. Five of the posters were specially selected for a novel 'posters on the podium' session in the main auditorium, where each presenter gave a brief synopsis of their poster. The poster-viewing sessions ran concurrently with a Technology Exhibition in which 78 companies displayed their wares in a simple table-top format.

The entire proceedings, running to 958 pages, were provided to delegates in hard-copy form as an invaluable reference. Non-delegates who wish to access the proceedings should consult the RDD website [101].

2. Meeting highlights

2.1 50th Anniversary of the pressurised metered dose inhaler

2006 marks the 50th anniversary of the introduction of the first pressurised metered dose inhaler (pMDI) by Riker Laboratories (now 3M Healthcare/3M

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Drug Delivery Systems). Therefore, it was appropriate that the meeting should begin with the presentation of the first Charles G Thiel award for outstanding research and discovery in pulmonary drug delivery to Charles Thiel himself, in recognition of a lifetime of achievement in the field. Charles Thiel was one of a small team of researchers who developed the first pMDI, a device that has subsequently become the backbone of inhalation therapy for asthma and chronic obstructive pulmonary disease (COPD). It was estimated by one speaker that pMDIs have now been used to deliver around 10^{12} individual drug doses.

The scientific programme began with a plenary lecture on the topic of 'Improving drug metering to the lung: making the patient the most important factor' that explored the theme of the pMDI, together with its strengths and weaknesses, in comparison with alternative metered dose technologies [1]. A special session on the future of the pMDI included presentations reviewing the history and future of transition from chlorofluorocarbon to hydrofluoroalkane propellants [2], fascinating video evidence concerning how the pMDI generates its spray (a process that at least hitherto was poorly understood) [3], novel actuator designs, novel closures and containers, and dose-counters. Another paper reviewed the methods of adapting the pMDI to deliver drugs other than those that are used in the treatment of asthma and COPD, including methods for achieving higher and more reproducible drug delivery, higher payloads and elimination of the need for priming shots [4]. pMDIs containing fewer than the traditional 100-plus doses would probably be needed for delivering relatively expensive drugs such as insulin. Regarding the likely future success of the pMDI, the general feeling seemed to be that the durability and low cost of the pMDI (at least for asthma and COPD medications) could result in the device still being available in another 50 years, and it was predicted specifically that a session on hydrofluoroalkane pMDIs would be held at RDD-XV in 2016.

2.2 Arrival of Exubera®

It is an interesting coincidence that 2006 marks not only a milestone anniversary for the pMDI, but also approval in both the US and Europe of the first inhaled peptide product for systemic delivery via the pulmonary route. This is Exubera®, inhaled insulin developed by Nektar Therapeutics and Pfizer. This event was marked by a podium presentation about the Nektar Pulmonary Delivery System, a dry powder inhaler device that has been developed especially for the particular challenges of delivering inhaled insulin reliably and reproducibly to diabetic patients [5]. This device delivers a powder formulation of particles with diameters of ~ 3 µm into a 220-ml spacer device, from which the patient inhales deeply and slowly. One of the 'posters on the podium' presentations provided some useful data on aerosol performance of this device following simulated long-term use and real-time patient use.

2.3 Alternative delivery systems

Several other presentations discussed in-depth alternative technologies for pulmonary drug delivery, notably the use of sophisticated particle formulations for delivery by dry powder inhaler [6]. Some of these involve manipulation of traditional micronised particle formulations, for instance modified carrier particle surfaces, fine-particle lactose or the use of ternary components such as magnesium stearate. Particles made by spray-drying techniques [7] and by supercritical fluid technologies [8] were also discussed. Another paper presented the first *in vivo* data from a novel soft mist inhaler, a unique condensation aerosol generator system [9]. Lung deposition from this device was high (> 80% of the emitted dose), and was virtually independent of inhaled flow rate or breath-hold pause after inhalation.

2.4 Patient psychology

Issues of patient psychology in using inhaler devices in general were also discussed. Patients make trade-offs between advantages and disadvantages when deciding how to manage their asthma or COPD: they see inhaler therapy positively as a means of controlling symptoms and avoiding exacerbations, but also negatively because of the need to take regular medication and possible stigmatisation [10]. Patient preference for inhalers may be associated with better adherence and better therapeutic outcomes. The need for a major training programme to teach patients how to deliver a wider range of drugs from a wider range of devices was highlighted.

2.5 Novel medications

In addition to its established roles for delivering drugs for local action in the lungs, and its new role for inhaled peptides, other treatment possibilities are currently being explored. For instance, the pulmonary route is also being used in situations where a rapid onset of action is needed, such as pain control or the delivery of inhaled apomorphine in patients with erectile dysfunction [11]. A session on 'Priming lung defences against 21st century infections' covered the areas of novel inhalants for protection against airborne infections, the use of pulmonary drug delivery as a first response to bio-terrorism, and a description of the WHO's project to deliver measles vaccine worldwide by the pulmonary route, using appropriately designed nebulisers [12]. Although inhaled droplets can be used successfully to treat a variety of respiratory conditions, exhaled drops of airway-lining fluid can be a vector for spreading infectious diseases. The delivery of isotonic saline to the airway lining may help to reduce the exhalation of viral-loaded bioaerosols, possibly preventing the spread of infectious diseases ranging from influenza to tuberculosis [13]. Liposomal ciprofloxacin is currently being developed for inhalational anthrax post-exposure [14].

2.6 Nasal drug delivery

Although the conference concentrated mainly on pulmonary drug delivery, nasal drug delivery was not ignored. Papers

discussed the possibility of delivering drugs directly into the brain via the olfactory region of the nasal cavity (nose-to-brain delivery) [15], as well as the opportunities afforded for novel powder formulations to be delivered by the nasal and pulmonary routes. Currently, the best evidence for nose-to-brain delivery is in animal species and there are relatively few human data. Targeting the olfactory region of the nasal cavity with currently marketed nasal pump sprays is not straightforward, and novel delivery systems would probably be required to make this delivery route viable.

2.7 Quality control and regulatory issues

Two related sessions covered pharmaceutical quality and regulatory issues. In the first of these, the relevance of process analytical technology to inhalation products [16], and the use of the pharmaceutical quality assessment system [17] were described. These presentations were followed by a panel discussion on the subject of 'Mitigating producer risk in a highly regulated environment', with a discussion about building concepts such as quality-by-design into the development of new inhaled drug products [18]. Practical guidance was given regarding the regulatory hurdles that one company had to address in obtaining 510(k) approval to market their nebuliser device in the US [19].

2.8 Other sessions

Other sessions at RDD-X were devoted to preclinical bioresearch tools in pulmonary drug development, predicting and realising improved *in vivo* aerosol deposition, and advances in physics and engineering. Notable among the papers in these sessions was a review of molecular imaging using positron emission tomography in animal models [20]. This approach allows biological processes such as inflammation, infection, ventilation and receptor occupancy to be visualised and quantified, and was seen to be a way of bridging the gap between preclinical and clinical investigations.

3. Expert opinion and conclusions

This was another outstanding conference in the RDD series, and its success was a tribute to the organisers' hard work and logistical skills. It helped to cement the reputation of RDD conferences in this area: if you can only go to one respiratory conference, make sure that it is RDD. In addition to the presentation of outstanding science in a stimulating environment, RDD has also become established as the best place to meet other scientists working in the fields of nasal and pulmonary delivery and, as is often the case, the discussions that took place outside the conference hall were probably just as valuable as those that took place within. The peer-reviewed RDD proceedings have become recognised as a key source of quality reference material about all of the aspects of respiratory drug delivery, and the proceedings from RDD-X will be no exception. The dates for the next meeting in this conference series have already been set for 11 – 15 May 2008, at the Westin Kierland Resort and Spa in Scottsdale, AZ, USA, and these dates should be marked in the calendars of anyone with an interest in the respiratory drug delivery area. Meanwhile, the second in a companion series of conferences (RDD Europe) will take place in Paris, France, between the 17th and 20th April 2007.

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Website

101. http://www.rddonline.com Respiratory Drug Delivery website.

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