Roundtable Proceedings
INNOVATIVE FORMULATION FOR INHALED DRUGS

"The troubled relationship between formulation and device: do we know enough to determine how a therapy is most effectively delivered?"

March 24th, 2021

Acknowledgements

The roundtable on 'the troubled relationship between formulation and device: do we know enough to determine how a therapy is most effectively delivererd?' was held on March 24th, 2021. The roundtable was organized by the European Respiratory Cluster Antwerp (eu.reca vzw).

For this meeting eu.reca brought together a group of experts for an in-depth discussion on 'innovative formulation for inhaled drugs within pulmonary medicine'.

Six technical experts (both industrial and academic) offered an insight into the variety of technologies that are currently being used or are under development. The purpose of the discussion was to explore state-of-the art and future opportunities and to see if it would be possible to align the medical expectations with the potential benefits from new technologies.

The eu.reca network acknowledges Harro Höfliger and Lonza for their continued support of the eu.reca network and in particular for their keen interest into this specific topic.

Welcome

By Stefano Console, Workstream Formulation Ambassador and Advisory Board Member of eu.reca vzw

In his welcome address, Stefano Console, Workstream Formulation Ambassador and Advisory Board Member of eu.reca vzw, introduced the European Respiratory Cluster Antwerp (eu.reca), a young ecosystem entirely focused on everything that impacts the human lung.

To advance respiratory innovation, eu.reca brings scientific and medical experts together with entrepreneurs and other stakeholders. The network stands for a hands-on approach, not only tackling relevant challenges, but always reaching out to present possible solutions.

As eu.reca's approach is based on interaction, initiatives such as round table workshops and are important, especially in these trying times where interaction and brainstorming is somewhat impeded by the pandemic.

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In closing, Stefano welcomed all participants stressing that crossfertilization between industry, academics and clinicians is key to accelerate in the field of respiratory diseases.

Setting the scene: goals of the workstream

In order to successfully reach the target, respiratory therapies rely on a complex system called 'combination drugs', in which different components need to be designed and developed all together in order to guarantee a satisfactory result. However, the therapeutic active ingredients alone are not enough to treat the disease, a device to deliver the therapy to the lung is also necessary. Formulation and device must be developed together since they strongly influence each other as well as the final result.

In recent years innovative technologies created a lot of opportunities in formulation and device development, allowing to conceive new therapeutic treatments.

The mission of the Workstream 'Innovative Formulations for Inhaled Drugs' is to gain a clear insight into the benefits of these innovations, as well as to learn best practices on how to better treat patients.

This virtual roundtable discussion was initiated trough a number of questions to which all participants provided their answer. These proceedings capture the essence of the participants' combined answers.

Is there a preferred inhalation device? If yes why?

It is very clear: a one-fits-all solution does not exist. And the answer to the question will likely depend on whom you ask: the formulation scientist, the pharma company, the patient, the regulatory bodies, or the payers. The major goal of course is trying to define the best device given the (a) indication, (b) target population, and (c) market. Also, the issue whether an indication is considered acute or chronic is relevant to the final choice of the device.

We can say that there is probably a 'preferred' inhalation device for each given circumstance, but not for every individual patient. Very important is that the choice of device is best suited to the patient's needs and yet this part is often forgotten. The device must fit the formulation, the dose, the business model, but most importantly the patient. For example, if the patient deals with a coordination problem, you should not prescribe a device where coordination is necessary to give the dose.

The ideal device has to work independently from the patient and its effectiveness will not depend on the patient's specific airflow or useability. There are some developments in that way, for example, the K-Nexthaler which is only triggered after a certain airflow has been achieved by the patient. Today there also other technological options which make these new goals achievable and thus ensure a more effective therapy.

The answer is also related to the need: for some applications, you need something very simple and low cost, whereas other cases, will require a very specialized nebulizer device with electronics.

As a general recommendation all experts agree that a dry powder inhalation system would be preferred. A dry powder is more versatile, convenient with large doses and guarantees long stability. Furthermore, in comparison to a nebulizer it is relatively simple to develop.

Three main factors that influence the device choice are (a) the kind of formulation used – conventional, micronize drug or engineered particles – (b) the place where the particles should end up and (3) the patient condition, for instance will the device be used for COPD or cystic fibrosis?

The roundtable pointed out some practical remarks.

Most patients use several devices and from that point of view it could be interesting to consider putting all the drugs in the same device. If not, problems with regard to usability (and therapy effectiveness) can arrise when the patient must inhale with a low resistance device very slowly and for another medicine with a high resistance device inhale very forcibly. At this moment in the Netherlands, for example, more than 50 devices are on the market and the general practitioners lost the overview. Per region, a form is under development with devices that are to be preferred and are reimbursed by the health insurer. In particular, devices that can be used over the whole spectrum are chosen, for instance the Elipta device is overall, because they have all the different drugs; also the Brace inhaler is in the top list.

Can we dream of a formulation that fits any device? If not, can we dream vice versa a device that works with any formulation?

From the patient perspective, the patient does not know, nor does he care about the content of the device. Ask them if there is a liquid or a dry powder in the inhaler and they will not know. From the patient perspective, the only relevant determinor is wheter or not the device is easy to use.

Stability is an important parameter for the formulation and the regulators. From this point of view in the case of asthma or COPD dry powder is without doubt the best option. Only in a minority of cases and in hospital use, is nebulization to be preferred.

Dry powder inhalation (DPI) in general has the preference in a lot of situations. In comparison, pressurized metadose inhalers (pMDI) for instance are quite limited with the dose, whreas DPI offers a whole range of doses. On pMDI the carbon footprint is also becoming an important topic of discussion. Even the pMDI with HFA-134 is under debate in the UK and other countries such as Netherlands are following suit. The discussion was generated on the one hand by GSK, because they moved to the dry powder devices and less to the pressurized metadose inhalers, and on the other by studies that suggest that there is a reduction of mistakes with DPI in contrast to pMDI. Therapy compliance is related to this situation.

The big advantage of the pMDI, however, is the cost advantage due to mass manufacturing. In contrast, the complexity of the DPI often leads to a costly customized solution. The discussion on pMDI is still ongoing and some technologies are still under development such as soft mist inhalers and generic Respimate devices. It is unclear if the industry is open to it, but at the time when pMDI was brought to the market by 3M, it developed into a platform that is nowadays used by GSK, Boehringer Ingelheim, Cipla and many others. They all work on the same platform. The roundtable is wondering if Respimate, even though invented by Boehringer Ingelheim, could follow a similar trajectory and become a platform device that could be sold by 3M or by Aptar as standard technology, and can be used by other companies like Astra Zeneca or GSK to develop new formulations (of course, taking into account the limitation of the dose).

There is one strong argument against Respimate and that is the formulation in which the drug is used as a solution. This implies that the drug has to be soluble and stable in a water solution, which leads to strong limitations, despite Boehringer demonstrating that even a pure ethanolic solution could be handled by Respimate, which was accepted by FDA. However, do you really want to inhale ethanol ?

Another issue is that patients using Respimate often experienced coordination problems, something that needs to be solved. The patient has to inhale for at least two seconds, but if you look at the duration of the aerosol it is 1,7 seconds, meaning that if the patient starts too late with the inhalation, they cannot inhale the drug in its entirity. The device seems perfect, but it is often due to a lack of coordination. If you could could reduce the residence time of the aerosol, you could have a very nice platform.

Looking at the drug pipeline at the clinical stage, it is interesting to see that in the early stages the clinical trial often starts with the nebulization type of platform, because this is easy for the proof of concept. In the later clinical-stage, there is often a swift in the DPI formulation. This strategy is often used to speed up the safety part of the study.

So despite DPI being preferable because of the dose, nebulizers can have a role in the future certainly in formulations with liposomes and for the delivery of engineered particles.

Pharmaceutical companies nowadays are also more concerned with the sustainability and environmental impact of devices and put in place recycling guides. Is this a concern patients share? Usually patients ask:

> **(1)** *Is the device reusable? The answer is yes : a device can be made to be reusable, but this increases the complexity by a factor of two, three, or four, which in turn will make the device more expensive. At the end of the story it is often more sustainable to have a simple single-dose device disposable.*
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> **(2)** *Can you use biodegradable material for device manufacturing? The answer is no: there are very high regulatory requirements on the material.*
>
> **(3)** *Could you put electronics inside the device, make it smart? the answer is yes: but that would make it less sustainable, more complex and more expensive.*

The Syqe inhaler for cannabinoids for instance is a rather big electronic device and reusable as you load your track in it. It works like a single-dose nebulizer. This can be a step forward for the treatment of chronic diseases, and the reuse could decrease the footprint. However for acute treatment situations, it is not an option. A nebulizer can be helpful to decrease the carbon footprint compared to other devices, even if there are other possibilities being developed such as current research by Pharmadevices to make a dry powder device with a single polymer material, which makes it much easier to recycle.

▶ Do we need new devices? If yes, what should be taken into consideration?

Yes, we need new devices: we miss a DPI that can deliver a high dose, like several 100 mg, for the treatment of cystic fibrosis, or cancer diseases when you need need a big dose.

The Orbital device can handle large doses, but there is a need for more devices that can do so and are easier to use. In the US there was a recent launch of an inhaler device for levodopa which uses a large capsule (00). The cholestine Cyclops as well is developed for the delivery of a high dose. It contains 55 mg cholestine and is very effective. People with CF now use 160 mg cholestine by nebulization but with the new inhaler device, we could bring it back to 55 mg, with a waste of only 5 mg in one inhalation. Cyclops does the same with levodopa arriving at doses of 90 mg levodopa. Cyclop cholestine has an effectiveness of 90% which is extremely high, while with levodopa, the effectiveness is 50%. If the devices for asthma and COPD would be more effective, fewer excipients could be used. For example, the Elipta device needs some Magnesiumstearat that had to be added to the formulation to enhance the aerosol performance, but if the device would be a bit more effective you do not need it at all. We must always try to reduce the excipients as much as possible.

However, we need to keep in mind the maximum mg that could be inhaled via a DPI. The maximum amount is 50 – 60 mg, so if you need to admit several hundreds of mg you have to inhale multiple times. But it also depends on the flow rate: sometimes it's smart to have a higher resistance device to overcome the problem of the dose.

So it is crystalline clear once again: the device and the formulation have to go together from the beginning.

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How we should define an excipient acceptable for inhalation?

There is a relatively limited panel of excipients for inhaler formulations in comparison to other formulations. VITO in Belgium has a program of research with in-vitro lung cells that can be used to monitor the toxicity of products to the lung. So it can be possible to examine new and different excipients. But is there a need for new excipients ? Maybe we need to rephrases the question: can we formulate something without excipients ?

For COPD, lactose is the best choice by far. Several studies explore new excipients, even in clinical phase 2 and 3. There are new formulations with trehalose. Companies that performed research on inhaled insulin Exubera completed toxicological studies on a new excipient, but there are no incentives for performing toxicological studies for excipients for existing drugs because it's too expensive. That's the reason no new excipients are seen for inhaled drugs for COPD and asthma. The key is balancing the costs.

Lactose has a role as a carrier in the formulation but has no pharmaceutical relevance. One wonders if in the future functional excipients with treatment advantages, for example, excipients that can cause a sustained release in the lung, could reach the market? These functional excipients should be investigated more deeply.

Are we considering the right technologies to create the right product for the patients?

A new device should always be nice, simple, logical with a minimum of required steps to ensure correct use. The advancement of technologies should allow for the development of new devices. Look at the Airbus A318 airplane: it has been computer developed and it does fly. So if a man can make an airplane via the computer, should this not also be possible for a device? The answer is yes, the technology is available but the pharmaceutical industry is not ready. It is a common feeling among the participants that in the pharmaceutical industry the formulation development has to be taken out of the bakery age. The formulation development is extremely low tech and based on trial and error. At the same time products that are developed generate billions of dollars in revenues. Investments are made in clinical development, clinical trials, and marketing. However the device and formulation development is the cheapest and low-cost side of the overall budget. All agree that one issue is cultural: the mathematical models for the research are not a part of the teaching program of pharmaceutical universities and scientists curriculum. Although some among pharmaceutical companies are moving in that direction, there is still a long way to go.

Participants

Frédérique Bordes-Picard, Business Development Manager, Capsules & Health Ingredients Lonza.

Biochemist Engineer by training, Frédérique holds also a Master of Business Administration from KEDGE Business School. Frédérique has been working in the Pharmaceutical Industry for more than 20 years in the Innovative and Generic industries. Frederique joined Capsugel®, now Lonza, in 2010 as Pharmaceutical Business Development Manager providing technical and regulatory support for new capsule-based product developments. Frederique has developed specific expertise around capsule-based DPI product development & filing, supporting multiple companies in EMEA and US working on innovative or generic DPI projects.

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Paul Hagedoorn is Senior Technologist/Scientist Inhalation and head of the inhalation research laboratory of the Department Pharmaceutical Technology and Biopharmacy, Groningen Research Institute of Pharmacy, University of Groningen, Netherlands.

His research focus is developing of drug formulations for the pulmonary route and developing of effective dry powder inhalers. Paul has more than 25 years experience in the field of inhalation and is (co) author of more than 100 publications in peer reviewed journals, have 4 patents and is the (co) inventor of several DPI's like the Novolizer, Genuair, Twincer and the Cyclops. He is the scientific advisor and board member of the foundation Inhalation Medication Instruction School (IMIS) in the Netherlands and scientific advisor of the Lung Alliance Netherlands (LAN). Furthermore board member of the Inhaler Research Workgroup (IRW) and Medical Aerosol Thinktank in the Benelux. Paul is also author of a patient care atlas, patient care app and author of 3 books about inhalation technology.

Orest Lastow is the founder and CTO of Iconovo AB. He is also the former CEO of Iconovo and is the inventor of Iconovo's four inhalation device platforms.

Iconovo was founded in 2013 by people with long experience in inhalation development. The company develops inhalers and associated drug preparations that are used to treat asthma and COPD. However, Iconovo also has the competence to develop products for new types of inhaled drugs such as vaccines.

Marco Laackmann is Director Inhalation Technology at Harro Höfliger.

He has an Engineering degree in Chemical Engineering applied Biotechnology from University of Applied Science Emden in Germany and a MBA from Bradford School of Management in UK.

He has worked for P&G in Packaging Development of Fast Moving Consumer Goods, followed by a position of Packaging and Device Technology in Boehringer Ingelheim's department of Spiriva® Launch. In 2007 he became manager of Quality, Supply Chain and Medical Device Sales in RPC Formatec. Since April 2011, Marco Laackmann works in Harro Höfliger, where he is Director Inhalation Technology responsible for global business development, sales and product management of machinery for the Dry Powder Inhaler pharma industry.

His background includes 15 years of experience in various areas of Dry Powder Inhaler covering aspects of device development, manufacturing and quality control of medical devices as well as powder dosing technologies and process development.

Mohit Mehta is Director DPI Consulting at Harro Hofliger, Germany. He obtained a PhD in Pharmaceutical technology from Mumbai university (2013). Subsequently, he joined Respiratory center of excellence, Cipla R&D and gained extensive experience on respiratory API micronization, particle engineering and formulation development of dry powder inhalers. He led the team in successful development of Dry powder inhalers for key

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regulated markets. Later he worked with DFE Pharma, Germany, where he was responsible as technical lead and customer support for development of customized Inhalation grade lactose and in exploring new excipients for biologics. Mohit recently joined Harro Hofliger, where he is responsible for managing external consultancy projects related to product development of novel drug delivery systems and dry powder inhalers.

Stefano Console has 27 years of experience in the pharmaceutical and fine chemical business. The broad experience gathered with different CDMOs (Contract Development & Manufacturing Organizations) in Italy and Switzerland covered strategic roles managing a large number of successful projects for big as well as small Pharma partners across EU, USA and Japan. A vibrant passion for business development, organizational innovation and start-up initiatives, together with a relevant expertise in pharmaceutical particle engineering technologies (especially spray drying and micronization) and respiratory products complete the profile. Currently Stefano is Senior Advisor at Oriento SA, the company he founded in 2018, member of the Advisory Board at Eu.reca (European Respiratory Cluster of Antwerp) as well as scientific and business advisor for a number of companies in the life sciences space.

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