GUILLAUME BROUET, APTAR PHARMA

Guillaume Brouet is Vice-President, Analytical, Regulatory and Scientific Affairs for Aptar Pharma. He has 24 years of experience in the development and qualification of drug delivery systems as well as analytical and formulation development. He has spoken previously at multiple respiratory and nasal drug delivery conferences. Mr Brouet graduated from Ecole Supérieure de Chimie Organique et Minérale (ESCOM, Paris, France) and earned an MSc in Physical Chemistry, which he obtained at the University of Houston, TX, US.

In this interview with *ONdrugDelivery Magazine*, Mr Brouet discusses how Aptar Pharma uses its device development expertise and infrastructure to provide its pharmaceutical company customers a comprehensive services offering around device development, global regulatory approval and commercialisation. He discusses the range of services available, especially for respiratory devices.

Q Please tell us about your role and your responsibilities at Aptar Pharma?

A I entered the Analytical, Regulatory and Scientific Affairs role about two years ago to further develop the expertise of Aptar Pharma in these three areas. I am also responsible for developing the services offered by Aptar, around the device technology we offer to our customers, so that in addition to the device they receive a complete solution.

My responsibility is to manage the teams that look after analytical science, regulatory science and, from an operational standpoint, to develop this expertise and make sure it can be leveraged in the best way we can to help our customers get their products onto the market as quickly and as safely as possible.

My team consists of around 90 people, mainly located in Europe but also globally. One team, located in the US, is Aptar Pharma's speciality inhalables testing company, Next Breath (Baltimore, MD, US). Aptar Pharma acquired this company in 2008.

Q Aptar Pharma offers a range of services for drug development. Can you tell us more about these services?

A We have a solid leadership position in the market for devices used for respiratory, including nasal delivery. The range of services accompanies our device offering to share and leverage our expertise and know-how wherever it is useful to our customers to help them accelerate development, and minimise regulatory risks.

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Aptar Pharma's range of services includes extractables and leachables testing, for example. We manufacture these devices, we select the raw materials and define the bill of materials, so we're actually in the best possible position to establish the extractables and leachables profile as a service to our customers.

Our regulatory experience is very important. As a device supplier we are exposed to multiple product applications and thus multiple opportunities to interact with the different regulatory bodies around the world – primarily this is the FDA in the US, but elsewhere too, in Latin America and China for example. This expertise can be leveraged to facilitate the registration process for our pharma partners from the finished drug product, and answer any questions related to the device itself, the way it was developed and so on.

Our service offering also includes manufacturing support. We understand how the manufacturing lines at our customers' facilities will accommodate the device technology we supply, so we can make sure these lines run smoothly when an Aptar Pharma product is introduced. We ensure that these manufacturing lines are appropriately designed for the right manipulation and handling of Aptar technology.

Our range of services (see Box 1) helps our customers from early development all the way to commercialisation and beyond, with routine supply and support after a product has reached the market.

We work with big pharma all the time and a large pharma company will have a sizeable device group, but this device group may not have the range and diversity of exposure to the multiple device programmes that we have. Their experience would, by definition, largely be limited to the sorts of devices that are used by the company they are part of.

Moreover, we now increasingly work with organisations that don't have any device technology expertise, that don't have a device development group. In these cases,

BOX 1: SUMMARY OF APTAR PHARMA SERVICES

R&D TO PHASE I

- Aptar Pharma QuickStart™ kits
- Device design and rapid prototyping
- Filling and assembly support (animal adapters and filling kit)
- *In vitro* feasibility assessments and comparability
- Actuation system, actuation profile
- Container closure integrity
- Nasal cast deposition evaluation
- Biocompatibility testing
- Ready-to-submit IND package

CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

- Test methods to support batch release
- ICH Stability Program
- Impurities and degradation control
- Spray characterisation
- Structural equivalence (gel structure, deposition, spreading, dissolution, and absorption)
- Chemical specific particle sizing
- Finished product specification
- Temperature cycling and ageing studies

EXTRACTABLES AND LEACHABLES (E&L)

- Established extractables and related DMF file
- Ready-to-submit extractables report
- Routine testing and C of A
- Validation of extractable methods
- E&L reports
- Leachables studies performed on stability

CUSTOMISATION

- Fully integrated design house with rapid prototyping
- Quality-by-design customisation with complete design history file
- Customisation of branding and aesthetics
- Human factors (HF)-driven customisations
- Formulation, indication and patient-specific device optimisation

IN VITRO BIOEQUIVALENCE (IVBE)

- Method development and validation (Test and Reference Listed Drug – RLD)
- Feasibility assessment and comparability evaluation
- Dose performance testing
- Filling and assembly support
- Drug product and spray characterisation
- Priming and re-priming
- Labelling, randomisation and blinding for IVBE
- Statistical analysis (population bioequivalence)
- Ready-to-submit IVBE report

CLINICAL STUDIES SUPPORT

- Establishment of CMC acceptance criteria
- Drug product clinical release
- Device trainers for patient onboarding
- Formative HF studies
- Ready-to-submit HF strategy
- Threshold comparative analysis report

DIGITAL HEALTH

- Clinical trial optimisation
- Patient onboarding
- Fully integrated connected platform delivery systems in nasal, respiratory, ophthalmic, dermal and injectables, amongst others

REGULATORY SUBMISSION AND POST-LAUNCH SUPPORT

- Design history file
- Risk evaluation and mitigation strategy
- Release specs for individual device constituent parts
- Reliability
- FDA/PAI audit support
- Investigation management
- Change control management
- Data trending for critical quality attributes (CQAs)
- Device trainer kits for commercial sales support
- Annual product review

anything we can bring with respect to the registration of the device – in support of a US combination product approval for instance – will be extremely useful.

Pharma's expertise is in the molecule itself but Aptar's is in how you develop the device, how you industrialise the device and ensure that it does not begin to cause problems when you begin to manufacture at scale, once the product has reached the market. We're able to foresee and avoid problems that they might not be aware of, because of our extensive experience.

And beyond avoiding problems, it makes development easier, quicker, and safer if we can leverage the expertise we have built over many years within Aptar.

Q Aptar Pharma is a leader in respiratory. Can you tell us more about this particular expertise?

A Aptar Pharma is a leader in supplying metering valves for metered-dose inhalers and has also developed at least two dry-power inhaler devices, one of which was brought to the market in China and India. We have a lot of exposure to respiratory drugs related to device development.

Respiratory products are complex. Obviously, the device is a critical part of the overall finished product and needs to be very precisely designed, manufactured and controlled, otherwise the efficiency and potentially also the safety of the drug product can be compromised. Our expertise is not only in understanding the mechanical engineering part of the device technology but moreover making sure that this device technology meets the requirements of regulators, making sure the specifications meet the safety requirements. This includes things like extractables and leachables in MDIs and evaluating the bioequivalence criteria for nasal sprays.

Our scientists, from analytical scientists to formulation scientists to regulatory experts, have progressed with the company over the years, or acquired significant experience working for leading players in the industry.

We are also investigating opportunities in connected devices, specifically connected inhalers. Two specific partnership were made public, one of which is with Propeller Health (Madison, WI, US). This gives us the opportunity to develop expertise in the interaction of the drug product, and in particular the device part of the product, with the patient directly. We will expand and continue to grow this expertise in multiple fields wherever it brings value to our customers and their patients.

Q How do Aptar Pharma's respiratory services fit within the broader context of Aptar Pharma's services offering?

A Having been associated with the development of multiple respiratory drug products, respiratory is where we have naturally first built our service offering expertise. The complicated nature of respiratory drug development meant that it made sense to offer this expertise as a service. However, Aptar Pharma has a much broader offering, looking at other delivery routes.

Injectables and ophthalmics, for example, are complex combination products that also require solid device expertise when bringing a product to market, so it makes sense to expand our services offering into these areas as well.

We're probably not as advanced as we are in respiratory at this point, but the same principles certainly apply. For example, extractables and leachables testing is equally applicable to an ophthalmic drug product. It is important to avoid harmful extractables being introduced into the eye in the same way as it is important to avoid it in the lungs.

Q In addition to the services you mentioned earlier what other services does Aptar Pharma offer for respiratory drug development?

A We have built significant expertise over the years in the area of pharmaceutical testing and this is something we can really leverage to help our customers develop their programmes. For example, when we develop a dry-powder inhaler (DPI), we never claim that this inhaler will be suitable for every drug product. But we need to be able to make sure there's a good fit between the device technology and the drug it is required to deliver.

> "All of this knowledge is documented so that we can make it available to our customers alongside the development programme. What we can offer as a service package has become more comprehensive and now encompasses many dimensions of device development throughout the entire drug development process."

We have developed analytical methods to measure the pharmaceutical performance of DPIs with multiple drugs. We have developed analytical methods to test our own devices very specifically and we would conduct early feasibility studies to at least cover the initial development steps. We can also offer guidance as to how the drug could be formulated if it is to be used jointly with our device technology. So we have expanded into formulation and pharmaceutical testing as it relates to the development of products using our device technologies.

We can also customise the device itself for drugs that require specific adjustments in our technology. Examples of this include customisation for a specific patient population, or because of specific requirements based on the profile of the drug whether it's because it's a very high dose, a very low dose, highly moisture sensitive or highly potent. This capability to customise can clearly be very useful in developing respiratory drugs, so this is something we can leverage for the benefit of our partners.

Combination product regulatory compliance requires a lot in terms of how you document the device, including all the design controls that are associated with the development programme. We can provide a lot of documentation to our partners and package it so that it's a hassle-free exercise for them to document the device, the way it was developed and the way it functions, in accordance with the requirements from the user and from the profile of their particular drug.

Q Aptar Pharma has been involved in many combination product approvals. Can you tell us more about these and how you can help customers in their regulatory filings?

A We have been involved with numerous combination product approvals both before and since the regulation specific to combination products was introduced. Previously, the device present in a combination product was certainly important but not looked at with the same level of scrutiny by the agencies as it is now. Therefore, like the entire industry, we have had to upgrade our documentation not only internally but also in the files that are supplied to our customers and to the regulatory agencies directly.

We can help our customers with packaging this information. For each project we can make sure there is a documentation package that can be submitted to our customer and to all of the regulators and we can customise the split – what goes to regulators, what goes to customers, what is available for consultation on-site in case, for example, a facility is inspected for design control. We have all this pre-assembled, pre-packaged so that customers can quickly, and with no risk of delay, move safely through their development and on to the registration process.

Q Aptar Pharma obviously has expertise with regulatory filings and the regulatory agencies in the major markets, but what about emerging markets?

A Pharma companies want to introduce many of their products on a global level. This means not only in the US and Europe, but also having the same product introduced, in say, China and Brazil – both of which, like the US and Europe, have become very demanding regulatory bodies.

Aptar Pharma has a regulatory team in China, where we have had products registered for many years. We have had a presence at the forums organised by the CFDA and have had regular direct dealings with the agency. The same applies for Anvisa in Brazil. Next Breath is actually the only non-Brazilian laboratory registered to conduct nasal spray testing in Brazil and has a direct relationship with Anvisa.

We know how to format the documentation and select how much we need to document device technology in the context of a registration in different countries. That puts us in a position to support our customers on a truly global basis.

Q Aptar Pharma can customise the services offered to each development challenge. How does this work in respiratory?

A The primary expertise of the pharma company itself is more in drug development and formulation science, whereas for us it is the device. So we're proposing a new model whereby during development we undertake, as part of our service offering, *anything* related to the device that is useful for our customers. This might be developing analytical methods using the device, or developing customised lab-scale filling equipment, or larger equipment used for the final assembly of the drug product. We also conduct *in vitro* testing and package it all.

We can be present from the beginning of development all the way through commercialisation, and take on a share of the development activities for anything related to the device. This puts us in the best position to document this appropriately to regulators, reducing the risk compared with leaving these activities to another service provider with no background in device technology.

This model can also include utilising our in-depth understanding of human factors, which stems from having been exposed to multiple programmes and having devices that have been used in the context of multiple drug products. We have gathered extensive knowledge of how our patients interact with our device technology.

Take something as simple as actuation force. We need an understanding of how patients use a nasal spray and how much force they would be able to exert on a device to use it successfully. We have this knowledge. Through our medical director and partners, we have been conducting specific user trials.

All of this knowledge is documented so that we can make it available to our customers alongside the development programme. What we can offer as a service package has become more comprehensive and now encompasses many dimensions of device development throughout the entire drug development process.

Q How does Aptar Pharma's services offering help its clients deliver more patient-centric products?

A Aptar Pharma hired a Medical Director a few years ago and since then, we started systematically, for all new product developments, to conduct human factors research. We wanted to understand everything about the way the patient interacts with the device itself and perform design control risk analysis based on patients' needs and patient-related risks, from the very beginning. This means that when we are involved in the development, all this background documentation is in place and is available to our customers.

Of course, human factors testing also needs to be done in the context of the final product's intended patient population and in the context of the profile of the particular drug. It is very difficult to run a specific manufacturer study that is drug and disease agnostic without knowing what the finished product will be. But in the initial steps, the general background around how patients can use the device is built and then what we do jointly with customers is expand from that to complete the final studies directly related to the drug product itself and the intended patient population.

Patient-centricity feeds into connectivity. We've built expertise in the development of electronic devices from a technology standpoint. For example, in the area of connected inhalers, we have started working with Propeller Health. Connectivity gives us even more patient insights so that we can understand even better how patients interact with devices. Undertaking development using connected inhalers also teaches us what connectivity brings to the patient so that we can move forward with developing technology that is useful for patients.

Q Why do you think your customers like working with Aptar Pharma Services?

A Our respiratory expertise, experience and track-record are very important factors. We're continuously building this expertise, building teams over time so our customers can benefit from the experience of people who have had exposure to multiple situations, multiple device programmes, multiple drugs, multiple developments that are very valuable on the route to commercialisation.

Aptar Pharma has a great development team, people who are responsible for developing prototypes, and who are familiar with the constraints of manufacturing devices in the millions, and who know that these constraints must be considered from day one. This is a key part of Aptar Pharma's core device expertise, and we approach our services offering in the same way.

From day one, having this target of bringing the product to the market as quickly and as safely as possible is very important, and I think it's well-recognised by our customers. The fact that we bring the patient on board and are increasingly considering the needs and requirements of the patient is also appreciated.

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The fact that we are truly global – both in terms of our presence and our experience – is crucial. It costs around a billion dollars to develop a new drug product today and a company making that investment wouldn't then want to restrict their market to one or two territories. Being able to get support from Aptar Pharma in several parts of the world is something that our customers value.

Finally, customer orientation has always been very important in Aptar Pharma's culture. It sounds simple and obvious, but this has genuinely always been a very important dimension of how we organise ourselves, how we develop the culture of the organisation. Whatever we have established for our device technology offering flows through to the services offering we bring, the same customer focus and same customer orientation. It is something that we know our customers recognise and appreciate.

ABOUT THE COMPANY

Aptar Pharma provides innovative drug delivery systems, components and active packaging solutions to pharmaceutical, consumer healthcare and biotech customers worldwide, spanning a wide range of routes of administration, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma's portfolio of stage-specific service offerings are designed to address regulatory needs proactively and accelerate approval. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 12 GMP sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

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