

## Drug Developer's View on Combination Therapies

Interview with Dr. Claude Bertrand  
Global Head of Respiratory and Inflammation at AstraZeneca

Interviewer: Vincent Ma, TMTG

VM: Where do you think innovation is most relevant today, in the drug's itself or in the delivery system and why do you think one is more important or more relevant than the other?

CB: I don't think one is more important than the other. Referring back to some of the work we have done at AstraZeneca, prescribers and patients tell you that about 70% of innovation comes from the drug and 30% comes from the delivery system.

You have to bring innovation on both sides of the equation, which means you have to have an innovative drug and an innovative delivery system. That's the ideal situation.

Obviously, there are different situations. When you have a drug at the end of its lifecycle and you believe that significant improvement can be made on the delivery system, then this will bring innovation to the delivery system. But, in most cases we are trying to be innovative with the molecule as well as with the delivery system.

VM: Final drug delivery involves both drug formulation and device development, do you have a primary focus or are you involved with both aspects? Can devices improve the delivery or make a patient more compliant?

CB: Yes they can, but you need to understand AstraZeneca's perspective. We do a lot of interviews, called Insight, across different populations - patients, payers and prescribers. For inhalation and respiratory diseases such as asthma and COPD, we have done insight work

Just to give you an idea, for the inhaler insight work we conducted 150 face-to-face interviews within the three different groups, in China, Japan, the UK, Germany, and the USA. That Insight approach told us that different patients have different needs and sometimes the same patients have different needs at different times. Compliance with the use of inhalers is poor and tailoring to a patient's specific needs will help increase compliance.

For me, having the entire range of patient needs met by one inhaler is too big of a compromise. The lesson for us is, even for the same drug you probably need several inhalers or several delivery devices. This is dependant on which country, what type of patients and what type of disease you are treating with the patients. So there is not one size fits all: it is much more complex than that.

VM: It sounds like the combination is the important part and there is also some development in the device itself even though the development in the drug has ceased. Is there a path, are they developed in conjunction or is the drug developed first?

CB: They are absolutely developed in parallel. That is a key to success. You have to concentrate on the disease and the biological activity you are trying to get to through the mechanism of action being targeted. If your mechanism of action is for COPD (Chronic obstructive pulmonary disease), then it is going to be a different device, versus if it is for asthma or if it is for cystic fibrosis, because the morphology and the anatomy of the lungs look very different. The mechanism of action you want to tackle could be in a different place and the patient you are targeting could be very different. For example, in asthma, if you deal with kids you must have a very different device than if you deal with the elderly, who will have trouble dealing with the technical aspects of the device. If you are dealing with COPD, you have to go deeper in the lungs compared to asthma which is mostly targeted in large airways.

This thinking will apply to other delivery systems and to other parts of the body. But combination development is much more complex than people think.

When developing the device in parallel to the molecule, you need to consider that some molecules will be more amenable to a pMDI type of device because of the physical chemical properties; some will be more amenable to dry powder inhalation (DPI) and some will be more amenable to general inhalers, because of the dose and length of treatment.

**VM:** The factors you mentioned are indication in developing the device and age group, any other factors?

**CB:** The disease and the age group are two important factors, but you could spend an hour defining different needs for different patients. Our vision at AstraZeneca is that we have an integrated approach to the drug and the inhaler development, with both elements working together in synergy.

Another important element is to be patient centric. If you look at COPD, it is a very complex disease; you have different segments of the disease depending on if you are looking at getting bronchodilation versus anti-inflammatory aspects or inhibiting mucus secretion. The needs will be different and the place will be different.

**VM:** In your opinion is the development of a drug delivery solution a strategic need?

**CB:** Yes, absolutely, you need to think about it from day one. You will not be very successful if you only start thinking about device development at the latest stage when you already have a drug. The development of a new device or improvement of a device over what's already available probably takes as long as the development of the drug.

**VM:** Are there regulatory requirements?

**CB:** Absolutely. We use the Insight approach at AstraZeneca, which I personally think is quite unique, and look at the patient's needs, along with those of prescribers, and payers. The same goes with regulatory agencies' needs. We have a painful example at AstraZeneca where we could not get our Turbuhaler™ DPI dry powder inhaler accepted by the FDA (actually in Europe and the rest of the world it is very well accepted) because they believed that the variability of the doses administered was too big. So regulatory agencies are essential to keep in mind and maintain a dialogue with them when you start thinking about development of a new drug device. You have to make sure that it will meet market requirements and regulation agency requirements.

**VM:** What about the strategies for development? Can the discovery of a great delivery device initial the development of a molecule to apply to the device?

**CB:** It is an integrated solution. As a drug developer you have to start simple. First of all you have to think, why am I not going oral? If I'm not going oral, then hopefully there are very good reasons. One reason could just be technical, so if you think about Silence Therapeutics (siRNA) it is a major issue to get them orally bio-available. You have a better chance getting activity if you go locally. Most of the time getting safer delivery to right place increases your therapeutic index. Also some mechanisms will not work unless they were delivered locally. A good example is bronchodilation in respiratory diseases. You have to relax the muscle where it is and not across the body. That's the example that comes to the top of my mind, but I'm sure there are others.

**VM:** Would you rather develop your own device or outsource to partner?

**CB:** Historically, development was mostly done internally. If I look at GSK, Diskus™ was developed internally. If I look at AstraZeneca, the Turbuhalers™ have been developed internally. Over the last few years this has clearly changed. Even with the drugs we are developing now, we collaborate and form strategic alliances on a more regular basis. For devices, this is exactly the same, it is a race and we want to get the best and we will go wherever is needed to get the best device we need. So we do both, and develop as much internally as we do externally.

Our major competitors, BI Pharmaceuticals, GSK and Pfizer will also do things internally as well as externally. Pfizer for example started externally with Meridica a couple of years back and eventually acquired the whole company and the people with it. We all do the same thing, it's a race, it's a very, very complex area and we need to use all the brains available.

**VM:** Within a very competitive environment where generics are gaining in importance, could improved delivery systems be a protection against market share loss?

**CB:** We strongly believe so. We do not have enough examples of generics in respiratory and inhalation, but we know they are coming. We believe that there are several areas where we can still improve our delivery systems and we know how complex it is. I absolutely believe that we can help protect our market share for a longer time even with generics around.

It is not about marketing, it is about what patients, payers and medical professionals want. If you manage to get something that fulfils unmet medical needs, then you will win, but obviously not at any price. I believe that what we are concentrating on at AstraZeneca is to improve efficacy. That involves both what you put in the device and the device itself. That is what we have to concentrate on and it is driven by data.

When you look at data and clinical reports, it's a mix of the efficacy of the drug, how efficient your device delivers the drug to the target and how patients are, or are not, compliant using the device and the drugs in that device. The composite of all the data will tell you if your product is more efficacious than a competitor's product. And that's as true for generics as it is for your branded product.

**VM:** Will new combinations of drugs and delivery systems help get new indications and new patients?

**CB:** Yes. In the US we have seen that with Advair™ and Symbicort™. If you look at both products, they are a combination of very old mechanisms of action, but they clearly had an incredibly large penetration in the market place. There is nothing innovative in the mechanism, but the innovation is in combining both molecules into one device. Now that sounds simple on paper, but the only two companies in the world that have done this so far are AstraZeneca and GSK. It's definitely a very successful product and it's not because of marketing. It does something for patients, which having those two molecules in two separate devices cannot achieve. We now have plenty of Phase 3 clinical trials to show that adding two molecules in the same device is more efficacious than having two drugs in two different devices.

Take elderly patients, for example: They are not going to carry two, three or four inhalers in their pocket. If you can start combining things that we know work and will work better when associated and at the same time increase patient compliance, the overall efficacy in a Phase 3 trial will absolutely be outstanding. We just have some studies coming out where we combine three drugs. The next challenge is: will we be able to put those three mechanisms into one device and have a triple combination?

**VM:** Does AstraZeneca follow a strategy of product renewal, though improved product delivery systems? Please give an example.

**CB:** These are the only examples that I know of, but I'm sure there are others. Our main goal is to come up with new products and the right devices for those new products. When you start to combine older molecules in one device you get a new product. The driver for me is clinical efficacy and that's the only way you get them registered as a branded product. AstraZeneca is not a generic business; we are one of the few who are not in the generic business.



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