Oral delivery of macromolecules: Big Pharma keep searching for the Holy Grail

Representing 9 out of the top 10 income-generating products on the market, biological drugs are now undoubtedly the main growth driver for the pharmaceutical industry. Big Pharma are looking not only to expand their portfolio with new macromolecules, but also to differentiate by offering delivery routes less invasive than injection for their blockbuster products. Oral delivery, long considered to be the Holy Grail, has been investigated for that objective for several years. How do market players position themselves in this race? Alcimed, an innovation and new business consulting firm, explores past and present challenges of these developments.

Paris, August 27th 2018 – Since February, Novo Nordisk has begun to publish positive results from ten PIONEER clinical trials conducted to demonstrate the superiority of the oral dosage of its semaglutide – GLP-1 analogue used to treat diabetes – over its competitors' injectable formats. These results make Novo Nordisk the true pioneer in the oral delivery of macromolecules. Although this quest began several years ago, it has not yet been completed.

Difficult beginnings to remove technical and economic barriers

Research on the oral delivery of macromolecules was mostly focused on insulin. However, large molecules' low stability in the digestive system and their difficult absorption to reach the bloodstream have made these developments unsuccessful.
Indeed, to counter these barriers and be effective, oral macromolecules must be highly dosed, which leads to a twofold issue:

- Medical: there is a high risk of toxicity because the rate of absorption varies greatly depending on the individual's physiology and other ingested elements.
- Economic: the quantity of the active ingredient to be produced is very large, decreasing the profitability of the treatment, especially considering the price pressure governments impose on manufacturers in order to keep their health systems viable.

This last point prompted Novo Nordisk, a pioneering investor in the development of oral formulations, to stop the clinical development of its oral insulin in 2016, despite a significant investment and positive Phase 2 results.

First promises of future market launches

This unsuccessful experiment delayed Big Pharma's investment in the development of an oral formulation for insulin, leaving the field open to other biotechnology companies. For example Biocon – a major Indian biotechnology company – has continued its development of an oral formulation for insulin and could enter the Indian market in the medium term, granting positive results for its next pivotal trial in type 2 diabetes. Similarly, Oramed – an Israeli pharmaceutical company specialized in the development of oral formulations – has obtained FDA approval to initiate a Phase 3 trial for its oral formulated insulin for type 2 diabetes in the US.
Nevertheless, the issue with price/efficiency ratios remains and fierce competitions in the insulin market require very specific positioning strategies. For example, Biocon could plan to register the use of its oral insulin as a supplement to injectable insulin, while Oramed could save its oral low dosage insulin for patients with less severe diabetes not requiring injectable insulin, in order to delay the progression of the disease.
Even if oral formulated insulin seems likely to become a reality within the coming years, it is not a revolution that will sweep away insulin injections yet.

Novo Nordisk, currently leading the first stage

Beyond insulin (the initial lead), another diabetes treatment from Novo Nordisk called semaglutide represents a turning point in the oral delivery of macromolecules. Indeed, very good results of Phase 3 trials for the molecule's oral version have enabled the group to announce a market launch by 2020 for type 2 diabetes.
This drug class is less subject to price pressure than insulin, for which several biosimilars are available, and offers even more commercial interest as its use could be extended to other diseases such as obesity.
However, this product has required more than ten years of development after an approximately $100 million purchase of a license (royalties not included). Moreover, the technology developed is presumably not applicable to other molecules, limiting its interest in the development of an entire portfolio of orally-delivered macromolecules.

The next steps for oral administration

While these initial development successes will lead to the upcoming launch of several products, their technical characteristics remain rather disappointing. As a result, laboratories are still looking for an effective technology to transform their portfolio of injectable macromolecules.
As Big Pharma continue their quest, they invest in breakthrough technologies, which are captured more and more upstream–sometimes even before a proof of concept in humans–in order to ensure exclusivity for their therapeutic areas. Several have thus opted for a bioengineering solution initially developed by MIT: a technological pill to be swallowed, capable of injecting the active ingredient into the blood through the intestinal wall using miniature biodegradable needles. First Novartis in 2015, followed by AstraZeneca in 2016 and Shire in 2017, started developments and tests to orally deliver products from their portfolios of injectables, sometimes securing exclusivity in their preferred therapeutic areas.
Other pharmaceuticals laboratories have instead bet on the biotechnological path. For example, Johnson & Johnson incubates a start-up developing a technology based on bacterial proteins infecting the intestine.

These different approaches could one day broaden today's limited range of macromolecules delivered orally. *"The dynamic research ecosystem in the field of formulation and growing interactions between the public and private sectors should unlock technological barriers and accelerate the emergence of oral forms of new macromolecules on the market,"* concludes Marie Rolin, Project Manager at Alcimed's Healthcare Business Unit in Paris.

ABOUT ALCIMED

Created in 1993, ALCIMED is a consulting company specialising in innovation and the development of new markets, specialising in life sciences (health, biotech, agri-food), chemistry, materials and energy as well as in aeronautics, space, defence and public policies. It works with major industrial groups, ETIs and SMEs, investment funds and institutional players. Thanks to its 180 high-level employees, ALCIMED supports its clients in the exploration and development of their unknown lands: new technologies, market innovations, high-growth countries and prospective analysis. The company, which has its headquarters in Paris, is present in Lyon and Toulouse, as well as in Germany, Belgium, Switzerland, the United States and Singapore.
Alcimed is a member of CroissancePlus and the ACI (Association des Conseils en Innovation).

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