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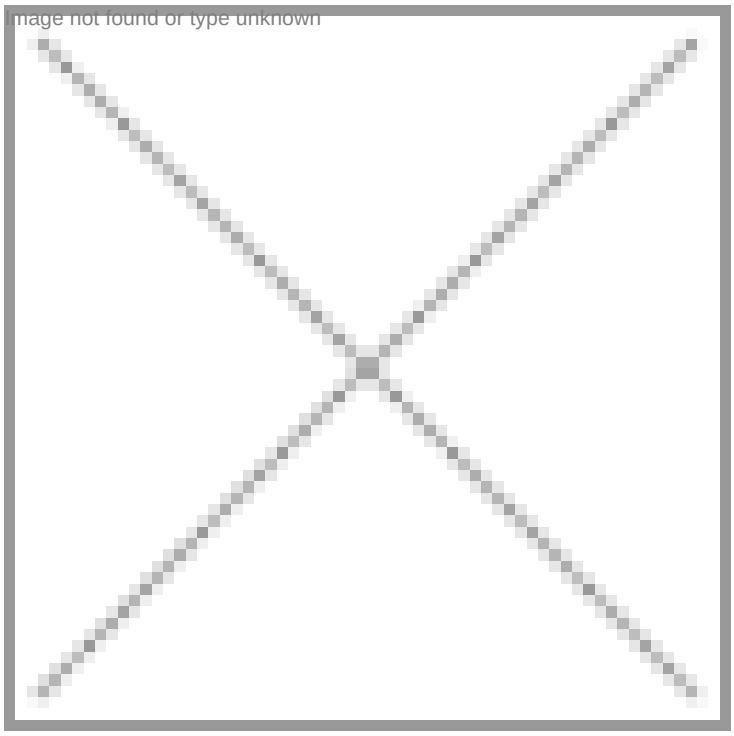

Is it end of inhalable insulin?

In October 2007, Pfizer, one of the largest global pharmaceutical companies, took the market by surprise by announcing its decision to discontinue the production of Exubera [rDNA origin], the inhalable powder formulation of insulin for the treatment of diabetes mellitus or hyperglycemia (high blood sugar). Pfizer explained that: too few patients were taking Exubera and since there are other medicines available that lower blood sugar, Pfizer will stop providing Exubera.

Three months later, Novo Nordisk, a world major in insulin drugs, threw in the towel for its inhaled insulin product candidate, AERx. The company said: it decided the product, meant to deliver inhaled droplets of liquid insulin, did not have adequate commercial potential, given the recent failure to attract patients by Pfizer's inhaled insulin drug, called Exubera. Additionally, Novo Nordisk spokesperson Mr Christian Qvist Frandsen said, "in simply looking at the market and the convenience of our device, we decided it is not really there".

More recently in March 2008, Eli Lilly & Company, the promoters of the first synthetic 'human' insulin using recombinant DNA technology in the early 80s, Humulin, terminated the development of its phase III AIR Insulin Program for the potential treatment for Type 1 and Type 2 diabetes, in partnership with Alkermes Inc. The company noted that: this decision is not a result of any observations during AIR Insulin trials relating to the safety of the product, but rather was a result of increasing uncertainties in the regulatory environment, and a thorough evaluation of the evolving commercial and clinical potential of the product compared to existing medical therapies.

Regulatory environment

Earlier in January 2006, the US Food and Drugs Administration (FDA) approved the first inhaled version of insulin, Exubera, from Pfizer's stable using the technology developed by Nektar Therapeutics of San Carlos, California. This inhalable form of insulin was seen as a major breakthrough after Insulin as an injectable agent was discovered by Banting and Best in 1921, offering an additional tool in the battle to fight diabetes. After 11 years of development, Pfizer, in May 2006 launched Exubera in Germany, Ireland, UK and the US for clinical use in non-smoking adults with Type I or Type II diabetes, without lung (pulmonary) disease. This offered a new hope to millions of diabetics over injectable insulin.

The launch of Exubera represented a paradigm shift from the earlier insulin injectable delivery system, due to a major technical achievement involving stabilization of large Insulin molecule to make it in a dry powder form. The new formulation with a particle size between 1mm and 5mm in diameter differed in route of administration, dosing units, and patient eligibility, which call for periodic testing for safety. Due to main effect on lung function, FDA made it mandatory for all patients to undergo a pulmonary function assessment prior to initiating the therapy with Exubera. Strange enough, most physicians treating diabetes do not have lung function testing machines in their offices and they refer the patient either to a specialist (pulmonologist) or to a center with testing facilities. This not only created a major hurdle for a patient to start on the new drug, but also raised an alarm in the minds of physicians on the drug's safety. It is pertinent to note that the FDA delayed its permission on Exubera for nearly two years, demanding additional safety studies before giving the green signal. The treatment was also limited due to unavailability of eligible patient pool. Nearly one-third of diabetic Type 1 and 2 patients were excluded from Exubera therapy at the screening level, due to smoking history and spirometry. Another 40 percent of diabetics who wanted to use Exubera were excluded from the treatment because of chronic lung disease.

What went wrong?

Physicians are generally known for their apathy to new technology. They are not willing to take on something new unless someone else tries it first. This reflects the lack of enthusiasm in doctors to understand how the device works and then teach the patients its proper usage. Further, majority of the healthcare payors across major markets were not convinced about the product's reimbursement method, and they conducted a cost-benefit assessment. These included Germany's IQWiG, which published a report on Exubera titled "No evidence of an additional benefit". It was followed by National Institute for Clinical Excellence in UK, highlighting that inhaled insulin is not recommended for the routine treatment of Type 1 or Type 2 diabetes mellitus. They said Exubera is for those who have a marked and persistent fear of injections and those who have problems with injection site (consequence of lipohypertrophy) despite support with injection site rotation. Other barriers to Exubera treatment apart from negative impact of reimbursement and low eligible patient pool include significantly large size of the device, bigger than most inhaled products; some patients found it embarrassing to use it in public as it resembled a bong for smoking marijuana. Additionally, Pfizer did not impart proper training of the inhaler device to the nurses and the certified diabetic patient educators who play an anchoring role in the diabetic patient management than physicians in deciding who to be put on insulin. Above all, the marketing of the product lacked the drive and enthusiasm as the company thought Exubera would sell by itself. Disasters followed: initial marketing of Exubera, like television advertisements, were late; samples were limited; and at the time of launch in the June 2006 session of American Diabetic Association meeting, the packaging facility in Terre Haut was not ready, resulting in a failure to ship the product in time.

Cost vs Revenue

In short, Exubera cost Pfizer a hefty $2.8 billion in pre-tax charges, while revenues were under $12 million. The company appeared to have been fighting a lost battle from the beginning. In a complete failure to win over prescribers, Pfizer went one step ahead. It not only stopped marketing Exubera, but also stopped manufacturing it, curtailing the hopes of thousands of patients who saw this product as a lifesaver, as well as those diabetic patients who were postponing insulin therapy to avoid injections. Thus the market for inhaled insulin products evolved and passed in the wink of time. After this decision to phase out Exubera, the company will be redeploying its dedicated Exubera workforce to other more profitable projects, and may have to phase out its Exubera manufacturing sites in the US and Germany, along with their employees. Consort Medical, a UK-based firm, had earlier won a contract to manufacture the Exubera device and the decision to drop the product will impact the company's profits by around $4 million next year. Pfizer also resolved its row with Exubera device and technology partner Nektar with a one time settlement of $135 million payment and returned all rights related to the product so that the device maker can hunt for a new partner. Exubera is the second disappointment suffered by Pfizer after the development of torcetrapib (drug to reduce cholesterol) was halted in December 2006 when phase III studies showed excessive mortality in the treatment group receiving a combination of atorvastatin and the study drug. Both these drugs were intended to contribute to Pfizer's top line and act as a possible shield to help buffer Lipitor losses (sales of over $13.5 billion) when it goes off patent in 2010, maintaining its lead position among the pharmaceutical conglomerates.

Insulin as a class threatened?

Other major companies like Novo Nordisk and Eli Lily have figured out that the FDA might apply the same restrictions as it did with Exubera and did not find it viable to go ahead. Interestingly Lily's press release mentioned two things: "Increasing uncertainties in the regulatory environment," and "Evaluation of the evolving commercial and clinical potential of the product compared to existing medical therapies". The statement highlights that insulin as a class of drugs could be threatened by the new class of drugs known as peptide analogs (incretin-based therapeutics).

After all, the treatment landscape for Type 2 diabetes is set to change with the advent of a new class of drugs grouped under incretin-based (non-insulin based) therapeutics. In Type 2 diabetic patients, the insulin produced in the body is not sufficient to control blood sugar level. These patients are started with oral anti-diabetic drugs to maintain blood sugars along with lifestyle modifications. With the advancement of this disease, the high glucose level in the blood needs to be curbed with conventional insulin management. However, the new class of incretin-based therapeutics are likely to be used as intermediaries in whom oral anti-diabetic and insulin therapy are no longer effective. The novel incretin-based agents aim to close the existing treatment gap by removing the need to initiate insulin therapy early in Type 2 diabetic patients and hence are likely to eat into the insulin market. Further, these incretin-based therapies achieve a lasting reduction in HbA1c, and unlike insulin, do not cause low blood sugar (hypoglycemia), and are not associated with weight gain or weight loss. The emergence of this new group of anti-diabetics is likely to change the diabetes market by being a strong competitor to insulin treatment, which is efficacious even though complicated.

Clinical efficacy: Exubera

The efficacy of Exubera was studied in several clinical trials involving over 4,700 Type 1 and Type 2 diabetics and found to have similar efficacy as subcutaneous regular insulin or rapid acting insulin analogs in diabetics with Type 1 disease. In a study on inhaled insulin, a meta-analyses of six trials (three each of Type 1 and Type 2 diabetes) of inhaled versus rapidly-acting insulin injections concluded that glycemic control was equivalent. On the other hand, patient satisfaction and quality of life was better with inhaled insulin. Several studies have shown an overall improvement in quality of life, such as convenience in taking inhaled insulin many times a day, offering mealtime flexibility and no social stigma attached to its use in the society.

Additionally, patients using inhaled regimen documented more positive perception of glycemic control and higher satisfaction rating, including physical and psychological wellbeing. It is pertinent to note that, if these results are translated into clinical practice then more diabetic patients may be willing to use inhaled insulin, resulting in better adherence with insulin therapy and overall improvement in glycemic control.

Long term trials necessary

Overall safety of this agent has been evaluated in over 2,500 adult Type 1 or Type 2 diabetic patients and around 2,000 patients were exposed to Exubera for more that six months and 800 patients for more than two years.

Pulmonary Safety: All trials put together the incidence of respiratory adverse events less than two percent in any treatment group in controlled phase II and III clinical studies.

Mild cough occurred within seconds to minutes of inhaled insulin and disappears over time and may be related to the delivery method including irritation from carrier of the active ingredient judged by its timing of occurrence. Around 1.2 percent of patients discontinued treatment due to cough studied in controlled clinical studies.

Dyspnea (breathlessness) and other Respiratory Adverse Events were reported as mild or moderate. About 0.4 percent treated with Exubera discontinued treatment due to dyspnea and a small number of patients discontinued due to other Respiratory Adverse Events.

In the lung function test, such as forced expiratory volume at one minute (FEV1), the carbon monoxide-diffusing capacity (DLco) seen in clinical studies declined slowly in the first several weeks of treatment but stabilized in studies of duration up to two years. Further in one study with Type 2 diabetic patients showed resolution in FEV1 six weeks after discontinuation of therapy. Long term studies including post-marketing surveillance trials are required to fully assess the effect of inhaled insulin on lung function.

Malignancy: There have been reported six cases of new primary lung cancer (five cases in clinical trails and one case in post-marketing study) treated with Exubera when compared with one newly diagnosed case among comparator treated patients. There were too few cases to determine whether the emergence of these events is related to Exubera. Interestingly all patients who were diagnosed with lung cancer had a prior history of cigarette smoking.

Due to the effect on lung function seen in short term trials, FDA made it mandatory that all patients should have pulmonary function assessed prior to initiating therapy and periodically with inhaled insulin, which includes spirometry (FEV1) and assessment of Dlco.

MannKind, Abbott, Coremed-left in the fray

The pharmaceutical industry since its evolution focuses to bridge the gap between current therapy and the unmet need by introducing novel drug with innovative technology in the from of devices aimed at different routes of administration. The development of inhalable insulin is intended to bridge the gap by providing convenience along with efficacy for diabetic patients who are postponing insulin therapy to avoid painful injections.

Of all the insulin in the market, there are two key characteristics in insulin efficacy that are still unmet. Novel insulin need have a similar onset of action profile mimicking the internal (body's) insulin pattern both between meals (prandial) and during night (basal) to control blood glucose levels. A Type 2 diabetic patient cannot produce the first-phase insulin release spike in relation to meals, and end up releasing glucose from liver and absorb additional glucose from the food. Therefore an unmet clinical need is to mimic the internal first-phase insulin release spike closely as no insulin preparation on the market that mimic this spike. Likewise an ideal basal insulin preparation needs to have no peak in its metabolic effect and exhibits 24-hour activity to control blood sugar level in the body. Second challenge for an innovative product candidate is to address inter/intra-patient variability (unpredictability in the absorption of insulin formulations).

California-based MannKind Corp, a small biopharmaceutical firm, with its Technosphere in late stage of development, is the only one left in the race to develop inhaled insulin after Novo Nordisk and Eli Lily dropped out. It is interesting to note that MannKind is developing this insulin system without a partner, and with no products on the market using its proprietary technology, its path to clinics may not be easy. Technosphere is likely to address one of the two unmet clinical need for insulin product development. According to the product profile available, it mimics the normal insulin secretion patterns and spike in the body response to meals effectively improving blood sugar level in a diabetic patient. Once this clinical benefit is proven during the phase III clinical trials, coupled with patient inhalation convenience, Technosphere might receive a reimbursement approval from the healthcare payors across the major markets after its expected launch in 2010.

Insulin pipeline: Subcutaneous and Inhalable insulin top the list

Currently, there are 12 candidates that are being developed in the insulin pipeline. These include, subcutaneous (3), topical-patch (2), oral (2), inhale (3), buccal/sublingual (1) and nasal (1) route of administration.

Apart from Technosphere other late stage insulin pipeline candidates include VIAject (subcutaneous injectable formulation) and Oral-lyn (formulation, aerosol, buccal formulation), likely to be launched around 2010 to 2013. Among these two advanced insulin candidates, Oral-lyn, a buccal spray formulation, developed by Generex Biotechnology Corporation, using RapidMist immunomedicine platform, is currently in advance phase of development for the US and European market. However, it is available for sale in Ecuador for the treatment of patients with Type 1 and Type 2 diabetes and has received regulatory approval for sale in India. Generex has partnered with Shreya Life Sciences for marketing and distribution for Oral-

lyn in the Indian market. Shreya is likely to launch the product in India in the second half of 2008.

Weak outlook for inhalable insulin

The outlook for innovative insulin products in the diabetes market, especially inhalable insulin, is not encouraging. Lack of physician enthusiasm about Exubera, reflected in the lower cost-benefit assessments by payors (Germany's IQWiG and the UK's NICE) has put the last nails in the coffin. In order to optimize the commercial potential of a novel mode of insulin application, the pharmaceutical companies need to focus on unmet needs, keeping in mind all key players: the physicians, patients and the payors.

However, MannKind's Technosphere is likely to address the unmet need (mimic normal insulin secretion pattern) coupled with patient convenience; it may receive a partial reimbursement approval from the healthcare payors across the major markets after its expected launch in 2010. This could address some of the concerns regarding commercial viability of this product and convince all stakeholders to take Technosphere to clinics.

*(**Dr Mir Khan** has been tracking biotechnology and pharmaceutical industry since a decade now. He is an author of many industry white papers and reports on a number of companies from the US, European and Indian biopharmaceutical sector. From the last two years he is associated with the healthcare division of Datamonitor.)*