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COMMENTARY

The Failure of Exubera: Are We Beating a Dead Horse?

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Abstract

Inhalation of insulin appears to have become an alternative for the subcutaneous injection of insulin for the time being. However, the recent withdrawal of one product that had already reached the marketplace or others that were close to approval raised severe concerns about the future of the pulmonary route for insulin administration. In view of the progress made with respect to the size of the inhaler and the many other options that would improve the pharmacodynamic properties of inhaled insulin, patient acceptance of this innovative approach, and (hopefully) a reduction in cost, we should begin with an open discussion about the future of inhaled insulin in order to avoid its premature death. This commentary discusses many of the advantages and disadvantages of inhaled insulin from the view of the patients, diabetologists, scientists, pharmaceutical industry, health care payers, and politicians. It is hoped that this unusual approach allows keeping an open mind about this interesting route of drug administration.

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Introduction

To make the point clear right from the beginning, I am a believer in inhaled insulin or, to be more precise, I regard the lung as an effective portal for drug delivery that is worth more attention. For a while it appeared as if we would have a large number of different inhaled insulins coming to the market soon; however, the current outlook is much more negative: Exubera was withdrawn from the market by Pfizer at the end of last year after it was on the market for only a year (which is a very unusual maneuver and reflects the very poor sales numbers); Novo has stopped at least a certain development (but not inhaled insulin in general!) early this year; and, more recently, Eli Lilly announced that they will not continue with their development as well. Especially the decision of Eli Lilly comes as a surprise for many as their last CEO had made some quite strong statements some months ago immediately after Pfizer's decision to withdraw Exubera about their confidence in their own development and inhaled insulin in general. Eli Lilly not only had an attractive inhaler (much smaller and easier to use than Exubera), they also had a sound clinical development program. In essence, that means that a number of billion dollars were spent on unsuccessful development, probably one of the biggest product failures ever in the history of drug development. In hindsight, it was a smart decision by Sanofi-Aventis

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Abbreviations: (ARIA) alternative routes of insulin administration, (EMEA) European Medicines Agency, (FDA) Food and Drug Administration, (IQWiG) Institute for Quality and Efficiency in Health Care, (RCTs) randomized controlled trials, (sc) subcutaneous

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to step out of the cooperation with Pfizer and to cash a huge amount of money for the world's second largest insulin plant in Germany and their share in Exubera development. It is most likely that Sanofi-Aventis had anticipated correctly the problem with the European health care systems (see later). As a result, the only company that is still active and that has a late phase of clinical development is MannKind. A direct consequence of this development is that other companies that are developing inhaled insulin formulations appear to have issues in finding adequate partners/investors in view of the billions of dollars burned by inhaled insulin (i.e., Nektar). The fate of inhaled insulin most likely also hampers the development of all other alternative routes of insulin administration (ARIA).

The aim of this commentary is not to critically review all the different developments of inhaled insulin since the early 1990s (this is simply the period of time when I began working with inhaled insulin), and I am also not going to repeat all the arguments for or against inhaled insulin in the conventional manner. I assume that all of us have seen, for example, the picture of the tennis court as a representative of the size of the surface of the lung too often by now. Interestingly, there is no thorough and critical review available on inhaled insulin covering all aspects and most probably no one will undertake such an effort as long as most scientists regard this as a dead horse! Rather, I will be following a different approach in this commentary, which I hope allows a fresh look at inhaled insulin while highlighting the advantages and disadvantages of the many aspects that are relevant. It is also hoped that this will also enable us to learn from the story of inhaled insulin for other developments, which I believe is important for the scientific community from a more general point of view.

Perspective of the Patients

For insulin-treated patients with diabetes, the needle required for a subcutaneous (sc) injection of insulin is the symbol for their disease. The pain associated with this route of insulin administration was reduced substantially in the last decades by the development of modern needles with their extremely sharp tips, a polished surface, and a coating that allows easy penetration into the skin. Therefore, once patients experience that a sc injection is more or less free of pain in most cases (when you do not hit a nerve ending directly), this is no longer a hurdle for most patients.

When beginning insulin therapy, the psychological barrier most patients experience in reality is not needle phobia, but a fear of all the other aspects of insulin therapy, be it the weight gain or the increased risk of hypoglycemic events. Inhaled insulin could have a big advantage if patients (and/or physicians) accept insulin therapy earlier than with sc insulin preparations so that insulin therapy can be initiated earlier than nowadays. The time elapsed before many patients that clearly require insulin are actually put on insulin therapy is annoying and the difference in this elapsed time are surprisingly different among countries. If earlier usage of inhaled insulin helps prevent hemoglobin A1c levels from rising to 9% or higher when insulin therapy is initiated, this might be quite beneficial in the long run. Unfortunately, this advantage can hardly be proven in randomized controlled trials (RCTs).

A huge wish of patients with diabetes is discretion. If you handle a syringe and a vial in public for a sc insulin injection, many people regard you as a drug addict and not as somebody who has a chronic disease. Patients would be happier if the procedure of self-monitoring blood glucose or insulin administration would not give them a certain stigma right away. However, when it came to the Exubera inhaler, this device (which was very smartly designed and constructed to optimize insulin application into the deep lung from a scientific point of view) was definitively not optimized according to the patient's wish of discretion. Even if the underlying technology works fine and is also reliable in daily practice, the inhaler was simply too big and cumbersome to handle. If you inhaled with this inhaler, for example, in a restaurant, you can be sure to receive a lot of attention. In addition, inhalation of a higher dose of prandial insulin became a time-consuming procedure with this inhaler. Insertion of a series of blisters and activating the air pump in the inhaler, plus inhalation of the standing cloud, can last for many seconds, maybe even minutes. In addition, selection of a specific insulin dose was not possible. Some sort of dose selection was possible using a combination of blisters with two different amounts of insulin, but this was cumbersome. Also, the teaching efforts necessary to use the Exubera inhaler adequately were underestimated by Pfizer. In view of the limited time available for a single patient in a busy practice, such arguments can be of higher relevance than one would believe initially.

In contrast to this rather inconvenient procedure, sc injection of insulin with an insulin pen takes a matter of seconds even with higher insulin doses. It is also possible to select defined insulin doses. Nevertheless, if you accept the quality of life data reported during the

clinical studies performed with Exubera, many of the patients were very much in favor of inhaled insulin. However, from the sales numbers of Exubera it appears that not too many patients were eager to use it in daily life; however, this might also reflect a number of other aspects in addition to the size of the inhaler and the convenience of its usage. Patients would clearly prefer having a small inhaler that allows discrete usage and also be able to apply a higher prandial insulin dose rapidly. Such inhalers would also be easier to carry around and ideally be easier to use. Only when such an inhaler becomes available would the avoidance of sc injection represent a real argument when it comes to convenience.

A very simple usage would also be of help in establishing insulin therapy in many elderly patients with type 2 diabetes. Here it is of reduced importance that the patients receive the optimal insulin dosage, it would be great if they receive any insulin at all for prandial insulin coverage. Such patients might have difficulties in inserting blisters into a small slot and to do all the other necessary manipulations required with the Exubera inhaler. However, imagine a small plastic device the size of a finger that, after a simple procedure, allows inhaling an insulin dose that induces the same metabolic effect as a sc insulin injection of 8 or 12 IU of prandial insulin. Such a convenient application form of insulin is not only simply something that is attractive for patients, in turn it might also increase therapy compliance. If insulin therapy is not regarded as something negative (cumbersome and painful), there is a greater chance that the patients will use their insulin more frequently.

From a patient's point of view, Exubera also had a big plus when it came to storage of the insulin blisters. That the insulin in this formulation is stable at room temperature for quite a while and need not be stored in a refrigerator reduces handling efforts in daily life. However, it appears as if such positive aspects were outnumbered by negative ones. It appears as if the manufacturers of new technical systems for patients with diabetes should have looked very carefully at their system from the consumer perspective in order to reduce the number of negative aspects as much as possible. You might smile about aspects such as convenience; however, nowadays it is very much the patients' wishes that drive the market success of new developments. If the patients are not convinced that a new diagnostics/therapeutic option is of help for them in their daily struggle with the disease, it will be difficult for their treating physician to get them to use this for longer periods of time. In contrast, if the patients see an advantage for themselves in a given development, they might simply ignore the statements of the health care professionals and jump on new developments and make them a market success. For example, it was the ease of practicing insulin therapy with insulin pens that led to the predominant use of such devices for sc insulin therapy instead of syringes nowadays (at least in Europe). When the pens were introduced into the market in the late 1980s, many diabetologists made very nasty comments about such devices and regard them as expensive "toys." However, when the patients realized that the pens helped them reduce the burden of insulin therapy, such comments were forgotten rapidly. It appears as if Exubera was not successful at all, especially in this respect.

In this context, the price of a given product is also clearly relevant, especially when no reimbursement is offered. Such was the case in many countries in Europe. When patients do not see a real benefit for themselves, why should they pay a premium price for this product? They are not willing to do so simply because the product is new. However, many patients would like to test such a system in order to find out for themselves about the advantages and disadvantages of such a novel system. Unfortunately, this additional option is not available any more, at least not currently.

Pharmaceutical companies tend to regard patients with diabetes as one group, especially the marketing department, which loves to put huge patient numbers into their calculations of a potential turnover/revenue with a given product. Such higher numbers are also welcomed by management for their business decisions. Pharmaceutical companies require a good return on investment from a given product and even the anticipation that this might not be the case can lead to the decision to stop development, as was the case with Eli Lilly and their inhaled insulin. However, when the companies would accept that probably only a certain group of patients would benefit from their product, in the case of diabetes this still would mean millions of people worldwide simply due to the enormous size of the market!

In hindsight, one wonders if it would have been smarter for Pfizer to have focused more on certain patient groups ("nice" markets) initially and not have tried to develop a product that can be used by each and every patient. For example, optimal insulin therapy of obese patients by sc insulin therapy is hampered by the fact that insulin absorption is delayed considerably in the subcutaneous

tissue in such patients. This hampers optimal coverage of the prandial insulin requirements even with sc injections of rapid-acting insulin analogues. In contrast, insulin absorption via the lung should not be impaired by body weight. Thus, treatment with inhaled insulin might be an attractive option to optimize (prandial) metabolic control in this group of patients. However, Pfizer never presented a post-hoc analysis of all the available clinical data sets (they must have thousands!) with respect to an improvement in metabolic control, especially in overweight people when using Exubera, in contrast to patients in the control group randomized to sc insulin. Also, to my knowledge, no single specific clinical–experimental study addressing this hypothesis directly was ever performed.

As mentioned before, elderly patients might also represent a huge group of patients that are interested in an easy-to-use inhaler that requires no dialing of the insulin dose on an insulin pen or complex handling of an inhaler. For many of these patients, optimal metabolic control is the therapeutic target but application of at least some insulin with each meal would help keep their postprandial glycemic excursions in an acceptable range. We should also not ignore the fact that in many countries of the world beside the United States and Europe self-administration of a substance/drug is disliked by patients because of cultural/religious reasons. For such patients, and their number is increasing rapidly, the possibility of inhaling a drug is a very attractive option. It might very well be that the big pharmaceutical companies of the western hemisphere, which are very much focused on the classical markets, will be surprised by the rapidity and consequence with which pharmaceutical companies in China or India will come along with developments specifically developed for their own countries, which do represent huge markets.

Perspective of the Diabetologists

Is there a pressing medical need for inhaled insulin? You simply have to say no! Due to the progress that sc insulin therapy has made since the early 1920s, with all the different insulin formulations that are now available, this is a safe and easy-to-use form of insulin application for nearly all patients. Therefore, many critical diabetologists raise the provocative question: Is Exubera an innovation or is it just a needless toy?

Many of our colleagues came to a rather critical and predominantly negative result in their evaluation of this novel application technique, at least with reference to Exubera. However, one has to be careful. Many other diagnostic and therapeutic measures that we regard as standard today, for example, blood glucose meters or insulin pens, were also regarded very negatively by most of the diabetologists when they were first introduced to the market. It might simply take some time to fully evaluate the full spectrum of usage of a new therapeutic option in practical medicine.

We should also not forget that even if we have a very well established route for insulin administration, the level of metabolic control achieved in many (if not in most) patients is not optimal. One can clearly discuss if this can be improved at all if the insulin could be applied by other routes or if, for example, intensification in diabetes education is a better measure to improve metabolic control. However, one has to acknowledge that insulin formulations with improved pharmacological properties or ARIA that allow a better coverage of the prandial (or basal) insulin requirements at least offer the opportunity to ease achievement of this target. Nevertheless, such developments are no magic bullet that allow optimizing metabolic control by just using them and all marketing campaigns that try to convey this message should be forbidden. As long as we have no technical cure of diabetes by means of an automated pancreas, it will remain the responsibility of the patient and his treating physician/health care team to use insulin wisely.

Exubera was developed in the course of one of the most intensive and exhaustive clinical development programs ever performed. The outcome of all these studies, in combination with a number of specific additional long-term studies requested by the agencies (these will be continued by Pfizer!), resulted in the fact that Exubera was the first product that achieved market approval by the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMEA) in Europe. While all these efforts helped fulfill the requirements of the approval procedure, many diabetologists were not happy with these studies. Without going too much into detail, the point was raised if the RCTs performed were adequate tools to evaluate the medical benefit of Exubera when it came to its usage in daily practice. For RCTs, patients are selected according to strict inclusion and exclusion criteria and such studies are usually performed by highly motivated and trained centers. Thereby, the patients recruited for RCTs quite often do not mirror the patients that are treated in daily practice. Attempts were made to set up adequately designed studies addressing these aspects in the format of so-called "real world studies." However, it turned

out to be difficult to design such studies in a manner that brought reality into the format of a clinical study while still fulfilling the expectations raised correctly by evidence-based medicine toward the data quality and robustness of the outcomes of such studies. The split between the different requirements may have been too difficult to achieve and the studies may not have reflected daily practice in reality. Unfortunately, the results of one large respective study performed with Exubera were not published until now, as only the results of a feasibility trial were published.

A bit in contrast to all the efforts put into clinical development, the launch of Exubera was not very impressive (some of the comments about the launch were much more drastic). In other words, presentation of the advantages of Exubera and how it could have been of help in insulin therapy was not convincing. Clearly this is at least in part due to the limited number of clinical trials with Exubera that were clearly focused on medical needs. However, we also probably have to acknowledge that the outcome of the studies was the best that could be achieved with Exubera in view of its pharmacological profile (see later).

One can envision that in the future, during the last clinical development phase (phase III), that the trials will not be performed solely to fulfill the regulatory requirements necessary to achieve market approval (which is key for the pharmaceutical companies) but also take medical aspects much more into account. Thereby, a good option to study more clinically relevant questions right away should be used. It must be mentioned that by doing so the costs of such studies will increase even further, as most probably the duration of the studies will be longer and the number of patients to be included will be higher. However, the outcome of such studies could be used right away in discussions about reimbursement (see later) and could also be very instrumental in this respect for the companies.

Many of the safety concerns that were raised during the clinical development process of Exubera (and that were studied intensively!) turned out not to be as dramatic as they seemed at first glance. Late in the clinical development process, it was detected more or less by chance that the use of Exubera induced the formation of insulin antibodies. The impact of the insulin antibodies on the pharmacodynamic effects of Exubera per se and on other parameters of insulin usage was evaluated intensively. It appears as if the antibodies were not of practical relevance. The formation of insulin antibodies was stimulated readily by using Exubera. However, after a certain level of antibody titers was reached, the stimulatory effect remained constant or the antibody titers even started to decline again. Also, the observed changes in lung function, which was reproducibly measurable, were of a given magnitude and did not worsen further during the usage of Exubera. Stopping the usage of Exubera resulted in a rapid decline in the impairment of lung function. It is worth mentioning that it was necessary to establish a massive improvement in the technical performance of lung function testing during the clinical trials with respect to technical aspects and training of the users before this became clear.

From a medical point of view, it is understandable that the patients who were willing to use Exubera in daily practice were required to check their lung function at regular intervals according to FDA-approved standards. However, in practice this raises a considerable hurdle for the usage of Exubera due to the costs associated (which has to be covered also by the patients) and the time required for performing such a lung function test. Another safety concern was the development of lung diseases and a potentially additive effect of insulin applied via the lung on the rapidity of the progress of diabetes-related late complications. At least in the studies performed that far with Exubera, which means several thousands of patients over a number of years, no occurrence of such cases was observed. Clearly one has to acknowledge that no results of real long-term clinical trials with systematic evaluation of such aspects were available until now (and probably will never become available). Nobody can say with certainty that usage of inhaled insulin will not increase the risk of lung cancer when used for 10 or 20 years. The question is whether we want to carry such risks even when proven-to-be-safe alternatives such as sc insulin are available.

If the performance of end point-orientated long-term studies will become a requirement in the approval process in the future, this will become an obstacle (you can also say a killing argument) for many, if not all, new developments. Such studies are very expensive because of their long duration (several years) and the large number of patients that would have to be included. At the same time, the number of years is reduced during which the company could sell its product before the respective patent expires in case the outcome of such long-term studies would, in fact, be beneficial and reimbursement would be granted. In such a situation the company would have to ask for a very high price to cover the development costs of this product and all other products that have failed during this procedure!

At the end, one has to acknowledge that many diabetologists have the following position: they regard inhaled insulin as an interesting and novel approach; however, they are not convinced that the medical needs of their patients were covered appropriately by Exubera. Many are waiting until the next generations of insulin inhalers come to the market that are smaller and easier to handle and have a more acceptable price.

Perspective of the Scientists

Insulin was a door opener quite often in the history of science. This hormone was

- the first protein of which the primary structure was fully analyzed
- the first protein that was fully synthesized
- the first protein of which the three-dimensional structure was discovered
- the first biotech product that was sold on a large scale

As a result, the hope was that the development of inhaled insulin would pave the way for many other drugs and substances suitable for this route of administration. The rather successful story of inhalation of nicotine showed that it is very well possible to administer pharmacologically active substances by the pulmonary route. Even if we do not wish to repeat this story exactly, there are many medically attractive substances, for example, immunoglobulins and incretin hormones, that one can envisage to apply via the lung. This route of administration is combined with a rapid uptake and a relatively high uptake (but see later), depending on the properties of the individual drug and all aspects of convenience and compliance discussed earlier.

In order to achieve a high acceptance for a new route of drug administration, it is helpful to have a successful front-runner that is used by many patients (and, at the same time, generates a respectful turnover). Therefore, the failure of Exubera will most likely hamper the development of other approaches for ARIA and other drugs for probably a long period of time. All ARIA are faced with the issue of a reduced bioavailability of insulin in comparison to the sc application route. In other words, you simply need more insulin per se to achieve the same metabolic effect. The question remains if a better pharmacokinetics/pharmacodynamics profile and/or a higher compliance with the insulin therapy outweighs a higher price?

The time-action profile of Exubera is not different than that of rapid-acting insulin analogues when it comes to the onset of action; however, other inhaled insulins exhibit improved properties. Also, the within-patient variability of the insulin action of Exubera is comparable to that of sc applied regular human insulin; again it appears to be even lower with other inhaled insulins. The lower fasting blood glucose levels observed in many clinical trials with Exubera (also with other inhaled insulins) in both types of patients with diabetes indicated that insulin treatment by this route has more to offer than it may seem at first glance. Also, body weight and the incidence of hypoglycemic events in the clinical trials with Exubera were at least comparable to those observed with conventional insulin treatment; in many studies, these relevant clinical end points also appeared to be better with this inhaled insulin. One wonders if a product that has an even more rapid onset of action (as demonstrated with Technosphere insulin, which is in clinical development by MannKind) will not only allow a better coverage of the prandial insulin requirements in clinical–experimental meal studies but also in clinical studies and in daily practice.

What irritated many physicians—and most probably patients with diabetes as well—was that the insulin dose was not given in conventional units but in milligrams in the case of Exubera or in other units with other inhaled insulin. Even if you tell the patients that x milligrams are comparable to the metabolic effect induced by x international units of sc injected regular human insulin, this is a source of confusion and error for the nonexpert (= many general practitioners). If the companies were forced by the regulatory agencies to use such numbers for the insulin dose, the practical usage of inhaled insulin is thereby hampered.

We should also not forget that inhaled insulin is still in its infancy. Clinical development is a time-consuming and complex procedure that requires that at a certain point in time no changes with respect to the inhaler and the insulin formulation are implemented anymore (“freeze”). Thus, all progress made by the continuing research of scientists at the same time cannot be implemented into the product. Improvements can only be implemented in the next generation of the inhaler/insulin formulation, when there is a chance to do so. Thus, the current generation of a given inhaled insulin never can represent the level of performance that is possible in principle.

A considerable number of options exist to optimize inhaled insulin not only with respect to bioavailability and biopotency but also to reduce manufacturing costs. One example that highlights the many opportunities in improving the properties of inhaled insulin is a novel manufacturing process developed by Baxter Healthcare and Epic Therapeutics. This allows producing an inhaled insulin formulation that contains practically no excipients but insulin particles of a very uniform size. It would be quite interesting to see if such an insulin formulation differs from others not only with respect to the metabolic effects induced but also with respect to safety aspects and side effects. Also, only some data have been available until now showing the possible benefits when it comes to the pharmacodynamic properties of inhaled insulin when absorption enhancers are added or a rapid-acting insulin molecule is used instead of the human insulin molecule in the insulin formulation (both measures are associated with additional safety concerns.) By such measures, improvements in the metabolic effect might be possible that allow even better coverage of the prandial insulin requirements than is possible with the currently available rapid-acting insulin analogues. We also learned at lot with respect to such topics if adequate head-to-head comparisons with the different inhaled insulin formulations were performed.

In view of the drastic improvements that we have seen from the first generation of blood glucose meters and insulin pens toward the current generation, one would also anticipate massive improvements with insulin inhalers from one generation to the next. In the case of Exubera, the second generation device appears to be a much smaller system; however, currently it is not clear if this will be developed to a product.

Perspective of the Pharmaceutical Industry

Usually the image of the pharmaceutical industry in this world is that of evil. However, without the activities of this industry we would have not seen the rapid developments and improvements in diabetes therapy in the last decades. One has to acknowledge that the situation for the industry has changed drastically in the last years, especially in countries such as Germany. New diagnostic and therapeutic developments face a much more unfriendly environment nowadays. In former times (these are only a couple of years back!) the situation was a relatively simple and straightforward one. Once the developing company was able to get market approval by the respective agency (Exubera was approved by the FDA and the EMEA) for their new product after performing the clinical studies required, the market success of that product was more or less guaranteed, depending more or less on the marketing power of the respective company (Pfizer was quite sure about this…). In such cases the companies could be sure about a good return on investment within a relatively short period of time. However, the system does not work that way any more.

In Germany, an independent institute [Institute for Quality and Efficiency in Health Care (IQWiG)] (www.iqwig.de) performs a critical review of the available evidence for the benefits of such a new product. Only if the outcome of this review is positive will reimbursement by the health care system be granted. One can discuss endlessly the methods and approaches used by such an institute; however, in view of the limited health care budget, one has to acknowledge that there is a need for such an institution. Politicians and health care payers are quite happy to have such an institution, which acts somewhat like a second approval level, at least when it comes to reimbursement. It was not a big surprise for most experts in Germany that the reviews for Exubera were negative; however, this was clearly another massive drawback for this product. The main reasons for the negative review were the mediocre quality of a number of the clinical trials performed during the clinical development process, safety concerns, and missing long-term data in relation to an outcome with respect to metabolic control that was not better than sc insulin therapy but at higher costs.

The poor sales of Exubera was clearly mainly driven by its price. Many people believe that it was simply the higher costs, which did not come with a clear clinical benefit, that killed Exubera. While it is understandable that Pfizer asked for a higher price (which also had to cover the costs for the inhaler) than that of a comparable sc insulin therapy in order to have a rapid return on all the huge investments necessary to develop Exubera to a product in a long and complex clinical development process (and to become the owner of the insulin plant in Frankfurt, Germany), the medical community did not see the need/reasons to pay more to achieve an identical metabolic control. If no such benefits can be demonstrated for other inhaled insulins or insulins applied by other ARIA, this will be a major obstacle for all of them. If health care payers are only willing to reimburse the price of comparable human insulin formulations for prandial or basal insulin therapy, this will clearly reduce the attractiveness of all such developments considerably. Such a negative change in the business model was stated to be the major reason for the withdrawal of Eli Lilly from inhaled insulin.

In addition to the development costs of Exubera, the major cost driver was the relatively low bioavailability/biopotency of inhaled insulin, which is in the range of 10 to 20%. In other words, application of at least a fivefold higher amount of insulin was necessary to achieve the same metabolic effect. When this fact became evident for the first time some 10–15 years ago, it was not regarded as a real roadblock by the pharmaceutical companies. At that time, discussions about costs were not that intensive in health care. The companies hoped that the higher costs of goods would be at least balanced by the greater convenience and other advantages of inhaled insulin. The expectations for Exubera were that it would become a new blockbuster with an annual turnover above $2 billion. In hindsight, it is fascinating to see how wrong the assumptions underlying such business models have been.

One should also acknowledge that many people inside Pfizer were frustrated by the very poor response of Exubera; they believed that they did the best they could. This became quite clear from the statement provided by their CEO when announcing the withdrawal ("Despite our best efforts…"). For decades, many diabetologists and patients have asked for an alternative to sc insulin therapy and complained about the inability of the industry to provide such a product. Now, when the first product fulfilling these expectations, at least in part, was developed successfully, the enthusiasm of physicians and patients was very low when Exubera finally came to the market.

Would the story of Exubera have ended differently if it was not Pfizer but a different pharmaceutical company that brought this product to the market? For most diabetologists and patients with diabetes, Pfizer does not have the reputation of being a "true" diabetes company. Pfizer as a company also has no history and experience with insulin therapy; it appeared as if Exubera was an unusual product for their sales representatives (to phrase it carefully). One clear lesson of the Exubera story is that relying on a huge marketing machine (showing specific advertisement spots for Exubera on TV!) and its position as the world's largest pharmaceutical company (with its deep pockets) is not sufficient to make such a product a success story. Pharmaceutical companies with more history/reputation in insulin therapy and a sales organization that is familiar with all the details of this type of diabetes therapy probably would have done somewhat better; however, the decisions made by Novo Nordisk, Eli Lilly, and some years ago by Sanofi-Aventis indicate that even such companies are not too sure about their market success.

Even if Pfizer was probably not the ideal company to bring the first such product to the market, Exubera would have found at least some acceptance and place in diabetes therapy if it would have been a real strong product with many good properties. However, it was such a disaster from a sales point of view that even Pfizer (with all the bad effects of such a move on its image) could not keep it in its portfolio. Put simply, the costs of keeping all the support lines up and running that are mandatory for such a product (about which most physicians, patients, and insurance companies have no idea about) are so high that even a big pharmaceutical company cannot cover this over a prolonged period of time.

Clearly Pfizer, to be more precise, its marketing department, was not able to convince either patients or diabetologists about the opportunities that Exubera offered during the unimpressive launch of this product (see earlier discussion) and the time thereafter. Just having a big booth at each diabetes congress is not sufficient. Talking with the sales representatives at the booth quickly revealed that they were trained to sell Exubera like any other drug but had no in-depth understanding of the advantages and disadvantages of this product. Also, a number of symposia organized by Pfizer at which experts (like myself) present only a positive view on Exubera (which I always tried to avoid…) does not fit anymore in a world in which physicians are able to critically review clinical study data themselves and are at the same time very cost sensitive. A more balanced and fair presentation, describing the benefits on one side while not ignoring potential risks and limitations on the other, is more adequate nowadays. A lesson for the pharmaceutical industry and their marketing departments in general is that you are in trouble when you cannot adequately convince your target population about the advantages of your product. The conventional approaches employed by the marketing people failed in the case of Exubera. Without an adequate adjustment of the marketing strategy, there is a high risk that this story will be repeated with other novel products.

At least in Germany the timing of the launch was very much against Exubera as fierce discussions about reimbursement for rapid-acting insulin analogues for patients with type 2 diabetes (there is current discussion for patients with type 1 diabetes) finally ended in a somewhat depressed mood for many people in the diabetes scene. During this launch in Germany, the talks at our table were much more about this story then about the future of Exubera. Therefore, there was not much public interest and positive responses when Exubera

became available and the negative review by IQWiG clearly added to this.

It also appears as if the respective people inside Pfizer did not receive good recommendations by "experts" for Exubera or that they did not listen to them. It is always the same group of experts (in some cases, also the author of this commentary) that are invited to scientific advisory meetings by the different companies. Most probably these experts gave more or less the same recommendations each time. Even if they gave honest and good recommendations (which may be critical and negative ones!) and did not try to please the company that invited them, the major question is, do the representatives of the company listen to these carefully and with an open mind or do they only pick those they would like to hear and which fit their internal view and strategy?

We should also not forget that the clinical development process of Exubera was a complex one as it was driven by two companies, Pfizer and Aventis. This required a lengthy coordination procedure; most probably better clinical studies would have been performed if the product would have been developed by just one company. As described earlier, the critical reviews of the results of the clinical studies performed with Exubera were the major reason for not providing reimbursement for this product.

Perspective of the Health Care Payers

In view of the avalanche of patients with diabetes we all are faced with, mostly driven by the changes in our lifestyle, along with demographic changes, the very sensitive reaction of the health care payers when it comes to new diagnostic or therapeutic options for this group of patients is fully understandable. Even relatively small increases in the cost per patient will add up to massive additional costs due to the millions of patients that potentially will make use of such new products. In view of the limited health care budget, the people in these organizations have to simply answer the following question: where shall we invest our limited amount of money while achieving the biggest benefit? Now, as stated previously, evidence-based medicine comes into the game (see earlier discussion).

Perspective of the Politicians

Politicians have the difficult task of keeping their voters happy while stopping the ever-increasing burden of costs spent on the health care system. Nevertheless, politicians should also not forget that talking about the need for optimal medical care for all patients and the huge improvements medical science will bring to the community in front of their voters will work only if the voices of all partners in this complex interaction are heard.

Many people inside the pharmaceutical industry are frustrated by the fact that their excellent work and new products with improved properties do not get a fair chance to show their merits because of a discussion that is very much driven by a sheer costs discussion with a sometimes limited scope. However, one can also regard this as a failure of the pharmaceutical industry to make their position and understanding clear to the politicians and the society more in general. One can regard it as a clear signal from the politicians and health care payers to the pharmaceutical industry that they are not willing (and able) to pay for each and every innovation (which as a matter of fact are not true innovations and progress in most cases) if they do not help address real medical needs.

Many people believe that the politicians use the reviews about new products such as Exubera provided by institutes such as the IQWiG as a fig leaf to avoid additional costs. As already mentioned, it is not easy to decide whether additional costs for improved products that help improve metabolic control are cost beneficial in the long run by reducing treatment cost for diabetes-related late complications or not. Accepting the need for looking at new diagnostics and therapeutics from an efficiency perspective requires that we start to talk about efficacy, direct costs, indirect costs, modeling, and so on. With Exubera, such pharmacoeconomic calculations have been made (each pharmaceutical company has own departments for these nowadays), but it was not a big surprise that the positive outcome of these calculations was challenged for not using the right model and correct assumptions. Because such discussions are not only difficult to understand when it comes to the details, one would wish to have an accepted model that allows a fair description of what can and cannot be achieved by an improvement in therapy (and diagnostics). Also, such discussions should not be limited to specialists but should include all partners hampered by the consequences, that is, also the patients. We must come to an agreement on a broader basis if we are more interested in short-term savings or in savings in the long run while also reducing the suffering and pain from diabetes-related late complications.

In view of the unbelievable amount of money that is spent for diabetes therapy each and every year worldwide—currently it was reported that the costs for diabetes therapy were already drastically higher in the United States than anticipated until recently—one should not only try to cut down the costs for diagnostic and therapeutic measures in a more reflex wise manner, but to analyze adequately which measures are the best to counteract the incredible economical burden. However, one should not be surprised if measures such as lifestyle interventions instead of a novel insulin formulation have a more positive outcome in such calculations.

Comment on the Comments

When you read the comments about the failure of Exubera in various diabetes-related journals and also in other media, this was the typical story: For most of the commentators it was clear right from the beginning that this story would end like this. My comment is, in hindsight, it is always easy to be smart. Interestingly, the number of comments made by all the scientists/clinicians that promoted this development for quite a while was very limited. However, probably this is also a typical part of the story.

Personal Perspective

We at our clinical research institute have a long-standing commitment for this route of insulin administration; we have studied nearly all developments in this area of research with respect to their pharmacokinetic and pharmacodynamic properties in glucose clamp studies. If the development of inhaled insulin does not continue, I would regard this as a missed opportunity. I clearly acknowledge and accept many of the concerns raised (especially the safety concerns), but if we are not willing to carry the risks, we may no longer see any more innovations.

We should also acknowledge the excellent and very skilled work of the many good scientists and clinicians at Pfizer (not to forget all the respective people at Nektar!) and other companies that also have tried to develop an inhaled insulin in the hope of developing a product that really helps patients with diabetes manage their disease better in daily life. Knowing many of these people personally, I believe it is necessary to make such a strong statement in their favor and not jump on the negative image about the pharmaceutical industry that is brought forward by the mass media over and over again. Clearly the health of people is a very sensitive topic, and a critical and careful view is absolutely necessary, but looking only at failures and mistakes is not an appropriate measure to improve the whole story.

I fear that a lot of precious knowledge built up in the last years inside the pharmaceutical industry about inhaled insulin will get lost rapidly and will not become available for other drugs that could be good candidates for pulmonary application. Inside the companies the teams are destroyed within a blink of the eye in order to save costs. This is understandable from a short-term economical point of view; however, it blocks, for example, publishing of data from all the clinical studies collected. Such a loss of scientific knowledge is not only a pity from a scientific point of view, it is also quite difficult from an ethical point of view. Many patients who participated in the clinical trials not only received some payment or free access to medication, they hoped to support medical progress. Also therefore publication of the study results should not be regarded as being of limited value by the respective companies. Nevertheless, as we ourselves encountered very recently, the scientific journals have reacted rapidly as well. They reject manuscripts reporting scientifically sound and relevant study results right away because they do not regard inhaled insulin as a "hot topic" anymore. They want to save the precious space in the journals for other papers.

Summary and Outlook

From my point of view, Exubera has not failed for one reason only but (as is the reality in most cases) an unlucky combination of a number of reasons. One should also not forget that other therapeutic options have become available in the last decade that now have a huge market share, such as long-acting insulin analogues and glucagon-like peptide-1 analogues/dipeptidyl peptidase-4 inhibitors. However, we are now encountering the risk of the premature death of inhaled insulin in general with many negative side effects. It cannot only induce a roadblock for all ARIA developments (often under development by relatively small and innovative companies), this can be an issue for the development and market success of many other innovative diagnostic and therapeutic options for diabetes treatment. The pharmaceutical industry will have a clear tendency to avoid all risky development in view of the amount of money necessary for product development. Also, developments for products for smaller patient groups will be blocked as they do not offer a sufficient business once approval is achieved. However, it is difficult to judge right away what meaningful and nonrisky developments are. Small companies will have a hard time convincing the big companies that their development is exactly

what they are looking for. However, the big companies are desperately searching for new blockbusters that guarantee their market share and income.

Is inhaled insulin a dead horse? To be honest I still believe/hope that this is not the end of the story, that inhaled insulin will survive in the long run (like a tumbler)! We should also not forget that at least one company (MannKind) is still very active and declares to file for market approval within the next years. The prandial inhaled insulin they have in development (Technosphere) differentiates itself from Exubera with a time-action profile showing an even more rapid onset of action. The hope of MannKind is that this mimics the first phase insulin response of healthy subjects better than any other inhaled insulin does. This should induce a stronger suppression of hepatic glucose production and better control of postprandial glycemic excursions. The shorter duration of action of Technosphere insulin should also reduce the need for a snack between meals. Because of its relatively long duration of action, Exubera was not better than sc regular human insulin in this respect. It remains to be demonstrated in the phase III trials currently underway with Technosphere insulin if these improved pharmacodynamic properties really result in an improved metabolic control and also allow reducing the incidence of hypoglycemic events. If this inhaled insulin formulation with its unique pharmacodynamic properties will be successful when it becomes an improved outcome over sc insulin therapy, this would really differentiate it from Exubera. MannKind, which is driven very much by a single person (Al Mann) and his own fortune, wants to submit their new drug application at the end of 2008 and hopes to launch the product in 2009/2010. We also have to wait and see if this company, without a strong sales and marketing force, can bring their product to the market. It is not clear at the moment whether any of the other big companies will come along as a partner for this development. The withdrawal of Pfizer and Lilly (and of Novo in part) put a high hurdle in front of MannKind. Currently, it is also not clear if Nektar (the inventor of Exubera) can and will continue the story of Exubera. They received certain payments by Pfizer and are actively searching for a partner. However, the negative perception of inhaled insulin induced by such developments will be difficult to overcome; many physicians and patients will not listen carefully to the same story (from their standpoint) once again. Nevertheless, I believe that this is possible with an adequate approach. I see the clear need to demonstrate a proven advantage for certain patient groups to achieve a good uptake.

One of the clear disadvantages of Exubera was the need for patients to still apply basal insulin via the sc route. Exubera alone does not allow patients to get rid of the needle. Therefore, patients would love to be able to apply basal insulin via the pulmonary route as well. In view of this and the massive increase in the number of patients treated with a long-acting insulin analogue (which is quite a big market nowadays), Novo Nordisk is trying to develop a long-acting inhaled insulin. This quite interesting approach is clearly combined with a number of open questions: Will patients really be willing to move on to inhaled insulin much earlier than with just one sc shot of basal insulin per day? Is the current treatment paradigm of initiating insulin therapy with basal insulin in combination with oral agents the optimal solution for most patients? Just supplying basal insulin is totally unphysiological (patients need most of their insulin postprandially). Many patients with type 2 diabetes might be better off with just using preprandial insulin. Introducing such an insulin therapy at an early stage in the disease is feasible due to coverage of the basal insulin requirements by the remaining endogenous insulin secretion capacity. Unfortunately, there are no good investigations on this strategy with inhaled insulin (also not with sc rapid-acting insulin formulations). Such patients must just apply some insulin (6–12 units) by inhalation of a rapid-acting insulin before each meal without even measuring blood glucose or trying to assess the amount of carbohydrates of their meal. Any over- or underdosing will be compensated for by their own insulin and these patients have a very low risk of hypoglycemic events. Clearly in the long run, such patients will also need basal insulin, so the development of an inhaled basal insulin appears be a good idea; however, without a rapid-acting insulin for inhalation, one leg of the optimal insulin therapy is missing.

It is most likely high time to open a scientific discussion that brings all arguments to the table. Such a discussion must include all players: patients with diabetes, diabetologists but also people from industry, regulatory agencies, and payers/politicians. By this we can hopefully also establish a situation that allows bringing innovative ideas and developments with a proven benefit to diabetes therapy in the future, as otherwise I fear that we run the risk that many promising developments may encounter a premature end. It would also allow us to understand where the roadblocks are, as it might very well be that they are more philosophical in nature than in differences about science and medicine.

The technically possible advantages in diabetes therapy have to come in accordance with what society is willing to pay for innovative products. An agreement on which activities academia/scientists, together with industry, should be striving for in order to support patients with diabetes in their daily struggle with this chronic disease, such as the achievement of a technical cure for diabetes (= automated pancreas), would not only be very helpful, it is mandatory.

Note Added

The recent announcement by Pfizer[1] that an increased number (not statistically significant different!) of newly diagnosed lung cancer cases was observed in ongoing clinical studies with Exubera [6 patients, all of whom were former smokers, vs 1 newly diagnosed case among comparator-treated patients] has created some shock waves. Because the low incidence of new primary lung cancer per 100 patient-years of study drug exposure was 0.13 (5 cases over 3900 patient-years) for Exubera-treated patients and 0.02 (1 case over 4100 patient-years) for comparator-treated patients, one has to be skeptical at this point in time whether these data truly indicate a cause and effect between Exubera (= inhaled insulin) and lung cancer. However, the reactions to this risk signal were quite prompt: Nektar[2] and MannKind[3] announced that they have stopped all negotiations with potential partners. In addition, Nektar announced that they will cease all spending associated with its inhaled insulin programs.[2] However, MannKind expressed confidence that the safety profile of their inhaled insulin is fine according to the outcome of their extensive preclinical and clinical programs. They had not observed a higher incidence of lung cancer than that expected in the general population.[3] However, clearly ensuring patient safety is always the primary concern of each physician, and these cases of cancer (even if they are probably not related to the usage of Exubera) might be the last nails in the coffin of Exubera or even inhaled insulin in general.

Acknowledgments:

In the last 15 years I have had numerous discussions with many people interested in inhaled insulin. This manuscript contains many of their ideas and opinions. My special thanks go to Tim Heise for some of his comments included in this manuscript as well.

Disclosure:

The author is CEO of a clinical research institute that has performed numerous clinical–experimental and clinical studies with companies that have developed inhaled insulin.

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