DRUG DELIVERY Executive

DBV TECHNOLOGIES: PIONEERING THE SAFE DESENSITIZATION OF PATIENTS SUFFERING FROM DANGEROUS FOOD ALLERGIES

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The goal of DBV Technologies is to make food allergy therapy a simple pharmaceutical treatment. DBV Technologies is focused on using a patient's own skin to solicit a desired immune system reaction, thus avoiding the risk of life-threatening anaphylactic reactions. Its VIASKIN® platform exposes a controlled quantity of a given allergen to the skin of the patient. The skin then naturally prevents the allergen from entering the bloodstream, making this a safe therapy. DBV's strategy is to focus on peanut and milk allergies. These products have already been tested on patients and make possible a $2-billion revenue opportunity for DBV Technologies. The company's initial commercialization effort is VIASKIN Peanut, whose development is supported by the NIH-funded Consortium of Food Allergy Research (CoFAR) and some of the most recognized opinion leaders for peanut allergy in the US. Drug Development & Delivery recently interviewed Pierre-Henri Benhamou, MD, Co-Founder & CEO of DBV Technologies, to discuss the VIASKIN platform and how it will whet the appetite of Big Pharma to lead an entirely new pharma franchise as big as statins or vaccines.

"We believe our VIASKIN® platform will stimulate the interest of the Pharma industry to build an entirely new franchise - a new paradigm in the treatment of allergy, even the most severe food allergies, bringing to patients a non-invasive and safe approach in specific immunotherapy. Pharma companies can now enter this multi-billion-dollar market, where there is no significant competition."

Q: What is VIASKIN and how is it a platform for allergy-immunotherapy?

A: The safe immunotherapy of patients suffering from dangerous food allergies has not been possible in clinical practice until now, due to the high risk of anaphylactic reactions. DBV Technologies has developed the VIASKIN epicutaneous delivery system, a technology platform designed to safely desensitize children and adults who have allergies. DBV is especially/currently involved in food allergies. The breakthrough and patented design of VIASKIN presents an allergen onto intact skin via a skin patch while significantly reducing the risk of the allergen's free passage into the bloodstream. VIASKIN thus safely triggers the desired immune reaction via specific immune cells so the body can gradually become desensitized to the allergen - while avoiding the risk of a life-threatening anaphylactic reaction.

Q: Why is DBV Technologies focused on food allergies?

A: Allergy is a growing disease, and food allergies represent the segment where life can be directly threatened - but no treatment is available. Until now, avoidance of the culprit food has been the primary acceptable solution. Treatment of food allergies is a significant worldwide unmet medical need. Indeed, there are 12 million food-allergic people in the US alone, and incidence of peanut allergy has doubled throughout the past 5 years in children. Because there are no treatments for food allergies, many children and their families live with the constant fear of ingesting a life-threatening food.

Q: How is DBV's approach unique?

A: Allergen-specific immunotherapy is the major strategy that treats the underlying cause of an allergic disorder. However, the conventional approaches of specific immunotherapy, using subcutaneous administrations, are associated with high risk of systemic life-threatening allergic reactions, such as anaphylaxis, and their use in food allergy is therefore limited. DBV Technologies is the only company in the world whose products are designed to epicutaneously deliver an allergen via a skin patch without any specific preparation of the skin. This process allows the allergen to reach directly the specific immune system through the wide immune network of the skin. DBV's proprietary skin patch technology, VIASKIN, involves maintaining an allergen on the intact skin of an allergic subject for repeated and prolonged periods in order to achieve clinical desensitization.

Q: How does your VIASKIN platform differ from conventional approaches to desensitization?

A: The goal of desensitization is to increase the amount of allergen the patient can eat or breathe without any symptom. Ultimately, the patient could become tolerant to the allergen and live normally. Conventional immunotherapy in the form of drops, pills, or injections (used for airborne allergens, such as pollens, and venom, such as bee stings) consists of exposing a patient to a controlled amount of allergen; but these conventional treatments are too dangerous for desensitizing food-allergic patients because their mechanism of delivery requires entering the bloodstream. A novel technology combining safety and efficacy is desperately needed by food allergists and patients. When the VIASKIN patch containing a specifically designed protein extract is applied on the skin of a patient with an IgE-mediated allergy, such as peanuts or milk, the allergens are deposited locally on the intact skin, ie, no specific preparation of the skin is needed before the application of the VIASKIN. Proteins do not pass the intact skin and do not reach the bloodstream, but are captured locally by the skin's immuno-competent cells, the Langerhans cells. These specialized cells, particularly efficacious in inducing or regulating immunity, uptake protein allergen and migrate to lymph nodes where they trigger the modulations of the immune responses. This epicutaneous exposure is non-invasive and thereby significantly reduces the risk of anaphylaxis. Epicutaneous delivery is also visually monitored: if necessary, its application can be simply halted with the instant removal of the VIASKIN patch containing the offending allergen. The VIASKIN patch is designed to be easily and painlessly applied by healthcare professionals and by patients or their parents/caregivers at home, which facilitates compliance with the treatment.

Q: Is there clinical data that suggests VIASKIN is safe and effective?

A: Results of a pilot study of VIASKIN that were published in a recent issue of the *Journal of Allergy and Clinical Immunology* opened a new path: patients severely allergic to cow's milk were able to ingest 10 to 600 times more milk after 3 months of VIASKIN treatment, whereas in the placebo-treated patients group, almost nothing changed. DBV Technologies is the only company whose products are designed to deliver an allergen via an epicutaneous patch to safely diagnose

and treat food allergies. DBV is developing two therapeutic products. Our first product in development, VIASKIN Peanut, is the first desensitization product for peanut allergy, a life-threatening and lifelong food allergy that is a major unmet medical need and thus an important healthcare concern. An IND has been granted to DBV by the FDA, and a safety 1b clinical study is underway at five select centers in the US. Additionally, the AFSAPPS in France has approved a pilot efficacy study sponsored by the AP/HP. Finally, the NIH allocated to the CoFAR a grant that will include a clinical study conducted with VIASKIN Peanut in the US.

Our second product in development, VIASKIN Milk, is specifically designed to treat patients with cow's milk protein allergy (CMPA), the most common food allergy in infants and young children. A pilot clinical study has been successfully completed in France.

Q: What is the mechanism of action for VIASKIN?

A: By contrast to conventional desensitization methods, such as drops, pills, or injections, which are too dangerous because of the risk of systemic allergen exposure, VIASKIN is non-invasive. VIASKIN creates an occlusive chamber on the skin that rapidly generates moisture and releases the allergens from the support onto the skin, allowing adequate diffusion of the proteins toward the more superficial layers of the skin without any passive passage through the skin, thus avoiding a systemic delivery. The allergen is captured by the skin resident specialized immune cells, the Langerhans cells. In preclinical studies, it has been shown that the capture of proteins activates these Langerhans cells and prods them to migrate to the afferent lymph nodes where they can activate specific immune responses able to modulate the inappropriate response against allergen and so start the tolerance process.

Q: What can your VIASKIN delivery platform offer the pharmaceutical industry?

A: We have developed a true pharmaceutical approach to allergy. DBV's VIASKIN technology is a disruptive platform in the treatment of allergy: it uses the skin route in a very unique way. This opens new possibilities for allergy treatment - in the short-term, the "safe" treatment for food allergy and a +$2-billion opportunity and in the medium-term, making mass desensitization as prevalent as vaccination is to infections in order to eradicate most atopic diseases like asthma and eczema. Every detail in DBV's work is focused on developing a business that is "pharma" compatible, ie, a business that can either be marketed and operated in partnership or acquired by large pharma companies.

Q: Why should the pharmaceutical industry be interested in DBV's manufacturing technologies at this time?

A: VIASKIN is a unique technology platform ready for mass production and well-protected by numerous patents. Although elegant in its concept, VIASKIN requires a very unique process technology to control the small amounts of allergen administered. DBV Technologies has developed and patented two proprietary manufacturing processes able to fix active dry compounds onto a polymeric backing film by electrostatic forces alone - (1) Static Powder and (2) Electrospray Deposit. DBV's technology incorporates many technology components, including its Electrospray Deposit Technology, a very precise means of layering a controlled solution of the allergen on the patch so that it is ultimately dry and stable. The US-FDA has reviewed our Electrospray Deposit Technology and has been satisfied with it to grant DBV an IND for clinical use in the US. The clinical equipment is pharmaceutically qualified and can be operated easily in a GMP environment. Our patented technology is adapted for large-scale production.

Q: How does DBV's Static Powder manufacturing process work?

A: DBV's novel Static Powder manufacturing process allows for the precise deposition of powdered compounds onto the polymeric backing of delivery systems, such as VIASKIN. The Static Powder manufacturing process creates a suspension of particles that are attracted and adhere to the polymeric backing film, resulting in a thin and uniform layer of powder. Bound to the backing of the patch

by electrostatic forces, these particles remain active as long as the delivery system is kept under dry conditions, but are easily released when the device is applied on the skin. Static Powder fits particularly for compounds that can be deposited onto polymeric backing films without any formulation. The only preparation is a fine grinding of the compound in order to get small particles. There are four critically important benefits of DBV's Static Powder manufacturing process: (1) there is no intermediate liquid formulation, as our Static Powder process fits with many active powdered compounds; (2) the active agent is deposited homogenously; (3) the whole localized dose is available to the skin; and (4) our process permits the deposit of chemical and biological substances alike.

Q: How does DBV's Electrospray Deposit manufacturing process work?

A: DBV's novel Electrospray Deposit is a manufacturing process that produces dry deposits of substances from liquid formulations. DBV Technologies has developed a pharmaceutical multi-nozzle production tool to deposit a mass ranging from a few to several hundred micrograms per cm2 to be deposited onto a wide variety of raw materials, such as backings, films, and glue. In adapted formulation, both chemical and biological substances are able to be deposited. Our proprietary manufacturing process is ideal for cutaneous devices requiring an immediate release of an active ingredient. Deposits can be either a spot or a homogenous layer. There are five critically important benefits of our Electrospray Deposit process: (1) the active agent is deposited homogenously; (2) accuracy of the deposit's mass is high - from 0 to 400 ng/cm2; (3) the process permits flexibility of the size and the mass of the deposit; (4) there is instant drying of the deposit; and (5) the deposit is highly soluble.

Q: Can you tell us more about you and how you started DBV Technologies?

A: After studying medicine in Paris, I graduated with a medical degree in Pediatrics and went on to specialize in pediatric gastroenterology. I have held a number of senior clinical positions, including Senior Consultant at St. Vincent de Paul Hospital in Paris. In 1989, I founded the first Pediatric Center for Digestive Disease in the Paris area. I also founded a clinic for digestive diseases in Pediatrics with Dr. PY Vannerom. I was extremely fortunate to receive the Altran Foundation Prize for Innovation in 2003 for my work on the development of patch tests for the diagnosis of cow's milk allergy.

Food allergies can cause death. It has been frustrating to me as a medical doctor and pediatrician that the safe desensitization of food-allergic children and adults has not been possible in clinical practice, until now. The reason for that is simple: conventional treatment methods, such as injections, drops, and pills, get into the bloodstream and may cause a systemic, life-threatening anaphylactic reaction in food-allergic people. As a pediatrician involved in gastroenterology and food allergy, I was very concerned by the absence of treatment for the children suffering from severe food allergy. I was especially obsessed by the consequences on their health and social life as well as the parents' difficulties for managing the daily risk of systemic reaction and their incredible demand for a safe treatment.

Along with my Co-Founders (Professor Christophe Dupont, MD, PhD, Head of Pediatric Gastroenterology Dept., Hôpital Necker, Paris, who also serves as Chairman of the DBV scientific board; and Bertrand Dupont, DBV's Chief Technology Officer) we have invented a very special skin patch technology that enables the body to safely develop immunity against a particular allergen, such as peanut or milk, while preventing the allergen from getting into the patient's bloodstream. We hope that when our products receive regulatory approvals that the positive impact on the lives of millions of food-allergic children and adults will be greatly enhanced and safeguarded. And if we can gain the support of the Pharmaceutical industry, the clinical benefits will be enormous. ◆