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The news magazine of the Technoflex group

The surge in pediatric research

Artificial intelligence and health care: a promising alliance

Abracadabox!

CPhI Pharma Awards WINNER

Technoflex wins big at the 2018 CPhI Awards

Editorial

Olivier Chesnoy
President & CEO

In this 13th issue, Flexmag sheds light on recent progress in pediatric drugs. Long constrained by a complicated history and difficulties setting up clinical trials with children, the availability of pediatric drugs has now improved thanks to the European Pediatric Regulation.

As for excellence in Quality, the new version of the ISO 9001 standard (which we recently renewed) involves all of our employees. The entire company is now working to meet our customers' requirements and ensure the highest possible quality.

As for the future, Artificial Intelligence (AI) is becoming more present in our daily lives and is now being used successfully in healthcare thanks to major advances in the past decade. The rise of AI is such that the FDA has just approved screening software. Our Perspectives section describes the latest innovations in screening and diagnostics.

Lastly, our Profiles section goes back to our main theme by presenting the "Coucou Nous Voilou" nonprofit organization, whose goal is to improve the daily lives of hospitalized children. Since Technoflex believes strongly in this approach, we naturally chose to support the organization by providing soft bags and the required connectors so demonstrations could be done in real conditions of use. What a wonderful organization to support!

Please note: Just before going to press, we received the CPhI International "Excellence in Pharma" award in the "Innovative Packaging" category. We are thrilled to share this success with you. Congratulations to all the Technoflex teams who contributed to this major development project!

Flexmag, a world of connections

Flexmag

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Quick facts

Strong growth in Indian generics

Streamlining of laboratory portfolios and an increase in the number of drugs approved by the FDA (Food and Drug Administration) have allowed Indian generics companies to boost their US market share by 5% in the last few months. Stricter regulations and pressure on proprietary drug prices have given Indian generics manufacturers 40% of the overall American health market, worth close to $60 billion. In the first nine months of 2018, almost 100 generic drugs were authorized by the FDA, the American regulatory authority.

Civica RX, the first nonprofit pharmaceutical company!

Civica RX, located near Salt Lake City, is a partnership between seven hospitals and three foundations. Its objective is clear: to provide generic drugs that cost 90% less than market rates. It will begin by producing essential drugs that are often hard to get because of constant shortages.

The Nobel Prize for medicine awarded to immunotherapy researchers

On October 1, James Allison (USA) and Tasuku Honjo (Japan) received the prestigious Nobel Prize for Medicine for their research into immunotherapy for treating cancer. Though the immune system that defends our organism recognizes cancerous cells, white blood cells (cytotoxic T cells) are not able to destroy them effectively. James Allison's research focused on the development of a monoclonal antibody that initial tests have shown to be effective against cancer cells. Takusu Honjo focused on a protein that ensures that T cells can effectively destroy the affected cells. These two new therapies target the immune system to provide it with new tools to combat cancer cells.

James P. ALLISON & Tasuku HONJO, 2018 Nobel Laureates in Medicine.

Agenda

1st & 2nd quarter 2019

Pharmapack Europe	February 6-7	Paris, France	Pharmapack	**Booth #A-82**
CPhI North America	April 30 May 2	Chicago, USA	CPhI north america	**Booth #1624**
ISCT International Meeting	May 29 June 1	Melbourne, Australia	2019 ISCT melbourne	**Booth #58**

Events listing available at www.technoflex.net

The surge in pediatric research

"We need to stop groping in the dark when it comes to pediatric drugs. Children are suffering and dying from diseases that we can treat, and yet we don't have the key data we need to deliver the appropriate, effective, and affordable medicines that could save them." Back in 2009, Doctor Carissa Etienne[1] was already condemning the lack of therapeutic treatments specifically developed for the pediatric population.

Sylvie Ponlot

Although one fourth of the world's population is made up of children under the age of 15, drugs for children are not developed as quickly as they are for adults. The first reason behind this discrepancy is ethical. The history of abusive medical experiments conducted on humans in the mid-20th century is partly responsible for this reticence. There was longstanding concern about weakening protections for the most vulnerable. As a result, children were excluded from clinical research, which focused only on adults until the 1980s. At this point, opinion gradually shifted. It became clear that for children to attain the same health outcomes as the rest of the population, they needed specific treatments that were adapted to them, and therefore studied explicitly for them. The results of studies conducted on adults cannot be transposed to children. Yet one main obstacle remains: obtaining the informed consent needed to participate in a clinical trial. While this consent can be hard to obtain from adults, it's even more difficult for minor children, because it must be given by both parents. Another reason is economics. While adults are a homogeneous group, the pediatric

population is split into several age range. Each group has a specific metabolism that reacts differently to treatment. A newborn eliminates the active principle slowly and requires low doses. The opposite is true for an infant. As a result, specific formulations must be developed and different trials are needed for the different age groups, making studies much more complex and expensive. Another key difference is that most illnesses that affect children are unique to them, or are orphan diseases[2]. This is the case in oncology, where 80% of pediatric cancers are specific to children. Clinical pediatric research therefore requires more significant resources, and a return on investment is more difficult to obtain. Yet specific clinical trials must be conducted on this population.

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Risky alternative approaches

Since many drugs do not have a pediatric Marketing Authorization, prescriptions of products that have not been tested on this population continue to this day. They are prepared using formats designed for adults: drugs are removed from their packaging to make smaller doses, tablets and capsules are split, dosages and dilutions are adjusted, etc. Products without pediatric Marketing Authorization are used off-label, without pediatric doses, and without formulations adapted to children. This exposes them to errors in use, errors in dosage, risks of toxicity, and treatment failure. Children are not miniature adults: their organs are in different stages of growth, with different metabolisms, and their immune systems are constantly changing.

The European Pediatric Regulation is stimulating pediatric clinical research

The European Pediatric Regulation was implemented in 2007. It requires pharmaceutical laboratories to submit a Pediatric Investigation Plan (PIP) for products under development as well as those that already have Marketing Authorization or are off-patent. Under the terms of the PIP, laboratories publish the necessary measures to prove the drug's quality, safety and efficacy on the pediatric population. In return, laboratories are given patent extensions or exclusivity. There has been an increase in pediatric clinical trials as a result. These trials now include populations that were previously not evaluated because of their fragility, such as newborns, and the required number of participants has been reduced to facilitate recruitment. 10 years after the implementation of the European Pediatric Regulation, the situation is encouraging. However, the drug development cycle is very long and it will take several years for the results to be clear.

Makeup of the pediatric population:

- Preterm
- Newborn infant (from birth to 1 month)
- Infant (1 month to 1 year)
- Young child (1 to 4 years)
- Child (5 to 11 years)
- Adolescent (12 to 18 years)

[1] Dr. Carissa F. Etienne was elected Director of the Pan-American Health Organization (PAHO) by the Member States of the Organization on September 19, 2012. She began her five-year term on February 1, 2013. From March 2008 until 1 November 2012, Dr. Etienne served as Assistant Director-General for Health Systems and Services at the World Health Organization in Geneva, Switzerland.

[2] Out of the 7,000 to 8,000 orphan diseases identified, half affect children under the age of five.

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Marketing Authorization (MA)

Following several years of development[3], medicines are subjected to pre-clinical and clinical trials. These trials determine how well the body tolerates the product, its optimal dose, and describe the risk/benefits of the candidate molecule. This last aspect is critical in obtaining marketing authorization. All of these results go into the marketing authorization application. Only the competent national and/or European authorities, such as the FDA, ANSM or EMA, are allowed to grant marketing authorization upon review of the application.

[3] *Flexmag # 6 – Injectable drugs: a long winding road.*

Major changes to ISO 9001

The purpose of the ISO 9001 standard is to ensure that products and services meet customer requirements. Technoflex was recently audited by AFNOR and once again successfully renewed our ISO 9001 certification in its new version.

Sylvie Ponlot

Published in October 2015, the fifth version contains many changes and represents genuine progress. It is more operational than the previous version, focusing on objectives to attain rather than the means to attain them. The first notable change in ISO 9001:2015 is that its structure was reorganized to match other international standards. Companies can now integrate elements from standards such as ISO 27001 for Information Security Management or ISO 14001 for Environmental Management Systems.

Another new aspect is that the first chapter now takes the company's context into account. This major change adjusts the standard to the company's configuration to determine the best Quality Management System (QMS). Additionally, documentation can now be used as a tool to improve performance. Each company conducts its own assessment of the documentation it needs while taking into account customer requirements and the standards in its business sector. As a result, documentation can be used as a communication tool rather than just a library of good practices! In this chapter, the concept of managing risks and opportunities also appears for the first time. It is important to identify them to take the necessary steps to address risks and create strategic opportunities for the company.

Another major change: the elimination of the "Management Representative". This person, previously designated by Management, was responsible for overseeing QMS performance and providing regular reports through the management review. The new version of the standard advances the concept of "leadership"[1] instead. This major change will more closely involve the company's Management in the QMS. Management must now demonstrate its commitment by defining the company's priorities, ensuring that the necessary resources are available to reach objectives, and encouraging its teams to contribute to this approach.

The application of this quality standard and the successful renewal of our certification is proof of Technoflex's active involvement in our quality approach and our commitment to compliance and customer satisfaction.

[1] Person or group of people at the highest level of the company.

Technoflex wins big at the 2018 CPhI Awards

Technoflex is proud to announce that our Dual-Mix®[1] innovation received the prestigious "Excellence in Pharma" award in the Packaging category. It was chosen from more than 250 candidates in 17 categories. Dual-Mix® is a patented and innovative packaging for molecules that are unstable in a solution. This single primary package contains two compartments that hold a powder/lyophilized drug and its diluent. With Dual-Mix®, the drug no longer needs to be prepared in the hospital pharmacy. Safe and quick reconstitution is important not just at a patient's bedside, but also in specific situations such as emergency or conflict zones.

[1] Flexmag #12 – Dual-Mix®, the innovative solution for error-free reconstitution.

Ger Standhardt, the Executive Director of HCPC Europe presents the CPhI Pharma Awards prize of Excellence in Pharma : Packaging to the Technoflex sales team (Christian Frayret, Nadine Goyeneche, Marie-Anna Curutcharry).

Artificial intelligence and health care: a promising alliance

The goal of Artificial Intelligence (AI), which emerged at the end of the 20th century, is to be able to think like humans. AI uses two principles to do so: logic and data. Applied to medicine, it could predict a disease and its evolution, anticipate an epidemic, develop a personalized treatment, or provide a diagnosis.

Sylvie Ponlot

AI has a promising future in the field of immunotherapy, as shown by a recent French study. Immunotherapy is a treatment that stimulates the immune system to strengthen the patient's defenses. Though it is widely used in oncology, only 30% of patients respond positively, and we don't know why. An AI algorithm was created thanks to collaboration between physician-researchers from the Gustave-Roussy Institute and INSERM, and engineers from Centrale Supélec. It analyzes scanner images and creates a computational signature[1] that could potentially predict the efficacy of the therapy on the patient. To do this, the information system was continuously fed thousands of scanner images from 500 patient exams. As a result, it learned to identify the different tumors for which immunotherapy appeared most effective. The AI was able to provide reliable information by examining a medical image without biopsy, making it possible to reliably assess new patients.

In the US, the Food and Drug Administration (FDA) has just approved screening software. The FDA based its decision on a clinical study

with 900 participants, some with retinopathy and some without. Nine times out of 10, the software program gave the correct diagnosis! This computer program uses an AI algorithm to detect early signs of retinopathy[2]. During a routine medical exam, the AI analyzes images of the eye taken with a retinal camera. In just several minutes, and without human intervention, the program provides a diagnosis, the related report, and instruction for care in compliance with the practices of the American Academy of Ophthalmology. Healthcare providers can use this program, called IDx-DR, to immediately and reliably assess for diabetic retinopathy. Patients benefit from early detection of the disease, thereby preventing blindness.

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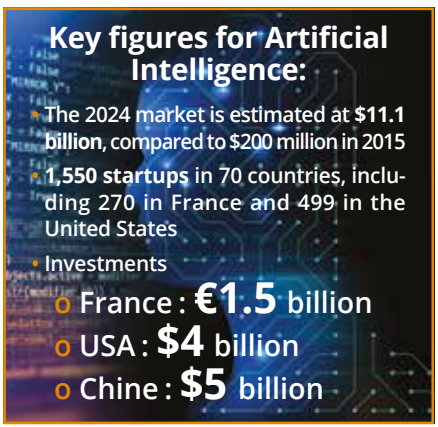
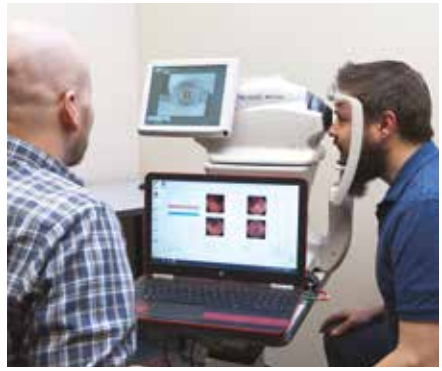
Dermatology is another field in which AI excels. In 2017, American researchers used Google's "Show and Tell" software program. Using "Deep Learning", this program consults millions of images captioned by humans until it is able to produce its own captions. By studying more than 130,000 images, the AI was able to distinguish between hundreds of skin diseases with 94% accuracy. Again in the United States, a study last spring confirmed the reliability of AI. Hundreds of images of melanoma and benign nevi[3] were fed to the computer, which analyzed them and was able to identify 95% of the melanoma (compared to 87% for dermatologists). It also reduced the number of "false positives,"[4] thus avoiding unnecessary surgical procedures. The program was fed 100,000 images of skin lesions to arrive this result.

It has only taken several decades for AI to move from theory to reality. This achievement was made possible thanks to the biggest tech companies, the GAFAM[5]. These companies are currently the only ones with big enough platforms to collect, store, and analyze such large volumes of data. Thanks to this incredible potential and some undeniable benefits, the future of Artificial Intelligence is bright!



Sources : The Lancet Oncology, FDA, Google, Microsoft, IDx.



IDx-DR, AI - system for the autonomous detection of diabetic retinopathy.

[1] In medical image computing, or radiomics, a computer analyzes medical images to produce usable data.

[2] Diabetic retinopathy is a complication from type 2 diabetes that affects 50% of patients. In France, it is the number one cause of blindness for those under 65.

[3] A natural brown mark on the skin.

[4] As opposed to a "false negative", a "false positive" gives a positive result that is invalidated by additional tests.

[5] Acronym of the most powerful Internet companies: Google, Apple, Facebook, Amazon, and Microsoft.

Abracadabox!

Sylvie Ponlot

Marc Salem, founder of Coucou Nous Voilou

Everyone feels apprehensive about hospitalization, especially for a serious disease. For children, this ordeal is even harder: they have a limited understanding of what is happening to them, are afraid of the unknown, afraid of pain, feel anxious, and so on. Children also find it hard to understand that certain treatments can be painful or at least upsetting: surgery, intravenous therapy, etc. Yet rehydration, nutrition, and even chemotherapy are all administered intravenously in hospitals. They require hooking up an IV, which is often frightening, especially to children. To help young patients[1] have a better hospital experience and tolerate their treatment, the Coucou Nous Voilou nonprofit organization created Abracadabox. This initiative has already been adopted by almost 100 French pediatric wards.

Abracadabox is a plastic box that was specially designed to hold an IV bag. Development prototypes were tested in hospitals, and feedback from healthcare personnel led to significant improvements that incorporate treatment requirements. Abracadabox complies with CE standards and now combines aesthetics, playfulness, and convenience. Installed on the IV pole, the casing on the back of the box is half open. Nurses can therefore easily access the bag without having to open the entire system. The side facing the child features cartoon characters on a colorful background, hiding the bag and the drip.

Technoflex supports this project, and regularly provides infusion bags. Demonstrations in pediatric departments were conducted in real conditions of use. A number of illustrators, such as Zep, Tébo, and Julien Neel, as well as the copyright owners of certain characters contributed their work and gave their agreement. Titeuf, the Smurfs, the Raving Rabbids and many other characters appear on the 3,000 Abracadaboxes that are distributed free-of-charge to pediatric wards in France. These boxes are very popular, as they not only boost the morale of young patients, but also serve an educational purpose. "The healthcare personnel use the cases to help children understand the reasons behind and the need for their treatment. This program is based on the idea that the first step towards healing is to believe in the treatment," says Marc Salem, founder of Coucou Nous Voilou. Enthusiasm for the Abracadabox shows no sign of abating, and is even crossing borders. Belgium has just received its first cases!

[1]*Two million children are hospitalized in France each year.*

Marc Salem, Coucou Nous Voilou conductor

"Improving the daily lives of sick children" could be Marc Salem's motto. After working for more than 20 years at Necker Children's Hospital, and then a charitable organization, Marc Salem took the leap and founded his own nonprofit organization in 2015. Coucou Nous Voilou's main mission is to finance projects to improve the well-being of children during their hospital stay: purchasing material and decorations, creating living spaces and activities, and so on. Coucou Nous Voilou represents 33 projects funded, 91 partner pediatric wards, 10,200 hours of work, and above all, 15,308 happy children.

For more information:
www.coucounousvoilou.fr

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