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The news magazine of the Technoflex group

Stem cells: 50 years of discovery and progress

Advanced design for cell culture

The Right to Try

Editorial

Olivier Chesnoy
Chief Executive Officer

One of the greatest developments in the health sector over the last two decades has been the shift from "chemical" therapies, based on molecules with defined properties (antibiotic, anticancer, or anti-inflammatory, amongst others), to more "biological" therapies, resulting in a whole new world of biotech companies. This change brings hope of many new treatments, especially for some illnesses which have no curative treatment. There is particular hope for current projects in the field of stem cells, cells that are similar to embryonic cells and which could potentially "repair" major damage, for example in cardiology or in articulatory infections. This is the subject of this issue's Focus section.

Innovative products are obviously required for manufacturing and storing these new applications. In this issue of the magazine, Technoflex is proud to present its new "SafeCell®" range, dedicated to cell culture applications. Find out more in the Business section.

This new range is fully in line with the tradition of innovation at Techoflex, and marks the 30th anniversary of the first bags produced by the company. Our first bags for the pharmaceutical industry came out in 1986. It has been an exciting journey, from PVC to FEP, via EVA and of course PP. The teams naturally celebrated this anniversary, during a wonderful evening at the Bayonne bullring.

With this anniversary, there is one thing the whole team at Technoflex agrees on: to keep providing you, our partners and clients, with the most appropriate and innovative solutions possible.

Happy reading!

Flexmag, a world of connections

Frontpage picture: Stem cell research

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Quick facts

From PVC to FEP- the first Technoflex bags are now 30 years old!

To commemorate the anniversary, Technoflex invited all its employees to the Bayonne Arena on 10/09 for an exceptional celebration.

Innovation: at the heart of our DNA

In 1986, the company, a connector manufacturer for the pharmaceutical industry, expanded its services and began producing flexible bags for injectable medication. From the first PVC bags to the new SafeCell® cell culture bags, Technoflex has always kept innovation at the forefront of its priorities. We have one aim: to support healthcare technology by maintaining patient and healthcare personnel safety. In these 30 years, the company has developed long-term partnerships with numerous pharmaceutical companies, including some of the largest, around the globe.

Today, 275 employees bring their expertise to the health sector, doing their utmost daily to provide innovative, reliable and easy to use products.

Agenda

1st quarter 2017

Pharmapack Europe	February 1-2, 2017	Paris Expo, Porte de Versailles	Pharmapack EUROPE	**Hall 4 Booth D-63**	
ISCT Meeting Annuel	May 3-6, 2017	ExCel London Convention Center, London	ISCT 2017	**Booth 600**	
CPhI north america	May 16-18, 2017	Pennsylvania Convention Center, Philadelphia	CPhI north america ICSE FDF	**Booth 3118**	
MD&M East	June 13-15, 2017	Jacob K. Javits Convention Center, New York	MedTechWorld M&M EAST	**Booth 1862**	

Stem cells: 50 years of discovery and progress

The hundreds of millions of cells that make up the human body are very diverse. Skin, blood, liver, and even nerve cells - there are no fewer than 200 different cell types. In adulthood, some cells are no longer able to divide and reproduce. This is the case for muscle, heart and even brain cells. Others, however, such as stem cells, maintain this potential.

Sylvie Ponlot

Stem cells are present during all living beings' first stages of development. Cell lines in human beings originate from stem cells. The very first embryonic cells are called "totipotent", and can reproduce indefinitely creating two perfectly identical cells. They can also adapt themselves to become any type of cell. They provide the necessary environment for embryo development *(the placenta and umbilical cord)*, and the human body's various tissues and organs. On the fifth day of embryo development, the embryonic stem cells become 'pluripotent.' They begin to differentiate and adapt specially to create all the different cells of the human body.

Despite its potential in regenerated medicine, embryonic stem cell usage raises a number of moral and ethical questions in different countries. For example, in the United States and United Kingdom, legislation has authorized a large number of research techniques. In France, the Biomedicine Agency has approved study protocols with some conditions, whereas in Germany or Italy, it is completely prohibited. In 2006, Professor Yamanaka *(Japan)* managed to regress some adult stem cells into pluripotent stem cells. This allows scientists to advance their research without using embryos, which means the main ethical problem is bypassed.

In adulthood, stem cells become 'multipotent.' This means that they produce a limited number of cell types, including mesenchymal stem cells *(MSC)* and hematopoietic stem cells *(HSC)*. The former is rich in adipose tissue which creates, among other things, fatty, boney and cartilaginous cells. They are mainly used in clinical trials [1]. HSC are located in bone marrow and are the source of blood components. They renew themselves every 120 days and play a significant role in the immune system due to the various cell types: red and white blood cells, or lymphocytes. Used routinely in bone marrow transplants since the 1970s, stem cells are also employed in the treatment of some blood and immune system diseases.

Finally, there are 'unipotent' stem cells. They only produce one cell type as they are so involved in a differentiation process. With the ability to self-renew, they ensure that the organs *(bones, cartilage, liver, skin, brain, etc.)* are functioning correctly by replacing the dead cells.

[1] *More than 350 clinical trials are currently taking place all over the world.*

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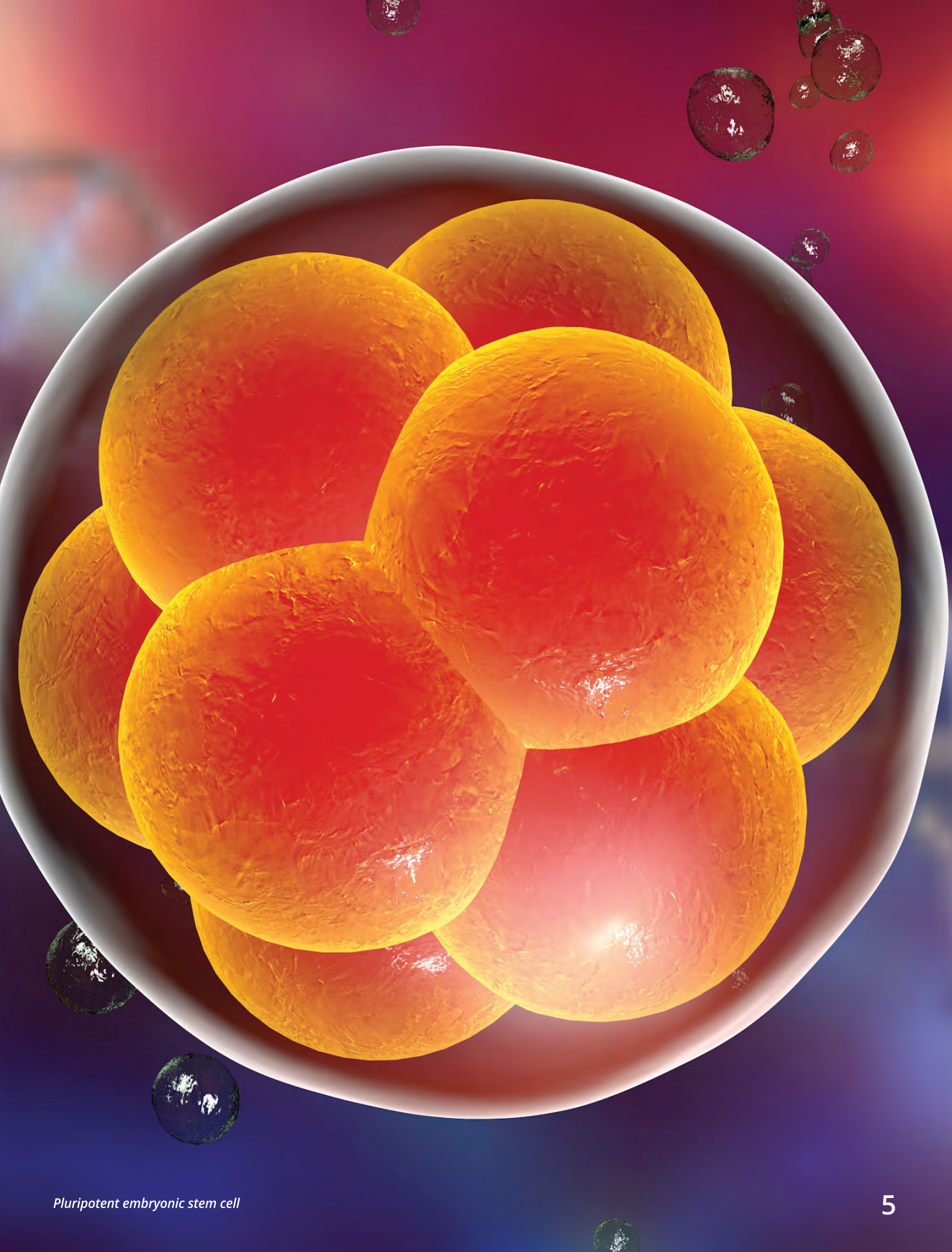

Pluripotent embryonic stem cell

Focus

Center for iPS Cell Research and Application, Kyoto University

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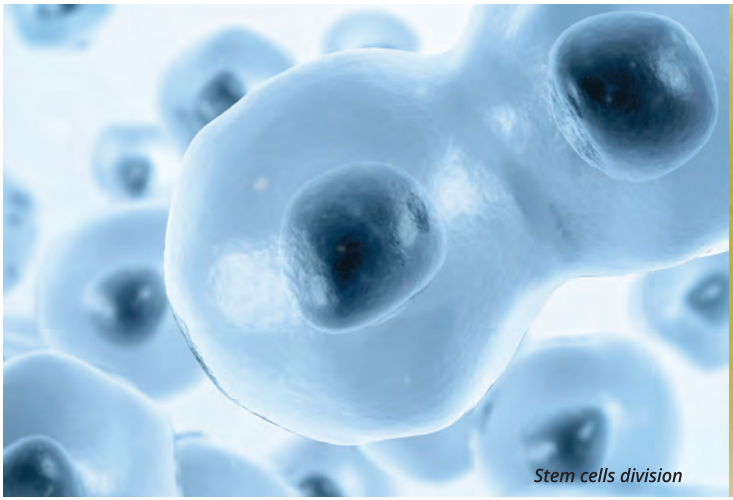
Reprograming human body cells – from dream to reality

In 2006, Shinya Yamanaka's discovery stunned the scientific world and earned him the Nobel Prize in Medicine 6 years later. He found a way to reprogram any pluripotent stem cell, called 'induced pluripotent stem cells', or iPS. These cells have the capacity to create every human body cell type which is something that, until that time, only embryonic stem cells could do. To achieve this, Professor Yamanaka took a combination of four genes, normally only present in stem cells, and subsequently inserted them into a mouse's skin cells, which led to the reprogramming of skin cells into iPS cells. Scientists are now able to reprogram human cells by adding less than four genes. There are numerous application prospects, which include providing unlimited quantities of cells and tissues for patients suffering from incurable diseases. In Japan, clinical trials of new therapies using this technology will

Dr Yamanaka



Stem cells division

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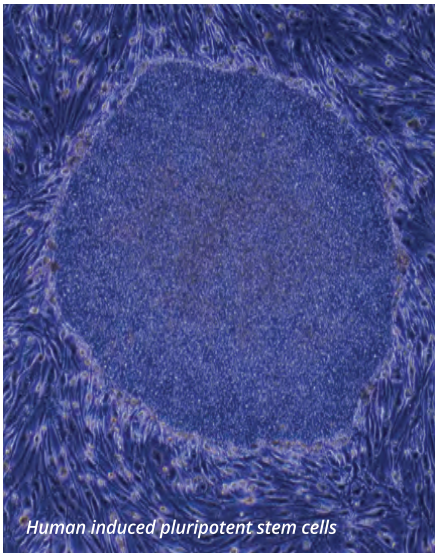


Human induced pluripotent stem cells

take place in the next few years. Treatments will be aimed at patients suffering from Parkinson's disease, diabetes, pathologies of spinal cord injuries and heart disease. The European, Japanese and American medication regulation agencies expect to have coordinated guidelines regarding the use of iPS cells in preclinical trials by the end of 2017.

Natural killer cells to treat leukemia

Acute myeloid leukemia *(AML)* is caused by the blood stem cell dysfunction. As they develop, the pathological stem cells turn into immature cells, called 'blast cells', which replace the normal cells. AML is known to evolve rapidly and most commonly affects adults. As it is resistant to chemotherapy, the likelihood of curing AML is very low. Results of an American experimental therapy publication last September have brought hope to patients. This new form of immunotherapy involves removing natural killer cells from a healthy donor, modifying them to attack the blast cells, and then administering them intravenously. Researchers have observed complete remission in 4 out of 9 perfused patients. More long-term trials are anticipated to prove the treatment's viability.

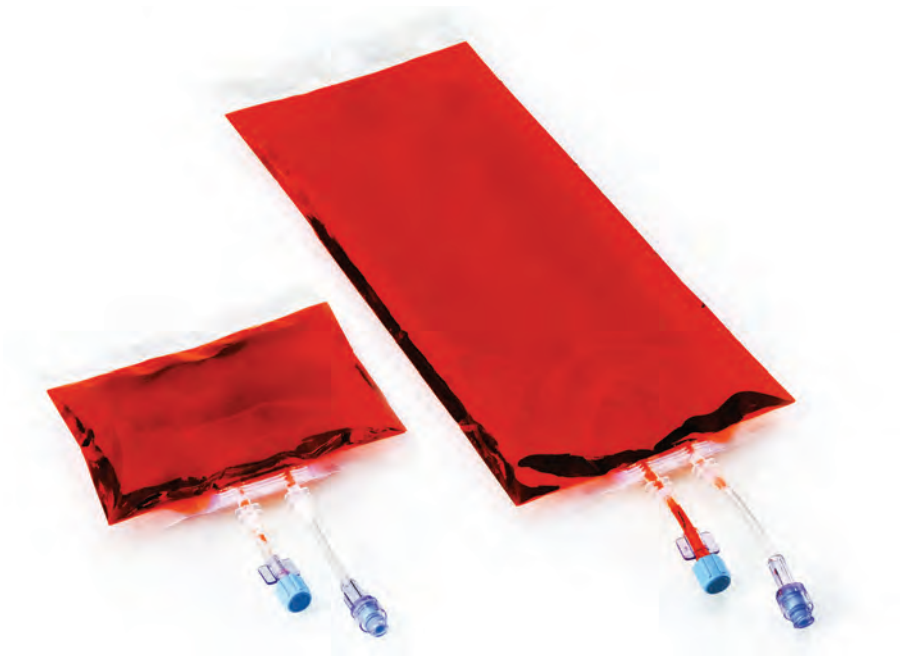
Human iPSC research

Advanced design for cell culture

Neurodegenerative diseases, cellular deficiency, cancers or even skin regeneration for burn victims – cell therapy has numerous applications. Ex-vivo[1] cell culture is a vital step in the development of cell therapy treatment. Its implementation is difficult, must adhere to certain conditions and requires material that guarantees cell safety. To meet this requirement, Technoflex has developed a range of bags especially dedicated to cell culture.

Sylvie Ponlot

The SafeCell® range is made of Fluorinated Ethylene Propylene *(FEP)* and provides the response to the demands of ex-vivo cell culture. FEP is chemically and biologically inert and perfectly adapted to cell suspension culture. Its anti-adhesive properties allow cells to float freely and develop in their culture medium. SafeCell® bags are permeable to gas *(oxygen, carbon dioxide and nitrogen)* and therefore allow the exchanges required for proper cell development, whilst providing another essential characteristic: water impermeability. The low evaporation rate of SafeCell® bags means that humid incubators which increase the risk of germs and bacteria growing do not pose a problem.



Cell culture testing

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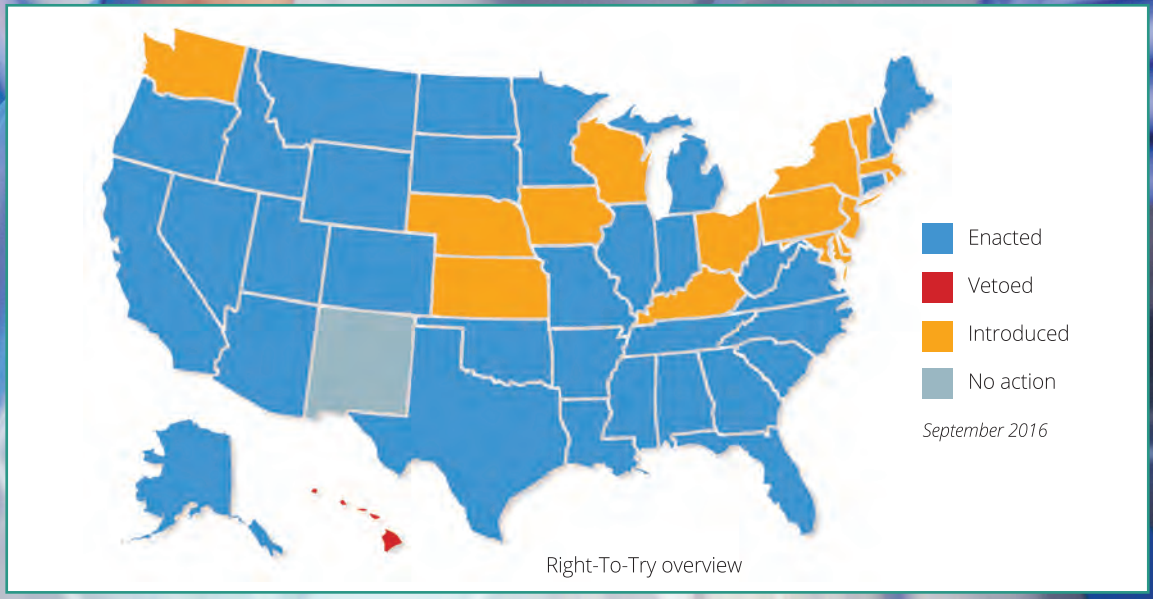
Contamination risks are considerably reduced

As any contamination can cause cell lysis [2], cell culture requires absolutely sterile conditions. SafeCell® bags are sterilized and protected by peelable overpacks. FEP is highly transparent and allows safe, easy cell observation under a microscope. The FEP double connectors welded directly to the bag limit leakage risks, thanks to their specific geometry. Finally, the tubes are equipped with a luer lock and a needleless injection site. This closed system guarantees tightness to microorganisms during filling, culture and emptying of the bag.

Last but not least, is the benefit of traceability, ensured through laser-marked batch numbers and bag unit identification. SafeCell® bags are produced in ISO7 clean rooms in compliance with GMF *(Good Manufacturing Practices)* and delivered with a certificate of compliance.

[1] *Outside an organism.*

[2] *Breaking down of the cell membrane resulting in its death.*



Right-To-Try overview

The Right to Try

A number of treatments currently in development could improve or even save lives. However, it may be ten years before the product is approved and out on the market because of product development times and trials. This is a bit too long a delay for terminal patients! In the United States, as in Europe, there are several alternatives that involve giving patients access to experimental treatments. Review the possibilities available.

Sylvie Ponlot

The first means of accessing experimental medication is to take part in clinical trials[1]. These studies are authorized and controlled by medication regulation authorities such as the FDA *(Food and Drug Administration)* or EMA *(European Medicines Agency)*. The aim is to evaluate the safety and efficiency of the product, the organism's tolerance to the treatment, and then compare the product to a commonly used medicine, if one exists. However, choosing to take part in a clinical trial does not guarantee access to the product in development. Most patients will be given a placebo[2], with only a restricted number receiving the validated treatment. This, however, is the only way of ensuring an objective study of new treatments.

Expanded Access *(Compassionate Use)* programs are another option. Set up by the FDA 20 years ago and since the year 2000 in Europe, they enable patients who have not had access to clinical trials to apply for experimental treatments from health agencies. Authorization is only granted under certain conditions, for example, proving that there is not already a comparable and satisfactory treatment, and that the pharmaceutical laboratory has submitted a clinical protocol compliant with regulations. Since 2010, more than 90% of access requests for Compassionate Use programs have been authorized in the United States.

A new American alternative, the 'Right to Try' law

In May 2014, Colorado became the first state to ratify the 'Right to Try' draft bill. Widely adopted by many states[3], the law circumvents the FDA authorities and eliminates the need for paper work. It provides the right for patients suffering from incurable diseases to directly request access to developing treatments from laboratories. The laboratories must have successfully passed Phase I clinical trials.

Despite its popularity among citizens and legislators, the law has given rise to much criticism in the medical world. Critics protest that the treatments have only completed one of three phases of clinic trials and that they do not have safety data about the severely ill patients. Others deem it to be against moral ethics due to the high level of responsibility resting upon the laboratory and the doctor, or due to its inequality[4]. It is also thought that patients may be less inclined to take part in clinical trials which are indispensable for companies to be able to make an NDA *(New Drug Application)*. From a federal perspective, the law is deemed unconstitutional by its opponents. However, it was brought before the American Senate last spring. There is no doubt that its review will cause much debates.

[1] Flexmag 6, Injectable medicine, the obstacle course

[2] A dose that lacks an active substance and is used for its psychological effect. Placebo effect.

[3] In September 2016, 32 American states had adopted this law and 17 had presented it for deliberation. Only New Mexico did not put it to the vote. After issuing a veto in 2015, the Governor of California, Jerry Brown had just enacted the law.

[4] Related to prohibitive costs not reimbursed by private health insurance. In some states, the patients risk losing their palliative care or home-based care.

Warehouse organization: a daily challenge

Distributing the right product at the right time and to the right place is one of the challenges faced by the Technoflex warehouse staff. With a 4,000m² surface area, warehouse management requires perfect organization. Headed by Miguel Duriveau, the team ensures first-class daily logistics support.

Sylvie Ponlot: What are the major challenges facing you and your team?

Miguel Duriveau: Our job is very diverse because we are involved throughout the whole supply chain process: receiving the raw materials, stock control, semi-finished products, packaging and dispatching finished products, preparing orders, and even recycling industrial waste. At Technoflex, twelve people work in the connector and bag department warehouses daily. I make sure that the team is well-organized and coordinated so that priorities are well managed.

SP : Technoflex's business is closely linked to the pharmaceutical industry. How do you adhere to regulatory requirements?

MD: Traceability is crucial. When raw materials arrive, they are entered into our SAP information management system. This first step enables us to know, for any batch of finished products, the batches of raw materials that were used to make it. Confirmation of compliance is another essential aspect. We collect and send samples for Quality Control to analyze and, as soon as we receive results proving their compliance, we can then release material batches and supply the production lines.

SP: Vigilance by warehouse personnel is a crucial aspect of your organization, isn't it?

MD: Of course! Every Production Order on each machine is created on the basis of a manufacturing file which states the necessary raw materials, their quantity and place of supply. The storekeeper has to convert this data into the number of film reels, tubes or the quantity of granules. They must also keep track of daily machine consumption to avoid raw material stock shortages.

SP: Are the connector and bag departments organized in the same way?

MD: In both departments, we manufacture to specific orders. In the connector department, we also have 'make to stock' production to be able to meet unforeseen orders. The difference between the two departments lies in the production planning. This means we have to do a bit of gymnastics when it comes to organization and storage in the connector warehouse!

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