

FLEXmag

April
2014

#07

The news magazine of the Technoflex Group

Focus

**Technoflex's
in-house lab: an
ongoing work ethic**

**Sensitive molecules
get their own bags**

**The rich promise
of biotherapy**

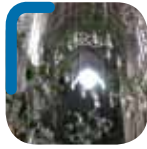
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As you have seen with each issue of Flexmag, patient safety – and therefore the quality of our packaging products – is the focus of our concerns at each and every stage of design and manufacture. Within this 'global quality' approach the Technoflex analysis lab plays a decisive role: Coralie, Florence and Emilie perform more than 10,000 analyses each year! From conformity controls on raw materials to analysis of the air and checks during the process, they closely monitor each step, as you will see in our Focus.

The same quest for performance characterises the work of our R&D team, whose developments (such as the 'butterfly' bag and the boat port) meet specific needs for more complex items such as blood products. Bags for blood products need to be filled in aseptic conditions due to their thermolabile nature, which does not allow autoclave sterilisation. This is a field in which Technoflex has become a genuine specialist in terms of development of innovative solutions – which we also apply to new approaches in the field of biotherapies.

Lastly, while the purpose of our day to day work is to contribute to the healthcare sector, it can sometimes lead to rather unexpected projects: an improbable combination of industry and conceptual art, the 'living sculpture' by Pascale Peyret was made using Technoflex bags. She shows how dreamlike, poetic creation can even be found in bags for pharmaceuticals! Additionally, her approach combines artistry with societal concern, thus reflecting the values of Technoflex. I strongly urge you to take a look at her 'Anamorphose' online.



Frontpage picture:
Emilie Cazaux, laboratory technician



Happy reading!

Olivier Chesnoy
Chief Executive Officer

FLEXmag

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Quick facts

EMA: new molecule authorisations

In 2013 the EMA authorised 38 drugs containing active substances that had never previously been used. Additionally, two new innovative-therapy drugs were recommended for approval in 2013. Derived from gene therapy and cell therapy, they offer new opportunities for the treatment of illnesses and injuries. The number of market approval recommendations for drugs designed for rare diseases has been constantly growing (11 in 2013 against 8 and 4 in the previous two years). 2013 also saw the first two positive opinions on market authorisations for biosimilar monoclonal antibodies. Across the Atlantic, the FDA authorised 27 new products, including 9 for the treatment of rare diseases.

Regulatory framework for biosimilar products in Brazil:

In a recent news release the Brazilian National Health Monitoring Agency (ANSIVA*) announced that by the end of the year, pharma firms will be required to subject so-called 'similar' drugs to the same bioequivalence tests as generics in order to guarantee their quality.

* Flexmag 03 - Page 7

New collaboration between the EMA and the FDA:

The two regulatory bodies have decided to launch a joint initiative in order to share information on inspections of bioequivalence studies of generics. An 18-month pilot phase will see joint inspections for approval applications submitted to the two bodies. A previous collaboration between the EMA and the FDA concerning GCP (Good Clinical Practice) was successfully carried out in 2009.

Schedule

Quarter 2 2014



May 31 - June 05

ISBT - Seoul, South Korea

Booth 605

June 10 - 12 June

Pharmapack
NORTH AMERICA

New York, United States

Booth 3544

Technoflex's in-house lab: an ongoing work ethic

Sylvie Ponlot

The pharmaceutical industry has a fundamental need: to provide high-quality drugs whilst guaranteeing patient safety. In order to meet this requirement the products have to be of impeccable quality, and total control over particulate and bacterial contamination is paramount. At Technoflex this means control over raw materials, the environment and products. This is the key mission of the company's in-house laboratory, which conducts physical, chemical and microbiological analyses.

It is an ongoing process that allows no exceptions. The raw materials are received in the form of pellets, films, tubes or sheaths and are then subject to an in-depth analysis. The first verification is a comparison between the batches received and a reference batch: only the results of spectrophotometer analysis and differential scanning calorimetry (DSC) can establish the conformity of the

materials. Once released from this phase they can integrate the manufacturing process. During differential scanning calorimetry the fusion and crystallisation temperatures of the polymers are evaluated precisely. These values will be useful for optimising the bag welding parameters and are also of significant interest to R&D developments (new projects, new formulations).

Staff members, tools and manufacturing processes are all potential sources of contamination. It is thus crucial, and indeed mandatory, to conduct regular checks on the environment in order to avoid any such contamination, either particulate or bacterial. Two of the recurring targets of inspection are the air and the work surfaces, in particular the critical zones due to their proximity to the product.

Sampled at the start, midpoint and end of the manufacturing cycle – after a strict environment inspection – the connectors and bags undergo exami-

nations to guarantee their purity and integrity. Suspect number one: non-visible particles, as they represent a major risk to patient safety and their presence may cause anaphylactic shock. The lab uses a light-blocking particle counter to calculate both the number and the dimension of these particles, in accordance with European pharmacopoeia 2.9.19. Bacterial endotoxins are another potential culprit. These are pyrogens with the particular feature of resisting terminal sterilisation. To check that the product is free of them, the lab uses a LAL (limulus ameocyte lysate) reagent. This is a rapid, reliable alternative method approved by the FDA. Conducted routinely on the entire production, it is a prerequisite to any validation, as each change of raw material or environment, or the

Limulus ameocyte lysate

Morphologically, the limulus (horseshoe crab) has not changed in 500 million years. Its particularity is that it has no immune system. To make up for this shortfall, its cells produce a protein that converts the haemolymph (equivalent of blood) into a semisolid gel-like substance. This gel quite simply blocks out bacterial infections. Since the 1970s limulus haemo-

lymph has been used to produce a reagent known as Limulus Ameocyte Lysate. It has the property of coagulating instantaneously when it comes into contact with pathogens.



Bioburden testing

arrival of a new machine, will have an impact on the whole process. The final step is an analysis of the bioburden. It is common knowledge that terminal sterilisation alone does not necessarily guarantee that the product is totally sterile. The efficacy of this phase depends on the initial burden of the primary packaging in terms of micro-organisms. To determine their number and nature, bioburden trials are imperative. Entirely carried out in a class A (ISO 5) laminar flow cabinet, this test ensures that the future terminal

sterilisation will be efficacious.

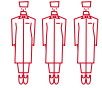
With more than 10,000 analyses conducted each year, the Technoflex physical and chemical analysis laboratory has proven expertise. Its integration has not only improved knowledge of raw materials and manufacturing processes, but has also resulted in better responsiveness to potential contamination, for example the rapid implementation of investigations. Thanks to all these inspections, Technoflex can guarantee the end-to-end integrity of its production.



Bioburden testing
Ultrasound bath

The lab in figures:

• **3 people**



• More than
10 000 analyses annually

• **12 inspections**

- DSC
- IR
- UV
- Non-visible particles
- Bioburden
- Identification of micro-organisms
- LAL
- pH measurement
- Heavy metals
- Calcination residue
- Search for reducing substances
- Non-volatile residue



¹Flexmag 03 - Particulate contamination
- Pages 4 & 5

Sensitive molecules get their own bags

Sylvie Ponlot

Blood products such as albumin or immunoglobulins are indispensable molecules for the treatment of over 70 pathologies, but they are sensitive and cannot withstand heat. Additionally, as their high molecular weight does not allow oral administration, injectable methods are preferred. It is thus imperative for the product to be filled aseptically, implying a separate sterilisation of the primary packaging.

With the increase in the number of biologicals, Technoflex has developed a standard line of Inerta® polypropylene sterile bags combining the company's latest R&D innovations. Fitted with either one or two tubes, these bags are specially dedicated to aseptic filling. Their 'butterfly' design¹ reduces the number of folds that form during filling and facilitates product flow. 'Boat ports'² welded directly onto the bag body replace the standard tubes. They guarantee tightness whilst avoiding any potential tearing when the outer packaging is opened. A twist-off is welded to the tubular part of the first boat port, and the second is welded shut. This system keeps the bag free of micro-organisms after radiation. To facilitate

product traceability, a specific area on the upper part of the bag is set aside for laser marking. Lastly, the volume of

or argon) for products sensitive to oxygen, such as immunoglobulins or albumin.



the bags (50 to 500 ml) allows the injection of gas (nitrogen

The primary packaging has to guarantee the stability and integrity of the drug. To meet the requirements of these complex, sensitive molecules, the bags are sterilised by Beta radiation, then placed in a double packaging in accordance with the ISO 11607 standard. This precaution maintains the sterility of the bags until they are used in ISO 5 controlled atmosphere areas. Remember that ISO 5 rooms do not in themselves sterilise, they merely allow products and equipment to remain sterile!

¹Flexmag 03 - Page 6

²Flexmag 04 - Pages 6 & 7

The rich promise of biotherapy

Sylvie Ponlot

Since insulin, the first biological medical product, was marketed in the 1980s, the biopharmaceutical industry has come a long way. Biologicals have brought advances in the prevention of serious illnesses, improving the lives of countless patients. They have opened up new therapeutic horizons for increasingly customised medical treatment. A glimmer of hope in the fight against serious and sometimes fatal diseases?

Bioproduction is based on bioengineering: unlike traditional drugs derived from chemical synthesis, biologicals are produced from living cells or the products of living organisms. This is known as biosynthesis. Biological drugs present molecular characteristics that are complex in terms of size, spatial conformation and chemical formulation. There are three main categories of biologicals: substitution proteins which make up for a deficit in the human body, vaccines, and therapeutic antibodies. The latter category alone accounts for almost half of all biological drugs. In 2013 more than 168 biologicals were marketed in France, 9 of which were new molecules.

Biological medical products obtained by extracting organs or living tissue are a thing of the past: today they are produced in confined, controlled devices known as 'bioreactors'. The

aim is to avoid the risks to the environment of dispersion. Thanks to genetically modified organisms called 'factory cells' there is no longer any need for raw materials of human or animal origin. With this process sophisticated biologicals can be produced on an industrial scale, as is the case of vaccines and proteins, among others.


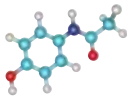
Blood products are another form of biological. Due to their human origin they are a possible source of pathogen transmission. But progress achieved in extraction and purification technologies has boosted the level of purity and quality of these products, opening up new perspectives for these concentrates. Blood products (immunoglobulins, albumin, etc.) meet important therapeutic needs and demand for them is ever-growing.

Moving towards 'custom' therapy

Biologicals are particularly effective for rare diseases (< 4 to 6% of the population). The treatment takes account of the patient's genetic characteristics. With the focus on the patient rather than the illness, this is a new therapeutic approach to medicine and health. The aim is no longer to observe the effects

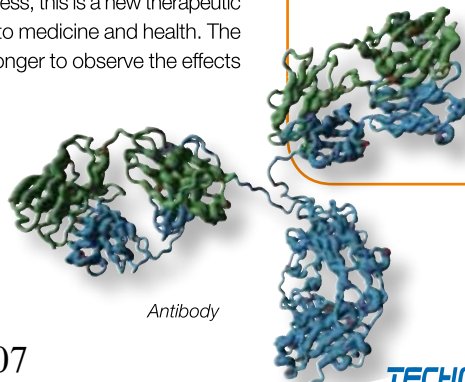
of a new treatment on the patient but to find a remedy to an identified malfunction. With more than 800 molecules in development in 2013, biological products are set to play an increasingly influential role in therapy. A highly promising future!

A few figures:

- **7000 to 8000** orphan diseases, half of which affect children aged under five 
- A market worth **€5.3 billion** in France in 2013 
- A world market estimated at almost **\$500 billion** by 2020

Sources:

- Ministry of Health - FDA
- Pharmaceutical Research and Manufacturers of America
- Leem - IMS



Antibody



'Anamorphose' for human love!

Interview
with photographer
and artist Pascale Peyret

On 10 October 2013, contemporary art took Paris by storm with the 12th Nuit Blanche ('sleepless night') event dedicated to art and culture. In the nave of Saint-Merry Church, IV bags, spiderwort cuttings, water, light and songs combined to create 'Anamorphose', a living sculpture by Pascale Peyret. Pascale is originally from Lyon and lives and works in Paris. We met her in her workshop in the 10th arrondissement.

Sylvie Ponlot: For those who have not seen the exhibition, can you tell us about 'Anamorphose'?

Pascale Peyret: The work was made up of wooden frames with plants, forming vegetal cells hanging from the arches of the church. We needed 17 km of nylon thread to hang 1100 IV bags filled with water. They were lit up by LEDs and had spiderwort cuttings hanging from them. The bags were arranged in ascending spirals between 50 cm and 2.50 m high, resembling a DNA chain. There was real harmony between the installation and the church, the cells and the ceiling rose, the plants and the frieze.

SP: 26 000 people came to admire 'Anamorphose'. What did they think of it?

PP: At night-time the installation was transformed into a starlit vault. The moment when visitors took in the extent of the work was a magical one. People touched the bags. One visitor, a professional singer, sang twice. One man wanted to dance, and a member of the team had the idea of sticking LEDs to his T-shirt. The result was magnificent. Word of mouth did the rest! The installation was the one that attracted the most visitors during the night.

SP: What made you choose the spiderwort?

PP: In France it is popularly known as Misère ('poverty'), but in Spain spiderwort is considered as a plant that brings good luck. They call it *Amor de Hombre*, human love. The symbolism is spot-on, because during the 10-day assembly period we worked with seven homeless people accommodated by the Aux captifs, la libération association. They worked really hard on 'Anamorphose'. We wanted to involve them in the work in order to help restore their self-esteem through art. Art is a kind of gateway, a healing process. If you don't commit to what you do, to the shape you want to give to the world and life, then you're missing out on something. You have nothing left to say. This work expresses a genuine social bond, the bond of my commitment.

SP: Quite a success for a temporary installation, wouldn't you say?

PP: It actually stayed there until 17 October, International Day for the Eradication of Poverty. We then took it down. Each visitor was invited to take away their sprig of *Amor de Hombre* and take care of it. Fireflies swarmed across the city, arousing the curiosity of passers-by. 'Anamorphose' metamorphosed! I received a lot of testimonials emphasising the humanist dimension of the work. The discourse on the refusal of poverty, the transmission of the installation's elements – the seven volunteers handed out each firefly – and the banquet we shared all helped fix 'Anamorphose' in time and space. I still receive 'news' of the cuttings that have taken root.



Scan the QR code
to access the video online.



Anamorphose



Dispersion

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