FLEX mag

April 2015 #09 The news magazine of the Technoflex Group

Focus

The plastics and medical industries united in the name of progress

“A fitness centre for high-tech equipment”

Connectors: it’s all in the design!

TECHNOFLEX

Editorial

In our two main areas of business, plastic injection moulding is a highly-specialised technique which represents a major asset for our medical packaging operations. While the bag itself is responsible for maintaining solutes or injectable medicines in perfect condition until the time comes for them to be used, it is the connecting components which make it possible to actually use these products at the patient's bedside. This context brings its own, highly specific, constraints: as well as providing access to the product, these connectors must also be absolutely watertight to avoid any risk of contamination after filling, while remaining practical and easy to use. These constraints define the nature of the challenges facing our design teams, who base their work as always on the specific demands of our clients, as Frédéric Bonnet, one of the project managers in our R&D team, is keen to point out.

While injection moulding techniques are well-known and widely-used in various industries, what sets Technoflex's activities apart is their application in the field of Healthcare, an environment which requires us to deal with some highly specific usage constraints: not only must our manufactured components meet the most severe quality standards – hence their manufacture under ISO7 and ISO8 conditions – but they must also be capable of resisting sterilisation, autoclave and radiation treatment for the purposes of aseptic filling. Yet more challenges for our R&D and Production teams!

Find out more about the different facets of this fascinating process in Issue 9 of Flexmag.

Enjoy!

Olivier Chesnoy
Chief Executive Officer

Sommaire

FLEXmag, a world of connections:

Front page picture: processing agent

FLEXmag

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Quick facts

Even more orphan drugs!

In 2014, 41 new therapies received the green light from the FDA. This made 2014 the industry's most prolific year since 1996, when 53 new drugs were authorised. Of these newcomers, 17 are designed for the treatment of rare conditions, pathologies affecting fewer than 200,000 Americans; this is the highest number of such drugs ever registered. Furthermore, almost two-thirds of these new drugs have not yet gone on sale overseas. Some of these authorisations benefited from accelerated assessment procedures including the "Priority Review Tag" and "Fast Track Review Route". In Europe, the EMA approved a substantial number of orphan drugs, with 17 of the 82 new products approved this year focusing on conditions for which existing treatments are very limited or non-existent.

FDA approves first biosimilar product!

The "Biologics Price Competition and Innovation" act, appended to the Affordable Care Act* signed into law by President Obama in 2010, opened up the American market to biosimilars. The FDA recently issued market authorisation for the first generic version of a drug derived from biotechnology. With clinical tests demonstrating efficacy and safety results identical to those achieved by the original biomedicine, this new product is approved for the treatment of five conditions. Most notably, it will be administered to patients suffering from leukaemia or cancer requiring a bone marrow transplant. Costing on average 30% less than their brand-name equivalents, biosimilars could pave the way for billions of dollars in savings.

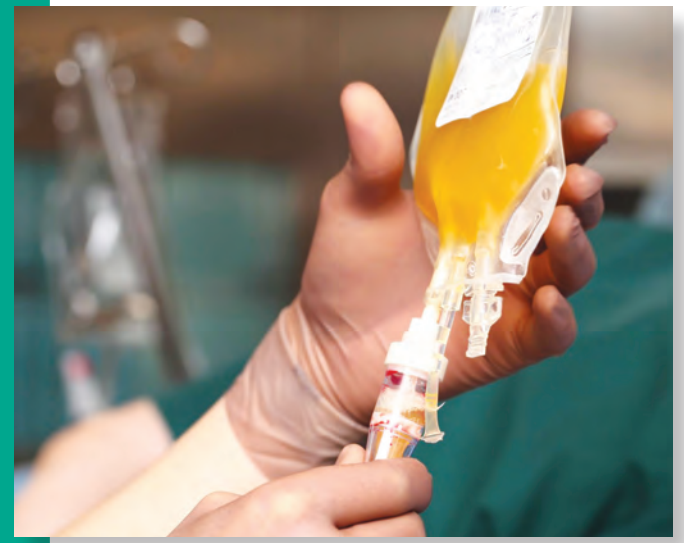
**otherwise known as Obamacare*

A change in status for blood plasma

As a crucial element in blood transfusions, until recently plasma was considered a labile blood product, handled by the French Blood Agency *(EFS)*. The implementation of a recent ruling from the European Court of Justice means that from 31st January 2015 onwards it is to be defined as a "medicinal product derived from blood." As the EFS is not an accredited pharmaceutical agency, it will no longer be authorized to manufacture blood plasma.

Schedule

2d quarter 2015	Show / Venue	Technoflex Booth
May 27th to 30th 2015	ASCO 2015 ANNUAL MEETING May 27-30, 2015 — Las Vegas USA	Booth 4100
June 9 th &10th 2015	Drug Delivery & Packaging Pharmapack NORTH AMERICA — New York USA	Booth 615



The plastics and medical industries united in the name of progress

Sylvie Ponlot

Plastic is the most widely used material in the world. Thanks to its many qualities it has become a permanent feature of numerous sectors, including the automotive, IT and aeronautical industries. It is also very prominent in the medical world.

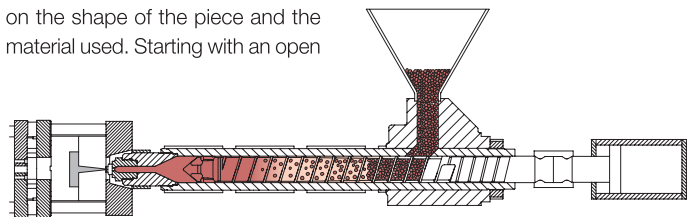
The functional characteristics of plastic offer huge advantages to medicine. Highly resistant, it can serve virtually any purpose. Inert, transparent, opaque, lightweight, flexible and strong, it can act as a barrier and offers good chemical resistance. It is easy to shape and can be processed in several ways: moulding, calendering, rotomoulding, thermoforming, extrusion or plastic injection. The transformation process is selected according to the type of polymer, but above all according to the final use and the form of the finished product. However, the production of injected plastics for pharmaceutical use involves numerous obligations.

The first requirement is irreproachable chemical stability. Plastic packaging is an integral part of the primary packing of injectable drugs, so the plastic must be perfectly inert in order to guarantee the integrity and purity of the solution. The use of additives is broadly prohibited, despite their ability to boost the specific properties of certain polymers *(UV protection, moisture barrier, clarifying agent, etc.)*. There is too much of a risk of interaction with the drugs, leading to a potential adversereaction in the human body. The challenge is therefore to ensure that the end product meets certain requirements without the use of additives. How? By using different thickness effects to obtain greater flexibility, for example, or taking advantage of the plastic's surface roughness in order to make it easier to manipulate. Another process is the mixing of special polymers, which undergo regulatory assessment in order to be awarded authorisation from the European Medicines Agency or the Food and Drug Administration.

The second imperative is that the material must have good physical

Plastic injection:

Plastic injection is the historic core business of Technoflex. It is a plastic transformation technique that has been used since 1972. It involves two phases. First there is plasticization: plastic granules are poured into a hopper which feeds them into a conveying auger positioned in a heated tube. The granules are mixed there and reach their fusion point, turning into a homogenous paste due to the rotation of the auger's screw. The second phase is injection. Under the pressure of the injection screw, the plastic fills a closed, cooled mould. As it comes in contact with the cold mould walls, it takes on the shape of the mould and solidifies. The mould then opens and the piece is ejected. The manufacturing cycle time varies depending on the shape of the piece and the material used. Starting with an open mould, the process comprises several stages: mould closure, injection of the material, pressurisation to prevent appearance defects, cooling, mould opening, and ejection of the piece.



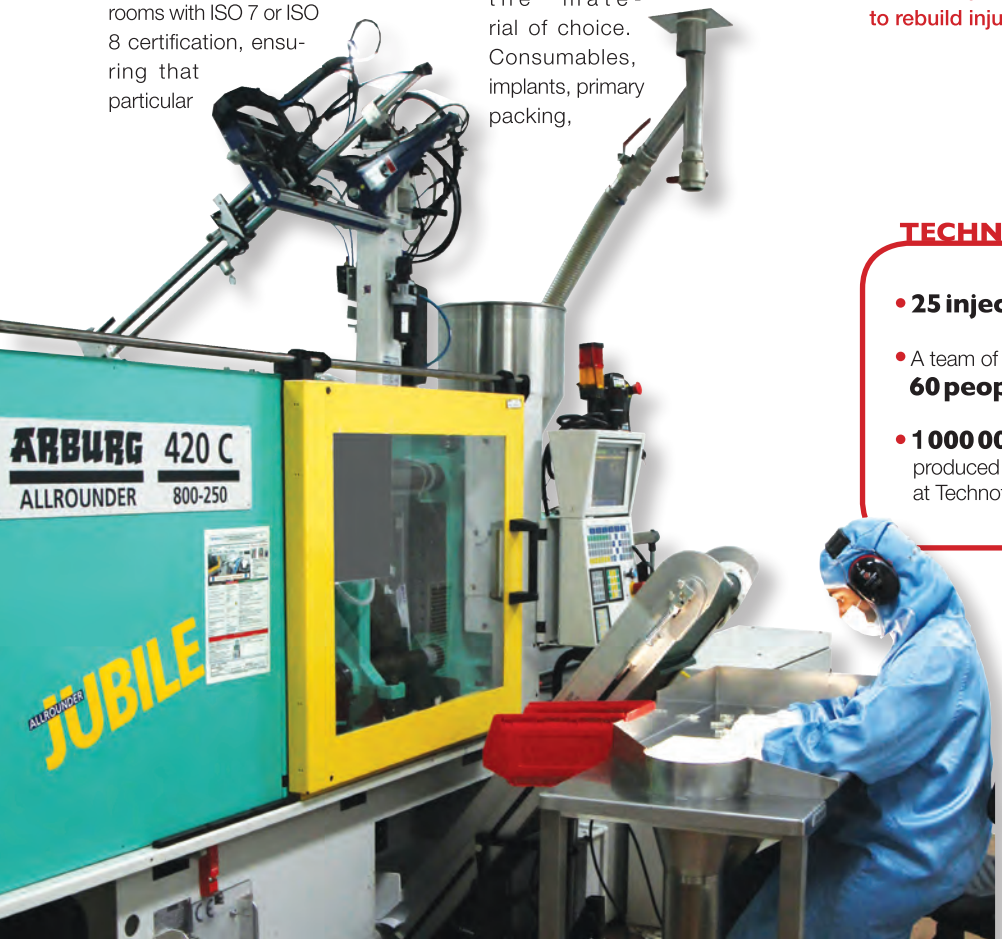
Injection moulding machine - © ARBURG

stability. In the medical environment where sterilisation is mandatory, connectors are subjected to high temperatures during the terminal sterilisation cycle1 and/or undergo radiation treatments *(Beta or Gamma)*. So the plastic has to be able to resist deformation caused by heat and any visual *(yellowing or opacity)* and mechanical *(fragility)* deterioration induced by radiation. Lastly, the third constraint is the production environment. To ensure optimal sterilisation, good manufacturing conditions are compulsory. For connectors, the injection presses are therefore located in controlled-atmosphere rooms with ISO 7 or ISO 8 certification, ensuring that particular contaminations can be controlled.2 As for the risk of microbiological contamination, this is reduced by automation of the manufacturing process and by injection procedures that bring the material up to temperatures ranging from 145°C to 300°C. In order to minimise these risks it is crucial for production staff to wear gloves, for equipment in contact with the product to be disinfected periodically, and for the controlled-atmosphere rooms to be cleaned daily.

Despite countless obstacles due to the highly regulated environment of the medical world, plastic has become the material of choice. Consumables, implants, primary packing, equipment, medical devices: plastic is omnipresent in the pharmaceutical industry and in medicine. Both reliable and innovative, it is full of promise and constantly evolving. New polymers emerge each year, bringing invaluable medical progress with them. Plastics and plastic processing still have a great future in healthcare!

[1] Flexmag 4 – Terminal sterilisation
[2] Flexmag 3 - The fight against particles

Did you know: Nano-polymers are used to transport active ingredients directly to damaged cells. Biocompatible polymers are also employed to rebuild injured tendons.



TECHNOFLEX :

- **25 injection presses**
- A team of **60 people**
- **1 000 000 connectors** produced each day at Technoflex

Connectors: it's all in the design!

Frédéric Bonnet, Project Manager at Technoflex, gives Flexmag a look behind the scenes in his work. He shows how the production of even the smallest pieces requires inventiveness, rigour and determination. The industrial process leaves no room for approximation.

Sylvie Ponlot: Each connector has a precise function. How do you go about developing such distinctive pieces?

Frédéric Bonnet As project manager, my job is above all about being able to organise, plan and supervise a project in order to bring it to fruition during the development phase. The design of a connector includes a great many stages, running from the specific request from a client *("specs")* through to industrialisation of the product.

The first stage is crucial: risk analysis. Here the aim is to identify and quantify the connector's critical points which could affect its level of safety during use. We perform a thorough analysis to identify all and any potential risks. Once this phase is over, we organise a brainstorming session to come up with new ideas. These ideas take shape in the CAD *(computer assisted design)* phase. 3D design gives body to the product, and modelling allows us to explore several avenues. With the most promising models we design test prototypes using stereolithography.1 A comparison between these prototypes enables us to choose such and such a development rather than another. The CAD phase accounts for 30% of the design time. Once the best development pathway has been selected, we start up the dimensioning process *(tolerances, dimensions, etc.)*.

This phase requires extreme care and attention, doesn't it?

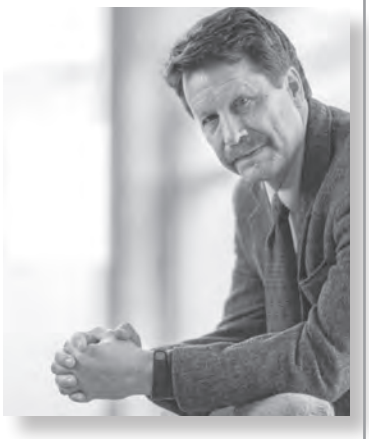
FB: It is by far the most important stage. It gives concrete form to the original idea and requires absolute vigilance. You have to take into account all the parameters that might have an impact on the finished product during industrialisation. This includes the layout and the dimensional and geometrical tolerances to be applied to the piece. Design is not limited to merely drawing a plan, doing a 3D design or producing a prototype. There are several parameters that need to be considered, such as the injection method. The position of the injection point can lead to poor filling quality with repercussions on the piece: traces of flux, visible weld lines, burrs… These are defects that absolutely must be avoided! The filling stage and the risk of venting require all our attention because the evacuation of gas from the plate results in traces of burns on the connector. It's also indispensable to define the method for ejecting the piece from the mould. We have to generate precise zones for the ejectors. Lastly, the person who designs a piece has to tell the toolmaker which level of shrinkage to apply to the mould. Shrinkage is the contraction of the plastic during the cooling process. A shrinkage dimension error can distort the whole piece!

SP: Next comes the control and conformance stage. How do you proceed?

FB: The specifications are our guide. They give us all the design input data. At the end of the process, it is crucial to do what we call the "design verification". Each input data has its equivalent output data. In this way, we demonstrate that the finished product complies totally with the client's request. We then make the final prototypes, which we present to the client for validation. They are manufactured in real production conditions. A mould is created and we inject the raw material requested by the client. Minor modifications are sometimes required. We adjust the dimensioning and make the necessary corrections. All in all, depending on the complexity of the project, it can take between 6 months and two years to get from specifications to final validation.

[1] Stereolithography is a method invented in the 1980s. This rapid prototyping technique is widely used at Technoflex for test prototypes. A digital file is used to manufacture pieces by polymerising resin with a laser.

Robert Califf the new FDA chief?



Founded in 1906 under the presidency of Theodore Roosevelt, the Food and Drug Administration regulates matters relating to foodstuffs and medicines. With the aim of liberalising the system for approval of drugs and medical devices, the US Congress is currently preparing to recast the system. One of the candidates with a good chance of successfully implementing these reforms is Robert Califf. Recently appointed Deputy Commissioner of the Office of Medical Products and Tobacco, he could well take over from Margaret Hamburg at the head of the FDA. In May 2014 he expressed criticism of a regulatory system that has stagnated because it is too time-consuming and costly for companies. Cardiologist and Cardiology Professor at Duke University School of Medicine, Robert Califf is the founder of the Duke Clinical Research Institute and has conducted numerous clinical trials. An official nomination by the White House is expected.

The pharmaceutical industry in the starting blocks

The new year always brings new challenges, and the pharmaceutical industry is no exception! The end-of-patent rush is slowing, new anticancer agents are emerging, access to drugs is becoming more widespread, and the markets currently named “pharmerging” are growing spectacularly, the global pharmaceuticals market is looking promising. Growth in 2014 saw the pharmaceuticals market exceed 1000 billion dollars, i.e. 924 billion euros. Mergers & acquisitions of pharmaceutical firms reached new heights in 2014 with a record 208 billion dollars, three times more than in 2013. With patent expirations encouraging firms to bolster their pipelines of products in development, these transactions are likely to continue in 2015. A recent study by Thomson Reuters Cortellis estimates that 11 new drugs set to hit the markets in 2015 are likely to generate annual sales of more than a billion dollars over the next five years. Among them are an anticancer treatment, a monoclonal antibody and a treatment for heart failure. At the same time, the generics market in the USA is likely to grow. Close to 3500 market authorisations are awaiting approval from the Food and Drug Administration. Biosimilars are set to become more prominent, with the door opened by the recent approval of the first one by the FDA. Lastly, “orphan” drugs are likely to continue their rise thanks to shorter MA times and clinical trials that no longer require thousands of volunteers. According to IMS Health, it could grow by a further 7% by 2018. The big change is likely to be the return of innovation, with high-performing products targeting a broad spectrum of the population. China could enjoy growth of more than 70% as its health system develops, reaching 19% of the world market. But despite this rise the USA will remain the leader in the pharmaceuticals market.

A glimmer of hope for antibiotics?

While most antibiotics were developed between the 1940s and 1960s, research since the 1980s has mainly focused on synthetic molecules, whether derived from natural antibiotics or not. The growing number of therapeutic failures point to a loss in efficacy of these treatments. The reason is the ingeniousness of bacteria, which have constantly adapted and invented ways to combat antibiotics. A new natural molecule discovered by Dr Kim Lewis and his team (Northeastern University Boston) gives rise to hope. Baptised “Teixobactin”, this new antibiotic could be the first in a new drug class. Efficacious and showing no adverse effects on mice, it may be able to counter serious human infections. Two-year studies on humans should commence shortly.

“A fitness centre for high-tech equipment”

In order to meet the exacting standards of the pharmaceutical industry, Technoflex is equipped with a fleet of high-tech machines which require regular maintenance. To find out more, we spoke to Cédric Vassal and Thierry Crabos, two experts from Technoflex’s maintenance workshop.

Sylvie Ponlot: Cédric and Thierry, with all the repairs and maintenance required by our machinery, you must be pretty busy?

Cédric Vassal: Yes, I do handle quite a broad variety of tasks. That means everything from identifying and preparing the right tools to conducting repairs on the production machines: the outfeed lines for IV bags, the tube fillers and the expanding mandrels which hold the reels of the printing film in place on the production lines.

All of these machines are dismantled and brought into the workshop, where we repair them. I also keep an eye on the filtration of the water in the autoclave, and look for ways to improve the work stations: that means simplifying tasks such as steering the autoclave trolleys, or moving the inspection tables for cleaning.

Thierry Crabos: My work is more focused on the plastic injection moulding side of things. I perform preventive maintenance on the machines. Maintenance work on the injection presses *(emptying and changing the hydraulic pipes, etc.)* takes place during the annual shut-down period. We also handle the assembly and disassembly of the moulds every time we switch between production series. We sometimes see burn marks appearing on the PVC components when the material spends too long in the injection port. When that happens we have to take the machine apart and clean it thoroughly. I also do repairs on some of the supporting equipment such as the conveyor belts, the grinders and the mould cooling system.

SP: How do you deal with the risk of contamination when you are called in to deal with a problem in the production facilities?

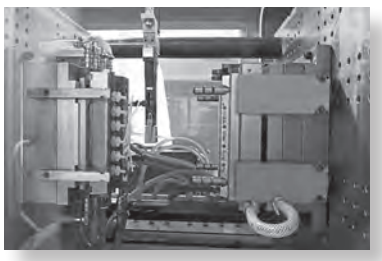
TC: We take every possible precaution to minimise the risk of contamination. When we’re called in to work in a controlled environment, we don’t bring in any tools from outside. We have a full sets of tools within the controlled zone, which are systematically cleaned after each use. Every time we change production series, we clean the moulds before installing them on the presses. They enter and leave the production zone via a special air lock which serves as a transition between the clean room and the outside world. As for the units in continuous production, we schedule maintenance breaks at regular intervals in order to clean the moulds.

SP: Does your technical expertise mean that you’re sometimes called upon for tasks other than maintenance?

CV: Yes, sometimes different departments within Technoflex call us in on account of our mechanical know-how. We develop prototypes for the industrial department and the quality control department. That usually means systems designed to test bags and their connectors.

Cédric Vassal

Thierry Crabos



Injection moulding machine in operation

Twist-off mould and injection screw