FLEXmag

October 2013 #06 The news magazine of the Technoflex Group

Focus

The silent pandemic

Japan, still at the forefront of innovation

Injectable drugs: a long, winding road

TECHNOFLEX

Editorial

The remarkable development of medicinal understanding over the past few centuries, from Pasteur's discoveries down to the present day, has led to the emergence of a healthcare industry fuelled by permanent research and innovation, working to constantly improve our quality of life and extend our life expectancy. But with the huge sums of money at stake, the pharmaceutical industry has also spawned legions of unscrupulous counterfeiters seeking to exploit our legitimate concern for our health and well-being to make a quick profit, even if that involves putting victims' lives at risk.

Long restricted to the world's poorer nations, and focusing on vital pharmaceutical products (malaria treatments, antibiotics etc.), this black market has expanded rapidly since the advent of the internet. Nowadays the counterfeiters have shifted their attentions to the 'therapeutic' drugs widely prescribed in developed nations.

More worrying still, in recent years we have seen the arrival of counterfeit injectable solutions onto the European and American markets! Imitating such specialised drugs demands greater technical know-how and resources, and is thus less profitable, and fortunately the use of flexible bags offers further protection against the risk of fakes. Such is the subject of this issue's Focus article.

It is for the sake of the patient's safety that the development procedures for a new drug are so complex and closely monitored. When this drug is packed in flexible bags the same requirements apply… Along with a few other specific constraints which you can read about in the Business section.

Lastly, while Technoflex is a thoroughly international company, we do not forget our close ties with the Basque Country, and are currently investing in the nearby ESTIA engineering school: learn all about it in our Profiles section.

Happy reading!

Olivier Chesnoy
Chief Executive Officer

Contents

FLEXmag, a world of connections:

Frontpage picture:
Design and prototyping / Emmanuel Arnault (Technoflex R&D)

FLEXmag

The Technoflex group magazine
Zone Artisanale de Bassilour
64210 BIDART – France

Web: www.technoflex.net
E-mail: flexmag@technoflex.net

Publishing Director: Olivier Chesnoy
Editor in Chief: Sylvie Ponlot

Printing: Varela + 34 943 45 89 25

Photo credit: Sylvie Ponlot
© pogocini - Fotolia.com

Design and production:
GENERIS + 33 (0)1 47 51 80 07

Translation: Hancock Hutton

Issue #06 – October 2013

Flexmag is printed on FSC® Mix certified paper

Quick facts

The nanomedicine revolution:

Thanks to its innovative nature, nanomedicine is used to manufacture drugs that interact from cell level through to molecule level. Nanomedicine significantly improves every aspect of medicine: screening, diagnosis and therapy. Nanoproducts or nanostructures can accomplish extremely precise tasks that were previously impossible. Capable of reaching diseased tissue, nanomedicines use smaller doses of active ingredients, thereby reducing the toxic effects of these ingredients. As they are so small they can target the diseased cells accurately without destroying the surrounding healthy cells. Already employed to treat cancer, diabetes and infectious diseases, nanomedicines are set to open up numerous new horizons, leading to high hopes of progress in neurology and regenerative medicine.

EASE, the innovative and productive school:

Early 2016 will see the opening of EASE (European Aseptic and Sterile Environment Training Center) on the university campus of Illkirch (Strasbourg). This highly innovative training centre dedicated to the clean room production professions will mainly be serving healthcare firms. Designed by and for pharmaceutical companies, it will facilitate the block-release training of qualified staff in real aseptic industrial conditions. With a capacity of over 4,000 students, EASE will meet all the requirements of Good Manufacturing Practice. EASE is the European hub of the BTEC International network, of which it is co-founder along with BTES-US (Raleigh, North Carolina).

Schedule

Quarter 4 2013	Show / Venue	Technoflex Booth
october 12 - 15	AAPS Annual Meeting & EXPO 2013 — Denver, United States	Booth 2026
october 22 - 24	InnoPack — Frankfurt, Germany	Booth 41F69
november 20 - 22	COMPAMED — Düsseldorf, Germany	Hall 8B Booth F10
december 03 - 06	CPhI india — Mumbai, India	Booth A33

The silent pandemic

Sylvie Ponlot

Today as many as 1 in 10 medicines sold internationally are counterfeits. In some emerging countries that figure may be closer to 7 out of 10. Counterfeiters target branded drugs as well as their generic alternatives. Responsible for up to 700,000 deaths worldwide every year, the scourge of counterfeit medicines has become a global pandemic.

The Pangea V & VI operations, simultaneously coordinated by Interpol in 99 countries worldwide, including France, led to the dismantling of several production networks and the seizure of millions of counterfeit drugs. Produced predominantly in Asia and then shipped to Europe, these false medicines enter the legitimate distribution chain via unscrupulous wholesalers. In recent year the trade in fake drugs has expanded dramatically in developed nations thanks to the internet. Online sales have become the preferred method of distribution for counterfeiters, attracting millions of web users. Every day more people buy drugs online, oblivious to the fact that 50% of the products on offer are fakes. People turn to the internet for their medicines in order to save time or money, or to freely buy medicines which would normally require a doctor's prescription.

©progcini - Fotolia.com

A serious health risk

Leaving aside the money lost by the legitimate pharmaceutical industry, by far the most important issue at stake here is the risk posed to patients. In the best case scenario, these counterfeit products contain little or no active ingredient. In such cases the medicines are ineffective and the treatment will not work. On the other hand, an excessive concentration of the active ingredients can have some very serious side effects. In order to simplify the manufacturing process, many counterfeiters have no qualms about using toxic substances such as lead paint, wax, arsenic or boric acid, all of which can prove lethal for the unsuspecting patient. Moreover, insalubrious production conditions can cause further complications, as many clandestine laboratories are crawling with bacteria and contaminant particles.

Bag packaging, a method of combatting counterfeits

Until 2010 it was generally only dry medicines which were at risk from the counterfeiters, but nowadays counterfeit injectables are also a serious problem. These drugs are used in the treatment of severe illnesses (cancer, heart problems, serious infections), and fakes have been found in a number of clinics in the USA[1]. However according to the IRACM (Institute of Research Against Counterfeit Medicines) no injectable solution packaged in flexible bags has yet been successfully counterfeited. Filling and sealing these supple bags requires sophisticated equipment and materials: a special filling nozzle to fill the bags, and an adapted connector to seal them (twist-off, luer-lock etc.) The filled bag can only be correctly sealed via a thermo-sealing process, which requires highly specialised equipment. Furthermore, injectable products in sealed bags are always packed in additional protective packaging. This additional level of security makes pouched products all the more difficult for counterfeiters to reproduce.

[1] *Flexmag #4 : The boom in counterfeit products P3*

Secret "laboratories"

Appalling figures of counterfeit drugs:

- **1 sold drug in 10** is likely a fake (FDA)
- Responsible for **700 000 deaths per year** (IPN – 2009)
- A **$ 75 billion** fake drug trafficking (WHO – 2010)
- **7 millions** doses of fake medicines seized by European Customs (EC – 2009)

EC: European Commission
FDA: Food and Drug Administration
IPN: International Policy Network
WHO: World Health Organisation

Injectable drugs: a long, winding road

Sylvie Ponlot

From research into molecules through to sale of the end product, 12 or 13 years are required to develop an injectable drug. The "gestation" of medicines in bags involves the same four phases as standard drugs, but with a few more specific constraints. Spotlight on a road fraught with pitfalls.

Once exploratory research and preclinical testing of the molecules have been completed, Phase I clinical trials start on healthy volunteers. They serve to determine the maximum dose tolerated by man, as well as the administration method. Phase II evaluates the dose-effects relationship, defines the drug dosage and detects short-term adverse effects. It is also the starting point for development of the primary packaging. In order to be compatible with the drug and to guarantee perfect stability, the material used for the future bag has to conform to numerous parameters. The aim is to avoid any interaction with the product that may pose a threat to the quality of the injectable and hence to the patient's safety.

Key point: the raw material of the bag. This material undergoes a study of **extractables** and **leachables**, then an assessment of toxicity and risks. At this stage, Technoflex R&D also verifies that compatibility between bag and spout is optimal (diameter, aseptic filling or not, etc.).

Factors other than the composition of the drug can affect the stability of the product in contact with the container. This is the case of ambient temperature and humidity. The stability study carried out also has to take account of low temperatures as well as the freezing/thawing cycles, particularly for biotechnologies and blood derivatives. For certain preparations[1] it is also indispensable to consider the effects of exposure to light.

Phase III could be called the "comparative testing" phase. The drug's properties are compared with a placebo or an existing drug. Only if an acceptable benefit-risk ratio is proven can a MA (Market Authorisation) be awarded. At this stage of testing, the injectable's primary packaging is ready: polypropylene, EVA or PVC depending on the nature of the drug. The final phase starts when the drug is marketed: this is pharmacovigilance. Knowledge of the drug in actual conditions of use is furthered in this way.

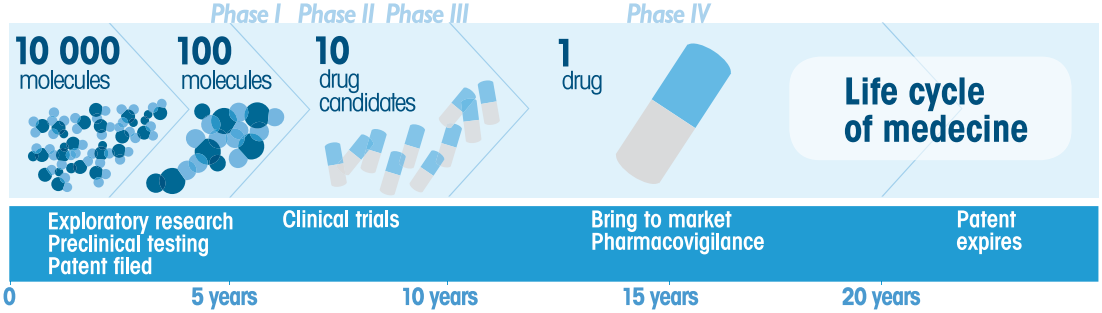
The goal of therapeutic research is to develop high-quality, efficient injectable drugs. It is a long, complex process. The expertise of all the main players is required for innovative treatments to emerge.

Statutory

Extractables and leachables

Extractables are compounds of plastics that can be extracted by solvents with physical and chemical properties that differ *under aggressive conditions*.

Leachables refer to compounds that can be released by plastics into the pharmaceutical products *under normal conditions of use*.



[1] *Flexmag #5 : The parenterale nutrition*

Japan, still at the forefront of innovation

An ageing population with a long life expectancy means that the cost of healthcare in Japan will continue to grow steadily. The Japanese drug market is the world's second largest behind the USA, with domestic firms still taking a 60% share. The continued dynamism of this market, and the government's efforts to promote innovation, have encouraged major firms to establish laboratories in Japan. Any company conducting R&D in Japan is eligible for substantial tax credits. Furthermore, the prices commanded by innovative drugs are protected from the severe reductions caused by the arrival of generic competitors on the market.

In recent years a number of Japanese pharmaceutical firms have also begun buying up companies elsewhere in the world, boosting their international presence. By investing in mature and emerging markets, they have been able to anticipate and offset losses linked to the expiry of patents. Some of these firms are now turning their attentions to oncology, and expanding their new product portfolios. A number of anti-cancer treatments and new molecules developed by Japanese labs are currently in Phase II or III of development or approval. Applications for the Market Authorisations required to bring these products to market will be submitted simultaneously with the relevant authorities in Japan, Europe and the USA.

The government's innovation support policies, combined with intelligent development strategies, have allowed Japanese pharmaceutical firms to continue growing and expanding their market share, unlike their Western counterparts. The Land of the Rising Sun looks set to remain fertile ground for the pharmaceutical industry for years to come.

A market under close scrutiny

Over the last decade or so the Japanese regulatory bodies have succeeded in cutting the Market Authorisation process down to 13 months. Firms must first register their requests with the Pharmaceutical & Medical Devices Agency, who assess the effectiveness, safety and quality of the new product. The Ministry for Health then issues an official decision, after consultation with the Council for Pharmaceutical Affairs, Food Safety and Public Health. While many foreign firms now launch new products directly without seeking local partners, some multinationals still prefer to form strategic alliances with specialists on the ground.

Japan in numbers:

- **128 million** inhabitants
- Life expectancy:
  Men **79 years**
  Women **86 years**
- Population below the age of 15: **13%**
- Population over the age of 64: **24%**
- Median age: **45 years**

ESTIA: a breeding ground for engineers and businesspeople

Sylvie Ponlot

Founded at the initiative of the Bayonne Chamber of Commerce and Industry in 1996, the École Supérieure des Technologies Industrielles Avancées is the top engineering graduate school in the French Basque Country. It currently has 170 students. Thanks to dual degree partnerships with the Bilbao Engineering School and three leading English universities, the courses are trilingual and provide future engineers with a French and European dual degree. The disciplines taught cover three main industrial functions: digital design and innovation, mechatronics and embedded systems, and organisation and industrial management. The programme alternates between theoretical classes and practical internships.

One of Technoflex's key undertakings is to foster and encourage the professional integration of people aged under 26. Technoflex R&D regularly takes on students between their 1st and 3rd years for placements. Depending on their level of qualification, they work on Technoflex's mechanical reinforcement modules and/or manage mini-projects. They are supervised by an R&D manager, an expert professor and external tutors. The 3rd-year placement lasting 6 months is an integral part of the thesis defended by the student.

ESTIA ENTREPRENDRE, the school's department dedicated to new technologies, has first-level and second-level business incubators. *"The first-level incubator supports the future structure during its initial development phases: validation of project feasibility, drafting a business plan, product development, identification of future clients... It currently hosts 15 business start-ups"*, says Jean-Roch Guiresse, Director of ESTIA. *"Once the project has been launched, the new company joins the second-level incubator. Throughout the start-up phase it is supported and monitored, and this help is indispensable to ensure it lasts"*. A recipe for success! Over the last 10 years more than 70 companies have started up, monitored, and this help is indispensable to ensure it lasts". A recipe for generating 700 jobs of which 75% are for engineers.

Strongly involved locally, Technoflex also invests in the ESTIA Enterprise Foundation, which it co-founded and which brings together companies keen to develop convergence between higher education and applied research. For the company it is an opportunity to showcase the plastics and healthcare professions to young engineers and to play a role in society. Five ESTIA engineers now bring their expertise to Technoflex.

Camille Azaïs, apprentice engineer

"I have been at ESTIA since 2010, taking courses for degrees in Organisation & Industrial Management and Industrial Engineering from the Bilbao school. My preparatory classes were in maths and physics with an IT option, so I had never worked in a company before. I decided to do my two-year apprenticeship at Technoflex. As well as being close to ESTIA, Technoflex has the advantage of being human-sized, but above all, it has a strong focus on IT. My tutor Eric Pariès has given me several development projects. For example I have developed and configured the integration of results of inspections on our products in order to integrate them into our computer assisted project management module. I also developed and configured the stock management applications of the warehouses and trained users in these new tools. I also had to migrate the management of training and accreditations from the project management module to a new SharePoint tool. All these projects aim to optimise the industrial information system at Technoflex."