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Injectables: slow but certain development

Dual-Mix™, the innovative solution for error-free reconstitutions

Healthcare's latest helpers

Editorial

Olivier Chesnoy
Chief Executive Officer

After more than two centuries of improvements, injectable drugs have brought many advances to medical treatments. This progress has been achieved in collaboration between the medical, hospital, pharmaceutical and industrial sectors. The "Focus" section of this issue takes a look at this long and incredible development.

One of the difficulties is that injectable molecules which are sensitive or unstable in a reconstituted medium, are recommended in many treatments. To make them easier to reconstitute and administer, our teams have designed and developed a double chamber bag which allows the main active ingredient in the form of a powder or lyophilizate and the associated diluent to be packaged together, thus facilitating the extemporaneous preparation of the infusion.

Another recent development is rapid access to products and treatments: for patients awaiting an organ transplant or people needing rescue after a natural catastrophe, every second is crucial. The use of UAVs in a military context is controversial, however they offer innovative possibilities in the healthcare sector, as for example in the transportation of bags to areas which are difficult to access. Read about this in our "Perspectives" section.

Finally, we always remember that every bag is intended to treat an ill person. Consequently, primary packaging for injectable medicines must be fault free. At Technoflex, the team in charge of release of finished products puts our bags/connector kits through an array of tests to prove that they have the excellence and high quality which is essential for the patient and our customers. We invite you to discover them on the "Profiles" page.

Happy reading!

Flexmag, a world of connections

Frontpage picture: © Auremar-Drug supplementation in dextrose solution

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Quick facts

China: Accelerated marketing of imported drugs

The China Food and Drug Administration (CFDA) is willing to authorize foreign laboratories to apply for a marketing authorization once international studies have been completed. The imported drugs could arrive on the market without having to undergo clinical trials again in China. A move which would stop many patients having to resort to the black market to gain access to innovative products!

A mutual recognition agreement between the FDA and the ANSM

Already inspected by the FDA in 2015, then reassessed in 2017, the ANSM (French Agency for the Safety of Medicines and Healthcare Products) has just been officially approved by the United States to inspect French pharmaceutical sites on behalf of the FDA. The new text definitively endorses the first agreement signed in 1998 and targets all pharmaceutical and biological products for human and veterinary use. The ANSM specifies that this step will allow the resources allocated to inspections within the European Union to be rationalized in order to roll out more resources in other regions of the world.

Boston, world biotech capital

R&D researchers, start-ups, big pharma companies, and virtually the entire international pharmaceutical industry has been based for several years in Boston. The interest generated by Boston began at the end of the 1970s when academic centres and laboratories began to create close links. Today, the biopharmaceutical sector has more than 60,000 employees, and more than 1,600 molecules are being developed in the state of Massachusetts.

© Sean Pavone

Agenda

1st & 2nd quarters

CPhI North America	April, 24-26	Pennsylvania Convention Center, Philadelphia	CPhI north america icse FDF	**Booth 2010**
ISCT	May, 2-5	Convention center of Montreal, Montreal	ISCT 2018	**Booth 408**
ISBT	June, 2-6	Metro Toronto Convention Center, Toronto	ISBT	**Booth 1315**

Events listing available at www.technoflex.net

Injectables: slow but certain development

When treating a pathology, the choice of drug and its galenic form[1] is governed by the patient's state of health and the desired administration method. Use of the injectable form, for a long time feared and denigrated, has increased significantly since the end of the 19th century. Today it is one of the star performers among pharmaceutical forms. A success which is also driven by developments in containers. A look back over more than 150 years of innovation and development.

Sylvie Ponlot

The idea of administering a drug parenterally to the human body is not recent. It first appeared back in the 17th century, shortly after the discovery of the circulatory system. But the unconvincing results of the first injections *(infections, gas embolisms, toxicity of products)* curbed their development. So much so, that at the beginning of the 19th century, Dr Barbier, a doctor at the Hôtel-Dieu in Amiens declared "we will just mention this procedure briefly. It has too many disadvantages, and is even dangerous, to ever become common". However, intravenous injection reappeared several years later. It was only carried out as a last resort, when the patient was in a critical state.

It wasn't until Pasteur came along that the cause of many cases of infections was understood. These were due to the presence of microorganisms in injectable drugs and the lack of asepsis during injection. In 1895, the French pharmacopeia published a method of sterilization which became compulsory for injectable forms. Thanks to this step and the introduction of good administration practices, the so long decried injectable drugs finally achieved recognition. At the beginning of the First World War, the first edition of the *Dictionnaire des Spécialités Pharmaceutiques*[2] listed 40 injectable products.

Increasingly sophisticated injectable products

At the beginning of the 20th century, the use of infusion solutes took off, particularly in the treatment of infectious diseases and hemorrhages. In 1926, the French pharmacopeia listed glucose solutions, then, ten years later, bicarbonate solutions. Their use in major wars around the world brought numerous improvements and preparations became increasingly complex. The first injectable lipid emulsions appeared in the 1960s and were recognized as essential for parenteral nutrition. Hospitals acquired specialized units for compounded formulations[3].

At the same time, a new technique came into being: freeze-drying[4]. A spin-off from the food industry, it created real enthusiasm in the pharmaceutical industry. This process, which preserves product structure, is used for serums, some vaccines and blood-derived products such as human plasma. In the last decades of the 20th century, the range of products able to benefit

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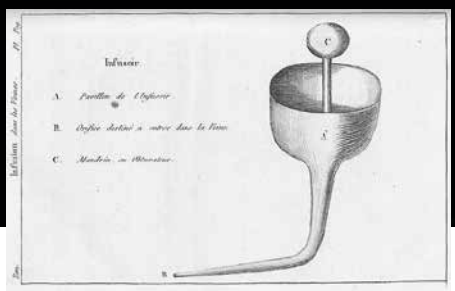
Nanomedicine



Reusable container for IV drugs – beginning of the 19th century

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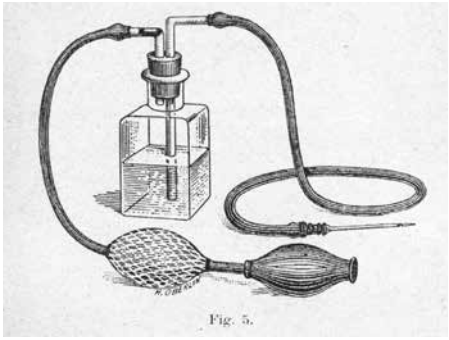
from freeze-drying extended to molecules which are unstable in solution and which require reconstitution before being administered to the patient.

Today, injectable drugs are almost exclusively made by the pharmaceutical industry. Scientific research carried out in laboratories is developing ever more innovative and effective products. The new galenic forms are mainly administered intravenously, with solutes acting as the therapeutic carrier. This is the case for example with nanomedicines [5].



Infusion set – end of the 19th century

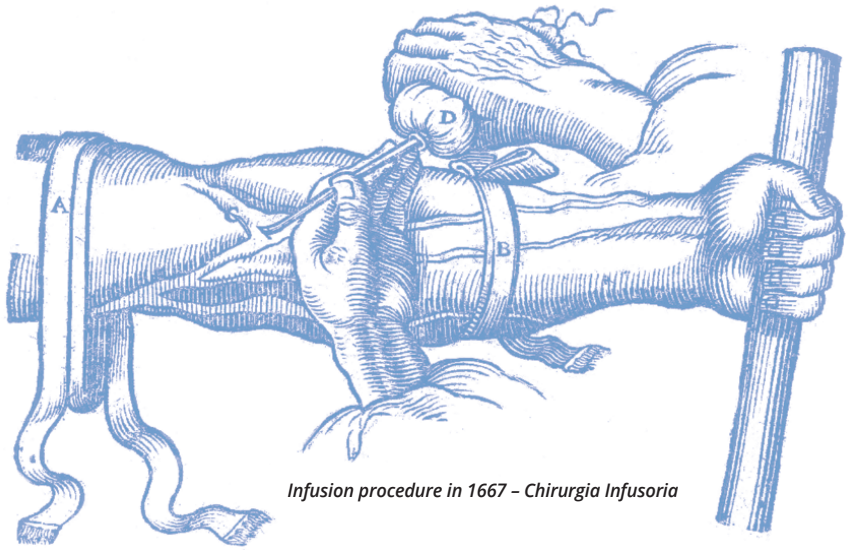
From the goose feather to the needle, from reusable to single use containers

The boom in injectable solutions is inseparable from the development of means of administration and containers. The arrival of new raw materials has shaken up administration practices and storage methods for intravenous products. In the 17th century, you had to reveal the vein and incise it before injecting with... a goose feather! As for injectable drugs, they were packaged in a reusable container extended by a pipe. Shortly before 1850, Charles Pravaz revolutionized the administration of injectables by inventing a hollow silver needle. The innovative glass body of the syringe allowed Pravaz to control the quantity of drug injected. Gradually, single use syringes replaced the traditional reusable glass syringes.

Pravaz syringe

At the end of the 19th century, the first single dose vials, which could contain up to 1000ml of solution, appeared. It was no longer necessary to decant the liquid, they were ready-to-use! The top part of the vial in the form of a hook was suspended while the lower tip, when broken, was connected to the patient by a tube fitted with a needle. So, the infusion operated through gravity. Graduated glass bottles *(reusable)* with a dropper chamber replaced them until the arrival of plastic materials. From the 1970s onwards, synthetic polymers were used in the manufacture of new containers: flexible bags. Hard wearing and lightweight, they are available in a wide range of volumes. First manufactured in PVC, then in PP, EVA or FEP, flexible bags, because of their intrinsic nature, are compatible with the majority of injectable drugs. And the advantages are considerable: a closed system, transparency, inert materials, multiple compartments, tolerance of negative temperatures, UV barrier, etc. They are also used for unstable products such as ternary mixtures for parenteral nutrition, some antibiotics and anti-cancer medications, in preparation at the time of use.

So, it was at the end of a long almost two hundred-year journey that injectable products reached the level of quality that we know today. Their development, closely linked to that of



Infusion procedure in 1667 – Chirurgia Infusoria

Vial with hanging hook for IV solution © Aguettant

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means of administration and containers, has made the drip simple and safe. For despite their late maturity, injectable drugs now play a dominant role in modern medicine. Something which the German Dr Michael Ettmüller predicted back in 1668: *"There's no quicker source of relief than the drip for sudden-onset, acute disorders"*.

[1] The galenic form of drug is the physical form in which it will be administered.

[2] Le Dictionnaire des Spécialités Pharmaceutiques was published by Louis Vidal and Henri George in 1914. Soon, only Vidal's name remained. In 1976 it became the work of reference for drug monographs.

[3] Flexmag 05 – Parenteral nutrition

[4] Lyophilization or freeze-drying consists in gradually removing water from a previously frozen product by lowering the pressure in its container. The water changes from a solid state to steam without going through the liquid stage.

[5] Flexmag 10 – The infinitely small revolutionizing medicine

Flexible bags for IV drugs

EVA - CryoCell® bag

Dual-Mix™ bag

FEP - SafeCell® bag

Sterile IV bag

EVA - 3-tube bag

PP - 3-chamber bag

Dual-Mix™, the innovative solution for error-free reconstitution

Drugs which are unstable in solution have, until today, been packaged in powder or lyophilizate form in glass bottles. They then need to be reconstituted at the patient's bedside, or in the hospital pharmacy, in aseptic conditions. There are many errors and accidents linked to reconstitutions which pose a real risk for patients and healthcare personnel: errors with diluents, dosage errors, needle stick injuries,contamination[1], etc. To reduce these risks, Technoflex has developed Dual-Mix™, an innovative primary packaging which meets three challenges: storing the drug to be reconstituted, making its reconstitution secure and ensuring the safety of healthcare staff and the patient.

Sylvie Ponlot

Dual-Mix™ is a patented bag which contains a drug in powder/lyophilizate form and the associated diluent in the same dual-chamber primary packaging. It facilitates and makes safe the packaging of very unstable molecules which need to be reconstituted just before administration to the patient. Designed in Inerta®[2] polypropylene, the material in contact with the main active ingredient and the diluent is fully compliant with European and American pharmacopoeias[3].

The bag is delivered sterile and consists of a lower chamber for the diluent and an upper chamber for the main active ingredient. The latter is the component which requires the highest protection. So, a peelable aluminum foil, placed on both sides of the bag, protects the powder or the lyophilizate from light and humidity. It is easy to remove at the time of use, and the nurse can very simply check the integrity of the product before its reconstitution.

The two chambers are separated by a peelable seal. It is sufficiently hard wearing not to break spontaneously during transport or storage, but is however easy to break by using simple appropriate pressure on the lower chamber to ensure that the main active ingredient and its diluent are mixed just before infusion. Reconstitution is achieved in under 10 seconds and in a totally safe way. The bag's closed system ensures that the product is sterile and avoids risks of contamination during handling. Finally, Dual-Mix™ has a twist-off compatible with the majority of spikes and infusion sets used in Europe and the United States.

Dual-Mix™ is available in three different volumes of 50, 100 and 250ml and opens the way for standardized ready-to-use doses of drugs.

Dual-Mix™ dual chamber bag

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By avoiding the need in some cases for preparation in the hospital pharmacy, Dual-Mix™ optimizes preparation and administration by medical staff. A not inconsiderable advantage and a great advance, making reconstitution and administration simple, fast and totally safe in a hospital environment, but also during hospitalization at home or in emergency or conflict zones.

[1] In the United States, 1000 people, 58% of whom are nurses, are affected every day by needlestick injuries, generating $1 billion in extra costs. (Source: Becker Hospital Review)
[2] Flexmag 01 – Extractables: storing drugs until they are administered
[3] EP 3.1.1 & EP 3.1.6 / 21 CFR 77.18.10 / USP class VI; DMF #19057; DMF #2007-070

Healthcare's latest helpers

Rural or mountainous regions, non-existent or impractical roads: supplying medical equipment and drugs to the most remote regions is a problem which affects many countries. Almost 750 million patients throughout the world have limited access to healthcare infrastructures. Drones, which have been used for several years in the military context and more recently in e-commerce, offer a solution. When applied to the healthcare sector, they have proved their effectiveness in delivering drugs and medical equipment.

Sylvie Ponlot

In 2016, Rwanda opened its first drone base on the outskirts of the capital Kigali. At speeds of up to 70 km/hr, drones make 150 deliveries of blood bags daily to rural clinics. The positive results of this operation led to the creation of a second base which was due to come into operation during 2018, thus providing coverage for the entire territory of Rwanda. In the same year, the transportation of hearts by drones was trialed in India. This avoids journeys which would be greatly slowed down by traffic jams in large cities or by impractical country roads. For patients awaiting a transplant, every minute is precious. The success of a transplant largely depends on the quality of the graft, and therefore on the speed of the transportation of the organ after removal. Reducing delivery time for the most fragile organs is the challenge being met by India.

The latest to launch such a project is Tanzania. With fewer than one doctor per 1,000 people and only 5,640 medical centers for a population of 56 million people, access to health care is not easy. In order to remedy this, the country is preparing to launch the largest drug distribution network via drones. From 2018, no fewer than 120 drones will carry out up to 2,000 deliveries of vaccines, drugs and blood transfusion equipment per day. The first of the four distribution centers will be based in the capital Dodoma. Each center will be equipped with 30 drones which will carry out deliveries within a 100-mile radius.

Although the advantages of drones have already been proved, there are still significant obstacles to be overcome in Europe. Amongst these are the regulations which govern air traffic. These are very strict and require the allocation of air lanes, authorizations and special training. Safety is also a central concern. The risks of crashing *(overhead electric cables, mechanical failure, etc.)* are very real, and drones are at the moment regularly refused permission to overfly urban conurbations. However, the European Parliament should soon be standardizing legislation on their use.

Medical delivery by drone

Release testing

Every day, the Technoflex team in charge of release testing ensures that products are compliant. Eight people check a representative sample of the batches of bags and accessories manufactured. These painstaking tests are carried out in extreme usage conditions.

Valérie Pichon – Stacking of bags on the sterilization trays before TS

Whether they are manufactured in PP, PVC, EVA or FEP, the bags are really put through the mill during the final tests. Their purpose is to ensure that the primary packaging is harmless, safe and reliable. The first points checked are the impermeability and resistance to pressure of the bag's connection system. After being filled and then plugged by an injection port, a cap or a twist-off, the single or multiple chamber bags are sterilized in an autoclave (122°C for PVC, 125°C for polypropylene). They are then checked for an absence of micro-leaks by being pressed at 0.5 bars of pressure. The seals of the tubing, bags and accessories are all inspected minutely.

EVA bags, a material which does not withstand the heat of terminal sterilization, are filled directly with water then placed in a press. The same procedure is applied to FEP bags, which are used for the suspension culture of living cells.

The second check is the self-sealing of the injection port. This consists in checking that the elastomer of the port remains totally impermeable after several perforations by needles or spikes.

Faultless physical resistance

During their use in a hospital environment, the bags must withstand being handled on multiple occasions: during storage, transportation to the patient's room, being dropped, etc. So, they are put through physical resistance tests. The first check involves the bag's suspension eyelet. In order to prevent any risk of splitting during use at the patient's bedside, the bags are suspended for one hour for volumes lower than 500 ml, and two hours for volumes greater than that. To this routine test is added a second test in compliance with the ISO 15747 standard. This requires the bag to be suspended for one hour with a weight of 1.5 kg attached to the twist-off. The Drop Test, on the other hand, ensures that the bag is resistant to being dropped. Once full, it is lifted to a height of one meter then dropped onto a rigid, hard, smooth surface at an ambient temperature between 20 and 30°C.

The primary packaging of injectable intravenous solutions must be completely fault free. Product batches are only released after completely passing these essential tests.

[1] Flexmag 4 – Terminal sterilization: a process which is never insignificant!

Leak testing – bags in a press

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