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Heat-Sensitive Health Products

The IIR publishes Informatory Notes designed to meet the needs of decision-makers worldwide, on a regular basis. These notes summarize knowledge in key refrigeration-technology and refrigeration-application domains. Each note puts forward future priority developmental axes and provides IIR recommendations in this context.

A significant number of health products (vaccines, insulin, labile blood products, biotechnology products, tissue, organs etc.) are heat-sensitive and a change in their storage temperature can render them unusable, inefficient, even dangerous. Among the top 10 medicines sold across the world, only one does not have any specific temperature requirements. Confronting the issues raised with regards to the temperature control of these health products throughout the distribution chain is essential, with health and economic factors being the priority.

In this Informatory Note, the IIR has defined the issues and challenges that need to be addressed in order to ensure that reliable cold chains, along the distribution chain of products essential to public health, are put in place.

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Healthcare products under controlled temperatures

What is a heat-sensitive healthcare product?

The World Health Organisation defines a healthcare product as any "product that contributes to obtaining or maintaining a state of complete physical, mental and social well-being" [1]. Some countries, like France, use a Public Health Code to give more precise lists of healthcare products, including in particular medicines, labile blood products, organs, body tissues, medical devices, breast milk, etc.

A number of these products are heat-sensitive; this is particularly the case for vaccines, insulin, derived blood products, oncology products, products for treating glaucoma or auto-immune diseases, biotechnology products and labile blood products (plasma, red blood cells, platelets, whole blood), urine samples, tissue for laboratory use, organs and tissues, etc.

What storage temperatures?

Storage temperatures are fixed by pharmaceutical regulations and permissions for market release. Stability studies conducted by manufacturers allow product storage temperatures and times to be determined.

The most common ranges are between +2°C/+8°C, +15°C/+25°C, <-20°C for medicines or +2°C/+6°C, +20°C/+24°C, <-30°C for labile blood products (LBPs). Beyond the difference in storage temperature between medicines and LBPs, an extra constraint – transportation time – is imposed for LBPs. Table 1 below illustrates this information and gives examples of the products affected.

Table 1: *Main storage temperatures for heat-sensitive medicines and labile blood products, and examples of specialties*

Types of products	Storage temperature	Transport temperature	Storage life	Transport time
"Cold" products	+2°C/+8°C	+2°C/+8°C	MA*	MA*
"Ambient" products	+15°C/+25°C	+15°C/+25°C	MA*	MA*
"Freezed" products	<-20°C	<-20°C	MA*	MA*
Other products	specific ranges (<-30°C, +2°C/+30°C,…)			
Untreated whole blood	+18°C/+24°C	+18°C/+24°C	<24h after sampling	< 24h after sampling
Treated whole blood	+2°C/+6°C	+2°C/+10°C	35 days	< 24h after the 24th hour of sampling
Red blood cells	+2°C/+6°C	+2°C /+10°C	35 days	<24h
Platelets	+20°C/+24°C	+20°C/+24°C	5 days	<24h

**Transport time and storage life depend on the products and are defined by the MA (marketing authorization).*

Concerned products examples	Humalog® (Insulin) Xalatan® (collyre for glaucoma) Rophlyac® (blood derivatives) Adotine® (blood derivatives) Evicel® (Plasma)	+2°C/+8°C +2°C/+8°C +2°C/+8°C <25°C <-18°C

Storage temperatures also depend on required storage times. This is the case in particular for Fresh Frozen Plasma (FFP) separated from a total unit of blood whose storage time depends on the temperature, as shown in table 2. This is also the case for urine, stool and sperm samples for laboratory analysis, as shown in table 3.

Table 2: *Maximum storage times for Fresh Frozen Plasma (FFP) according to storage temperatures. Data from the WHO (World Health Organization)*

Product	Storage temperature	Storage life
FFP	-65°C or less	7 years
FFP or cryoprecipitate	-40°C to -64°C	24 months
FFP or cryoprecipitate	-30°C to -39°C	12 months
cryoprecipitate	-25°C to -29°C	6 months
cryoprecipitate	-20°C to -24°C	3 months

Table 3: *Maximum storage times for samples for analysis according to storage conditions. Data from GBEA (Guide for the Proper Performance of Analyses for Medical Biology)*

Analyses	Maximum delivery time	Storage temperature
Cryobacteriological examination of the urine (CBEU)	24h	2h at ambient temperature 24h in refrigerator
Coprology, Parasitology	24h	2h at ambient temperature 24h in refrigerator
Looking for blood in the stool	The same day	In refrigerator
Semen Analysis	<30 minutes	<37°C
Sputum (spit)	<2h	Ambient temperature
Additive	Lapsing date	4°C to 25°C

What effects does temperature have on these products?

Temperature variations can have significant effects on health products [2].

They can be affected by the degradation of their active ingredient, by the modification of their excipients or by the deterioration of their packaging and wrapping. These temperature impacts can make these products unusable, ineffective or even dangerous. In all cases, through bad treatment or absent treatment, they lead to increased risks for the patient [3].

Temperature effects on health products can be of microbiological, physical or physico-chemical type. The effects of high temperatures, “heat effects” and the effects of low temperatures, “cold effects” should be distinguished.

“Heat effects” can be of physicochemical, microbiological or chemical type, like the deterioration of the form of a dosage, the denaturation of the active ingredient, the appearance of toxic products or degradation. Heat progressively deteriorates the active ingredient of vaccinations or insulin, making them ineffective. For labile blood products, heat can alter blood’s recombinant coagulation factor VIII and cause death through haemorrhaging, and can also cause bacterial development that can lead to a fatal septic shock. These effects are in general cumulative and progressive. The deterioration of health products generally follows an Arrhenius equation.

“Cold effects” are essentially physicochemical and are linked to freezing, but also sometimes to chilling. They can be translated by a change in the configuration of protein-based products. Vaccines and insulin are denatured by freezing, while hydrocortisone and lactulose are destroyed by chilling. Patients who receive these products have not received the proper care. For labile blood products, refrigeration can lead to the destruction of the

membrane of red blood cells (haemolysis) and the release of haemoglobin, which causes pain, fever, jaundice and death. Refrigeration can also cause glass ampoules to break, irreversible crystallisations and the loss of a product's homogeneity or precipitates that make products unusable. "Cold effects" are threshold effects, immediate and generally irreversible.

Issues relating to controlled temperatures in the health sector

Logistical issues in maintaining controlled temperatures in the healthcare supply chain

From the drug laboratory to the patient, medication supply chains are becoming increasingly diverse and complex, while the quantities to be stored and transported can vary from a single dose to several million doses.

An increasingly international market with transactions on a global scale, specifications imposed by some producers, and the development of generic drugs and new compounds, particularly in the biotechnology sector, have all led to developments in laboratory logistics, with a much greater requirement for controlled temperatures for periods that may extend over several weeks. At the other end of the supply chain, changes in clinical practices including the delivery of hospital care in the home[4] have changed distribution requirements, especially where controlled temperatures are concerned.

The diagram below shows the vast range of different actors in the supply chain for pharmaceuticals in the French market. The challenge of ensuring that each actor in the chain maintains the correct temperatures to preserve the products in question represents a substantial issue.

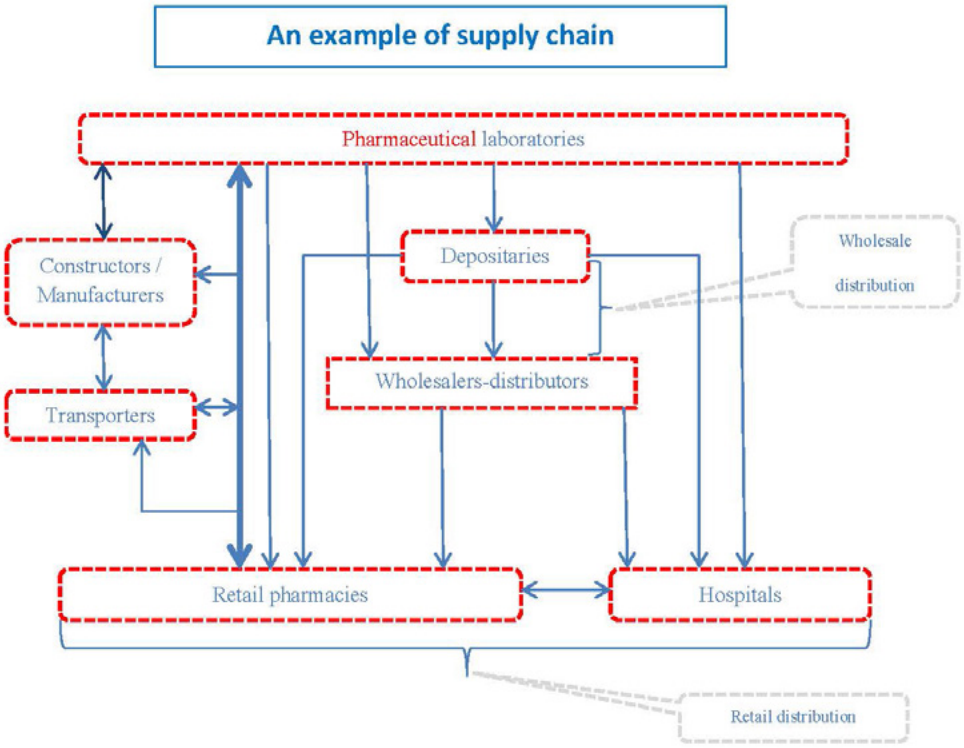

Figure 1: *Players in the pharmaceutical supply chain*

Hardware issues

Even though there is a well-established cold chain for "cold" products to be stored in the range of +2°C/+8°C, frozen products to be kept below -20°C and for blood products, there is no established method of maintaining "ambient" temperatures in the range of +15°C/+25°C or more generally for products to be kept below +25°C or +30°C.

Refrigerated products may be stored in refrigerated warehouses, floor spaces or rooms, or temperature-controlled chambers of all sizes ranging from a few liters through to several thousand cubic meters. Duplicates may be produced for major products, but for this to be effective, there must be full redundancy, which is not always the case.

Refrigerated or frozen products are transported in isothermal or refrigerated packaging, in temperature-controlled vehicles, and by air or sea containers. These various solutions often compete with one another but they are more complementary than competitive where the transportation of pharmaceuticals are concerned: the packaging assists in managing transfers more effectively, and vehicles help to manage the conditions created by packaging and the environment.

Hygiene and financial issues

There are around 50,000 drug product lines worldwide. "Cold" products represent around 500 of these lines, with 1 to 2% of the market by volume in France, yet 10 to 20% by revenue. They are experiencing substantial annual growth rates of over 20%, due in part to products emerging from biotech labs. The prices of these products vary greatly. While vaccines may cost just a few euros, the prices of certain specialist biotechnology products may exceed EUR 1,000. The average value is around EUR 60 per dose. Among the world's ten best-selling drugs, representing 8.6% of the market, five should be stored at temperatures between +2°C and +8°C and four between +15°C et +25°C, with only one not having a specified temperature range [5].

Table 4: *The world's 10 best-selling drugs in 2012, based on data from IMS Health*

+2°C/+8°C (5 products out of 10)* **<+30°C (4 products out of 10)***

Product	Laboratory	Therapeutic class	Global market share in 2012
SERETIDE	GSX	Anti-asthmatic	1.8%
HUMIRA	ABBOT	Anti-rheumatism	1.0%
CRESTOR	ASTRAZENECA	Anti-cholesterol	1.0%
ENBREL	PFIZER	Anti-rheumatism	0.9%
NEXIUM/INEXIUM	ASTRAZENECA	Anti-ulcerous	0.9%
REMICADE	MERCK&CO	Anti-rheumatism	0.9%
ABILIFY	BMS/OTSUKA	Neuroleptic	0.8%
LANTUS	SANOFI	Anti-diabetic	0.8%
MABTHERA	ROCHE	Anti-neoplastic	0.7%
CYMBALTA	LILLY	Anti-depressant	0.7%
TOTAL			**8.6%**

The market for vaccines is highly concentrated, with 5 laboratories sharing 80% of the global market. Vaccines represented less than 3% of the drug market in 2009, but are experiencing annualized growth in excess of 11.5%. Annual revenue is expected to reach USD 52 billion (EUR 42.3 billion) in 2016, compared to USD 25 billion (EUR 20.3 billion) in 2012 and just EUR 9.7 billion in 2006. European manufacturers produce 90% of the world's vaccines, with 84% of their production being exported, equivalent to 3.5 billion doses annually out of the 4.7 billion that are consumed by a global population of over 7 billion.

Biotechnologies are not yet a mature market, with only 11% of formulations being commercially available, 19% undergoing approval and 70% of products still in development. They currently attract annual revenues of EUR 1.5 billion in France and EUR 219 billion in the USA.

Blood products are a vital part of the sector, with almost three million blood donations taking place in France annually across 17 suppliers with a total of 152 sites, giving a total annual revenue for the French blood industry of EUR 868 million in 2012. In 2012, Brescia Hospital in Italy assessed the value of a blood bag at EUR 800.

Regulatory issues

All hardware and transportation and storage solutions must be fit for purpose. At present, there is no sufficiently developed regulatory or standards framework [6] at a national or international level. Best practice guidelines for bulk distribution of medication intended for human consumption [7] remain very vague on the terms used and therefore leave the door open to differing interpretations, with terms such as “appropriate and adapted vehicles” and “approved packaging.” The only obligation that matters is to achieve the correct result: demonstrating that the medicine’s storage requirements have been complied with throughout the process of warehousing and transportation.

The World Health Organization (WHO) publishes rules, recommendations and requirements for certain products, with a particular interest in vaccines and vaccination campaigns funded by the United Nations. Its PQS program [8] therefore defines requirements for the cold chain for vaccines and for equipment and solutions used in this context. Similarly, the WHO has issued technical specifications for transportation of labile blood products.

European, American, and Japanese pharmacopoeia specify certain rules in relation to heat-sensitive pharmaceutical products, defining the principal temperature ranges in particular.

Standards for qualification tests and calibration of temperature monitoring hardware as well as transportation and storage equipment do exist, but the latter in particular generally require some adaptation in order to meet the requirements of the pharmaceutical sector.

Problems to solve for a quality cold chain

Get to know the behaviour of products

Knowledge of temperature sensitivities of health products requires long and expensive stability studies. To access the market quickly, these studies can be abbreviated, which leads to more serious storage constraints. Accordingly, in 2011, 50% of medications introduced in France must be kept between +2°C and +8°C, while more detailed surveys could help to reduce these constraints. For example, a stability study of an Adenovirus vector demonstrated its stability at +4°C, whereas up until that point, it was kept at temperatures of less than -70°C. The economic as well as the sanitary challenges are consistent between -70°C and +4°C.

Optimising the storage of heat-sensitive health products is necessary to consequently reduce costs.

Know the constraints, needs and establish appropriate requirements

To establish a quality cold chain, it’s essential to know the needs of the users, logistics circuits, hospital routes, dispatchers’ rounds, and international logistics circuits. It’s also essential to take the constraints of the patient at home as well as in hospital into account, but also any possible flexibility and any corresponding challenges, including financial.

Communication between the health and refrigeration fields is essential to bring the best solutions from the refrigeration field to solve problems in the health field.

Developing solutions for ambient products is a significant challenge when taking their importance on the market into account. Knowledge of genuine needs, temperature or time tolerances for example, is critical.

Choose and develop the right solutions

The solutions that have been developed and put into place so far are very often solutions that have been developed for other uses. The household refrigerator is often used as a climate chamber at dispensing pharmacies, the standard refrigerated lorry is used to transport temperature sensitive health products, which have a low inertia and are fragile [9],...

It's necessary to see how adequate these solutions really are when it comes to fulfilling needs; to modify them, as the case may be, to properly respond to requirements, or even to develop targeted solutions [10]. The technology and equipment exist to answer the needs of temperature sensitive products.

Qualify and certify solutions

The qualification of these solutions and equipment is crucial [11]. This can be carried out by each user, but more efficiently by independent certification and labels. For this, technical guidelines must be established as well as testing and performance standards. Labels exist for packaging and transport equipment. Standards have been set up for packaging (NFS 99700 [12]) and time-temperature indicators and integrators (NF 18 100). Projects are on course for the qualification and certification of fixed and mobile chambers (FD X 15140 and CEI 60068-X [13]), and the normalisation of thermometers and recorders (NF EN 12 830 [14]). The work must be carried out and consistent on a worldwide level. These labels, certificates and standards must also be recognised by pharmaceutical regulation and the correct authorities, and passed by the guides of good practice.

Implement good practice guides

The existence of adapted solutions is not enough to guarantee a quality cold chain-practice is of the utmost importance. It's necessary to explain, raise awareness, and inform health professionals as much as logistics or refrigeration workers about the specificities of the cold chain for health products.

Laboratory professionals, logistics professionals, transporters and distributors, dispensary and hospital pharmacists, patients during dispensing, refrigeration professionals, builders and manufacturers, contractors and maintenance companies must all have adapted quality information.

Measure, analyse and improve

It's not an efficient cold chain without tracking and recording temperatures, and regular evaluation of the solutions put in place and their efficiency. As pharmaceutical data retention periods can be very long, so it makes sense to choose ways of recording this data that are adapted to needs. The use of information technologies, resorting to "big data", analysis in real time, automation of data analysis, and connection of equipment will be essential in the future. The reliability of this tracking and recording will also be characterised by regular and adapted calibrations and meteorological testing.

Conclusion

The cold chain for health products, or more precisely the logistics of heat-sensitive health products under controlled temperatures, represents not only a major public health challenge but also a financial challenge. Temperature control throughout the chain, and its traceability, allows us to significantly improve the efficiency of treatments, to reduce risk for patients and the costs for the society.

At a time when the costs of certain treatments are spiralling and governments of all countries are striving to reduce healthcare costs, refrigeration professionals can contribute to the significant improvement of the efficiency of the distribution and storage of heat-sensitive products. How? By ensuring the best and most adapted systems, solutions, practices and guides are made available.

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Recommendations

In order to adequately address health-related and economic issues concerning the distribution of heat-sensitive health products, the following factors regarding the implementation of reliable cold chains need to be considered:

- a sound knowledge of product temperature sensitivity, thereby allowing optimal, cost effective storage conditions, as well as addressing any logistical constraints linked to patients' needs,
- the introduction of adequate refrigerating equipment in order to meet the above goals. This requires close co-operation between healthcare professionals, prescribers of the products, as well as refrigeration specialists responsible for providing the necessary technical solutions,
- the qualification of these solutions and equipment based on recognized norms and standards,
- the implementation of good practice guides in order to raise awareness, inform and train health professionals, as well as logistics and refrigeration specialists, about the specificities of the cold chain for health products,
- continuous monitoring of the reliability of this cold chain thanks to temperature recording and regular evaluation of solutions that have been implemented.