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BRIEF REPORT

Thermolabile Drugs. Operating Procedure in the Event of Cold Chain Failure☆

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KEYWORDS
Drug stability;
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Refrigeration;
Cold chain

Abstract
Objective: To establish a standard operating procedure in the event of cold chain failure.
Method: We selected thermolabile drugs included in the hospital's pharmaceutical guide. We performed a review of the available literature, classifying each drug into a given category with an intervention protocol for each one.
Results: We reviewed 254 drugs (162 active ingredients). Categories were: A (stable ≥28 days at 25 °C): 65 drugs; B (≥7 days at 25 °C): 47 drugs; C (≥48 h at 25 °C): 30 drugs; D (<48 h at 25 °C): 47 drugs; E (unstable >8 °C): 12 drugs; F (batch-dependent) 22 drugs. Thirty-one drugs were not classified into any category.

The intervention protocol consisted of establishing a system to monitor the products concerned, and discarding or returning them to the laboratory if they were to exceed the time or temperature limit indicated for each category.
Discussion: The aim of this study is to make intervention quicker in the event of cold chain failure.

PALABRAS CLAVE
Estabilidad;
Conservación de fármacos;
Refrigeración;
Cadena de frío

Medicamentos termolábiles. Protocolo de actuación en la rotura de la cadena de frío

Resumen
Objetivo: Establecer un procedimiento normalizado de trabajo en caso de rotura de cadena de frío.
Método: Se seleccionaron los medicamentos termolábiles incluidos en la guía farmacoterapéutica del hospital y se revisó la bibliografía disponible, clasificándolos en categorías con un protocolo de actuación en cada caso.

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Resultados: Se revisaron 254 medicamentos (162 principios activos). La distribución por categorías fue: A (estable ≥ 28 días a 25 °C): 65 medicamentos; B (≥7 días a 25 °C): 47; C (≥ 48 h a 25 °C): 30; D (< 48 h a 25 °C): 47; E (no estable > 8 °C): 12; F (depende del lote): 22. No se clasificaron en ninguna categoría 31 medicamentos.

El protocolo de actuación consistió en establecer un sistema de seguimiento de los medicamentos afectados y desechar o devolver al laboratorio en caso de superarse el límite de tiempo o temperatura establecido en cada categoría.

Discusión: El trabajo realizado pretende facilitar la rápida actuación en aquellas situaciones de rotura de la cadena de frío.

Introduction

The cold chain is the set of logistical links that guarantee that a temperature between 2 °C and 8 °C is maintained during the processes of storage, handling, transport and distribution of drugs. If this is not done, drug properties are liable to change in varying degrees, depending on the temperature reached and the time spent at that temperature.

There are procedures for receiving, storing and distributing drugs in hospitals to ensure that the cold chain is maintained. Standard operating procedures and facilities ensure that the proper temperature is maintained. The complexity of drug distribution processes in hospitals means that there are cold storage facilities available in a large number of locations in the pharmacy department storage areas, as well as the drug storage areas of inpatient units, day hospitals, operating rooms and outpatient clinics, among others.

The cold chain may be broken in many unexpected ways during daily practice (e.g., due to a power failure, cold room breakdowns, inadequate transportation or an error in storage conditions). These incidents may affect just a few units of a drug in a hospital ward or may affect complete clinical containers due to a refrigerator failure.

Administering a drug which has been inadequately stored can have highly variable potential consequences for the patient. Some medications are affected by a temporary and an isolated break in the cold chain: a number of drugs may lose some efficacy of little clinical relevance, while others may have a total loss of activity or may even become toxic.[1]

In addition, a break in the cold chain may have a significant economic impact for the hospital if the full activity of a drug cannot be guaranteed and it has to be disposed of, and there were no conditions established for its return to the pharmaceutical company supplying it.

The potential clinical and economic impacts posed by the loss of this group of drugs make it necessary to have a protocol for maintaining the cold chain and establishing actions if it is broken. This includes a drug stability report, including the time and temperature to which the drug has been exposed. It is also important to provide information about any such event, as affected batches will have to be withdrawn, and it is important to know whether they can be used or not.

The aim of this study was to establish a standard procedure for a break in the cold chain, prepare an updated list (to 2010) on the maximum stability of thermolabile active ingredients at room temperature, classify them according to the possibility of re-using them for certain time periods and provide a communication system on the hospital intranet and via the Internet.

Method

The main active ingredients to be kept at a temperature between 2 °C and 8 °C or in the freezer were selected from the hospital pharmacotherapeutic guide.

A review of previously published studies in PubMed with the MESH Drug Stability, Drug storage, refrigeration and Cold chain was carried out.[2–10] The information available from the summaries of product characteristics (SmPCs) was taken and the pharmaceutical manufacturer was consulted by fax or e-mail if there was any doubt or lack of data.

An Excel table was prepared, which included speciality-specific data, bibliographic references, and the contact details of the pharmaceutical company department, where appropriate.

Table 1 Classification of Drugs.

Category	Stability	Action
A	Stable ≥28 days at 25 °C	Label if it meets the conditions. If not, discard
B	Stable ≥7 days and <28 days at 25 °C	Label if it meets the conditions. If not, discard
C	Stable ≥48 h and <7 days at 25 °C	Label if it meets the conditions. If not, discard
D	Stable <48 h at 25 °C	Evaluate individually depending on the time and temperature reached
E	Not stable outside the fridge (>8 °C)	Discard
F	Stability depends on the batch	Consult laboratory

Table 2 Recommendations After Breaking the Cold Chain.

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Abciximab	Reopro® vial 50 mg/ml	Lilly	8 days at 28 °C (192 h)	Consult lab 28/07/09	916635000	B
Carglumic acid	Carbaglú® 200 mg tablets	Orphan Europe	1 month at <30 °C	SmPCs (2003)		A
Adalimumab	Humira ® 40 mg prefilled syringe	Abbott Laboratories	8 h	Cobos Campos et al., 2006[3]		D
Agalsidase alfa	Replagal® 3.5 mg vial	Shire Human Genetic Therapies	24 h	SmPCs (2006)		D
Alemtuzumab	MabCampath® 30 mg vial	Bayer Healthcare	7 days at 25 °C	Consult lab 20/2/09	934956500	B
Alfacalcidol	Etalpha® ampoules 1 mcg	Leo Pharma	1 year at 25 °C	Bovaira García et al., 2004[4]	932213366	A
Alfacalcidol	Etalpha® ampoules 2 mcg	Leo Pharma	1 year at 25 °C	Bovaira García et al., 2004[4]	932213366	A
Alfacalcidol	Etalpha® drops	Leo Pharma	1 year	Consult lab 16/02/09, Bovaira García et al., 2004[4]	932213366	A
Alprostadil	Alprostadil® 500 mcg/ml	Pfizer	4 months	Cuervas-Mons et al., 2004,[6] García Vázquez et al., 1997[7]		A
Alteplase	Actilyse® 20 mg	Boehringer Ingelheim Spain	3 years at <25 °C	Bovaira García et al., 2004[4]		A
Alteplase	Actilyse® 50 mg	Boehringer Ingelheim Spain	3 years at <25 °C	Bovaira García et al., 2004,[4] Cuervas-Mons et al., 2004[6]		A
Amphotericin B	Abelcet® 50 mg vial	Cephalon Pharma	1 day outside fridge = 9 days in fridge (change expiry date)	Cobos Campos et al., 2006[3] Cuervas-Mons et al., 2004[6]	Specific recommendation	
Amphotericin B	Fungizona® 50 mg vial	Bristol Myers Squibb	2 weeks-1 month	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004[6]		B
Digoxin antidote	Digitalis Antidot® 80 mg vial	Roche Farma Farma	20 days up to 40 °C	Silgado et al., 2006[2]		B
Asparaginase	Erwinase® (ME) 10,000 IU vial	Opi	2 years	García Vázquez et al., 1997[7]		A
Asparaginase	Kidrolase® 10,000 IU vial	Opi C	48 h (1), 7 days (2)	Cuervas-Mons et al., 2004[6] (1) García Vázquez et al., 1997[7] (2)		

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Atosiban	Tractocile® 37.5	Ferring	24 h at 25 °C	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004[6]		D
Atosiban	Tractocile® 6.75	Ferring	24 h at 25 °C	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004[6]		D
Atracurium	Atracurio® 25 mg amp.	Inibsa	1 month 30 °C (loss of 8%)	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004[6]		A
Basiliximab	Simulect® 20 mg vial	Novartis Farmaceutica	4 days at <25 °C	Cuervas-Mons et al., 2004[6]		C
Bevacizumab	Avastin® 100 mg vial	Roche Farma	9 h at 30 °C; 5 days at 15 °C	Consult lab 20/2/09	913248100	D
	Avastin® 400 mg vial	Roche Farma	9 h at 30 °C; 5 days at 15 °C	Consult lab 20/2/09	913248100	D
BH4	Tetrahydrobiopterin® 10 mg	Schircks Laboratories	≤−20 °C: 36 months//≤−10 °C: 18 months//≤+5 °C: 4 months//>6 months at 25 °C: maintains >99.5% activity (although may turn yellow or break more easily)//20–30 °C: expires in 2 months//Can be re-frozen	SmPCs (review year not available)		A
BH4	Tetrahydrobiopterin® 50 mg	Schircks Laboratories	≤−20 °C: 36 months//≤−10 °C: 18 months//≤+5 °C: 4 months//>6 months at 25 °C: maintains >99.5% activity (although may turn yellow or break more easily)//20–30 °C: expires in 2 months//Can be re-frozen	SmPCs (review year not available)		A

Bleomycin	Bleomicina® 15 IU vial	Almirall	28 days	Cobos Campos et al., 2006,[3] Sala et al., 2004,[5] Cuervas-Mons et al., 2004,[6] Silgado et al., 2006[2]		A
Busulphan	Busilvex® 60 mg vial	Pierre Fabre Iberica	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 20/02/09	934833000	F
Calcitonin	Calcitonina Hubber® inject. 100 IU	Valeant Pharmaceuticals Iberica	1 month	Cobos Campos et al., 2006[3]		A
Calcitonin	Calcitonina Hubber® nasal 200 IU	Valeant Pharmaceuticals Iberica	1 month	Cobos Campos et al., 2006[3]		A
Carboprost	Hemabate® 250	Zlb Behring	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 20/02/09	933068117	F
Carmustine	BiCNU® (ME) 100 mg vial	Bms	The appearance of droplets indicates that the product is not fit to be used	Cobos Campos et al., 2006[3]		F
Caspofungin	Cancidas® 50 mg	Merck Sharp Dohme	48 h	Cobos Campos et al., 2006,[3] Sala et al., 2004,[5] Cuervas-Mons et al., 2004,[6] Silgado et al., 2006[2]		C
Caspofungin	Cancidas® 70 mg	Merck Sharp Dohme	48 h	Cobos Campos et al., 2006,[3] Sala et al., 2004,[5] Cuervas-Mons et al., 2004,[6] Silgado et al., 2006[2]		C
Cefonizid	Monocyd® 1 g IM/IV	Rottapharm	18 months	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004[6]		A
Cetuximab	Erbitux® 100 mg vial	Merck Sharp Dohme	20 h	Bovaira García et al., 2004[4]		D

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Cisatracurium	Nimbex® 10 mcg/ml	Glaxo SmithKline	1 month at 25 °C: 5% degradation 1 day outside fridge = 10 days in fridge	Cobos Campos et al., 2006,[3] Sala et al., 2004[5]		Specific recommendation
Cisatracurium	Nimbex® 2 mcg/ml	Glaxo SmithKline	1 month at 25 °C: 5% degradation 1 day outside fridge = 10 days in fridge	Cobos Campos et al., 2006,[3] Sala et al., 2004[5]		Specific recommendation
Liposomal cytarabine	Depocyte® 50 mg vial	Mundi Pharma Pharmaceuticals	72 h at 25 °C	Consult lab 20/02/09	913821870	C
Chlorambucil	Leukeran® 2 mg tablets	Glaxo SmithKline	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 22/12/09	918070301	F
Chloramphenicol	Colircusi cloranfenicol®	Alcon Cusi	Storage: 15 days at 25 °C Once open: 1 month	Bovaira García et al., 2004,[4] Silgado et al., 2006[2]		B
Chloramphenicol	Colircusi de Icol®	Alcon Cusi	Storage: 15 days at 25 °C Once open: 1 month	Bovaira García et al., 2004[4]		B
Anti-inhibitor coagulant complex	Feiba® 4 1000 UF	Baxter	6 months	Sala et al., 2004[5]		A
Daclizumab	Zenapax® 5 mg/ml	Roche Farma	14 days at 25 °C, 7 days at 30 °C	Bovaira García et al., 2004,[4] Silgado et al., 2006[2]		B
Daptomycin	Cubicin® 500 mg vial	Novartis Farmaceutica	60 h at 25 °C	Consult lab 16/02/09	933064200	C
Denileukin diftitox	Ontak® 300 mg/2 ml	Ferrer Farma	No information available	Consult lab 20/12/09	936003700	F
Desmopressin	Minurin® drops	Ferring	1 month	Cobos Campos et al., 2006,[3] Sala et al., 2004,[5] Cuervas-Mons et al., 2004[6]		A

Desmopressin	Minurin® inject	Ferring	24 h	Cobos Campos et al., 2006,[3] Sala et al., 2004,[5] Cuervas-Mons et al., 2004[6]		D
Dinoprostone	Prepidil® 0.5 gel	Pfizer	1 month	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004[6]		A
Dinoprostone	Propess® 10 mg	Ferring SAU	<24 h at 2–8 °C: re-freeze. If thawed completely: 4 weeks at 2–8 °C. Room temperature: 24 h	Consult lab 03/08/09		D
Dinoprostone	Prostaglandina E2® 10 mg/ml	Pfizer	1 month at 25 °C	Cobos Campos et al., 2006[3]		A
Dopamine hydrochloride	Duodopa gel intestinal cassettes 100 ml	Solvay Pharma	4 days at 25 °C	Consult lab 05/03/09	934954500	C
Dornase alpha	Pulmozyme® 2.5 mg amp.	Roche Farma	24 h at 30 °C (1) 2.5 days at 30 °C (2)	Cuevas (1), Sala et al., 2004[5] (1), Silgado et al., 2006[2] (2), Bovaira García et al., 2004[4] (2)		D
Doxycycline	Vibravenosa® 100 mg	Pfizer	1 month	Cobos Campos et al., 2006[3]		A
Doxorubicin (=adriamycin)	Doxorrubicina® 50 mg vial	Ferrer Farma	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 20/02/09	936003700	F
Liposomal doxorubicin	Myocet® 50 mg vial	Cephalon Pharma	<1 month	Cobos Campos et al., 2006,[3] Silgado et al., 2006[2]		B
Pegylated liposomal doxorubicin	Caelyx® 20 mg vial	Schering-Plough	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab, Sala et al., 2004[5]		F
Drotrecogin	Xigris® 20 mg	Lilly	72 h up to 28 °C	Silgado et al., 2006[2]		C
Drotrecogin	Xigris® 5 mg	Lilly	72 h up to 28 °C	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		C
Eculizumab	Soliris® 300 mg vial	Alexion Pharma Spain	6–7 days	Consult lab 20/02/09	932723017	C
Epirubicin	Farmorubicina® 200 mg vial	Pfizer	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 15/02/09		F

Table 2 (*Continued*)

Eptifibatide Active Ingredient	Integrilin® 20 mg vial Drug Product	Glaxo SmithKline Manufacturing Laboratory	2 months Stability at Room Temperature (22–25 °C)	Cuervas-Mons et al., 2004[6] Reference	Contact Telephone No.	A Category
Erythropoietin alpha	Eprex® 40,000 IU prefilled syringe	Janssen-Cilag	1 h 6 h	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004,[6] Silgado et al., 2006,[2] Bovaira García et al., 2004[4]		D
Erythropoietin beta	Neorecormon® prefilled syringe	Roche Farma	3 days	Cuervas-Mons et al., 2004,[6] Cobos Campos et al., 2006,[3] Silgaro, Sala et al., 2004[5]		C
Streptokinase	Streptase® 750,000 IU	CSL Behring	Keep at temperature ≤25 °C	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		D
Streptozocin	Zanosar® (ME) 1 g vial	Pfizer	Note batch no., expiry, temperature and exposure time and contact laboratory	Cobos Campos et al., 2006,[3] Silgado et al., 2006[2]		F
Etanercept	Enbrel® 25 mg prefilled syringe	Wyeth Farma	24 h at ≤25 °C; >25 °C contact laboratory	Consult lab 21/12/09	913346400	D
Etanercept	Enbrel® 25 ng/ml paediatric vial	Wyeth Farma	24 h at ≤25 °C; >25 °C contact laboratory	Consult lab 21/12/09	913346400	D
Etanercept	Enbrel® 50 mg prefilled syringe	Wyeth Farma	24 h at ≤25 °C; >25 °C contact laboratory	Consult lab 21/12/09	913346400	D
Factor IX	Factor® IX 600 IU	Behring	3 months at 25 °C (do not re-refrigerate)	SmPCs (2010)		Specific recommendation
Factor VIII + Von Willebrand factor	Fanhdi®	Grifols	2 years at 25 °C (1) months at 40 °C (2)	Cobos Campos et al., 2006[3] (1), Cuervas-Mons et al., 2004[6] (2)		A
Recombinant Factor VIII	Advate® 1000 IU	Baxter	6 months at 25 °C (do not re-refrigerate)	SmPCs (review year not available)		Specific recommendation

Recombinant Factor VIII	Advate® 500 IU	Baxter	6 months at 25 °C (do not re-refrigerate)	SmPCs (review year not available)		Specific recommendation
Factor IX plasma	Inmunine® Stim plus 600	Baxter	3 months at 25 °C	Sala et al., 2004[5]		A
Recombinant Factor IX	Benefix® 500 IU	Baxter	1 month at 25 °C	Cuervas-Mons et al., 2004,[6] Silgado et al., 2006,[2] Sala et al., 2004[5]		A
Recombinant Factor VIII	Refacto AF® 1000 IU vial 4 ml	Wyeth Farma	3 months at 25 °C. After this time, do not re-refrigerate	SmPCs (review year not available)		A
Recombinant Factor VIII	Refacto AF® 250 IU vial 4 ml	Wyeth Farma	3 months at 25 °C. After this time, do not re-refrigerate	SmPCs (review year not available)		A
Recombinant Factor VIII	Refacto AF® 500 IU vial 4 ml	Wyeth Farma	3 months at 25 °C. After this time, do not re-refrigerate	SmPCs (review year not available)		A
Factor VIIa	Novoseven® 1.2	Novo Nordisk Pharma	24 h at 25 °C	Silgado et al., 2006,[2] Bovaira García et al., 2004,[4] Sala et al., 2004,[5] Consult lab 18/02/09	913349800	D
Factor VIIa	Novoseven® 2.4	Novo Nordisk Pharma	24 h at 25 °C	Silgado et al., 2006,[2] Bovaira García et al., 2004,[4] Sala et al., 2004,[5] Consult lab 18/02/09	913349800	D
Factor VIIa	Novoseven® 4.8	Novo Nordisk Pharma	24 h at 25 °C	Silgado et al., 2006,[2] Bovaira García et al., 2004,[4] Sala et al., 2004,[5] Consult lab 18/02/09	913349800	D
Phenylephrine	Colircusi fenilefrina®	Alcon Cusi	1 month (1) 15 days (2)	SmPCs (1), Cobos Campos et al., 2006[3] (2), Silgado et al., 2006[2] (2)		B

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Phentolamine	Regitine®	Novartis Farmaceutica	7 days at 25 °C or 2 days at 30 °C	Consult lab 21/07/09	933064200	B
Fibrin	Tissucol® 2 ml	Baxter	48 h. Do not re-freeze	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		D
Filgrastim	Neupogen® 300 MU	Amgen	7 days, 9–30 °C	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Silgado et al., 2006,[2] Sala et al., 2004[5]		B
Filgrastim	Neupogen® 480 MU	Amgen	7 days, 9–30 °C	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Silgado et al., 2006,[2] Sala et al., 2004[5]		B
Filgrastim	Neupogen® vials	Amgen	7 days, 9–30 °C	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Silgado et al., 2006,[2] Sala et al., 2004[5]		B
Fluorescein + oxybuprocaine	Colircusi fluotest®	Alcon Cusi	15 days	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Bovaira García et al., 2004[4]		B
Folinic acid	Folinato calcico® 10 mg/ml	Ferrer Farma	7–14 days at 25 °C	Consult lab 22/12/09	936003700	B
Galsulfase	Naglazyme® 5 mg vial	Biomarin Europe Ltd	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 22/12/09	620988250	F
Antiophidic immunoglobulin	Viperfav®	Sanofi Pasteur MSD	7 days	Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		B
Anti D immunoglobulin 3	Rhopylac® 300 mcg syr 2 ml	CSL Behring	24 h at 25 °C	Consult lab 25/08/09	933671870	D

Specific immunoglobulin	Gamma Anti D® 1500 IU	Grifols	3 months at 25 °C, although discarding is recommended	Cobos Campos et al., 2006[3]		E
Specific immunoglobulin	Gamma Antihepatitis B 200 IU/ml	Grifols	3 months at 25 °C, 2 months at 35 °C, although discarding is recommended as it is a vaccine	Cobos Campos et al., 2006[3]		E
Specific immunoglobulin	Gamma Antitetanos® 500 IU	Grifols	12 months at 25 °C, 3 months at 35 °C, although discarding is recommended as it is a vaccine	Cobos Campos et al., 2006[3]		E
Specific immunoglobulin	Imogam® 150 IU/ml	Sanofi Pasteur MSD	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 21/12/09	913717800	F
Non specific human immunoglobulin	Kiovig® 10 g	Baxter	9 months (do not re-refrigerate)	SmPCs (2006)		Specific recommendation
Non specific human immunoglobulin	Kiovig® 2.5 g	Baxter	9 months (do not re-refrigerate)	SmPCs (2006)		Specific recommendation
Non specific human immunoglobulin	Kiovig® 5 g	Baxter	9 months (do not re-refrigerate)	SmPCs (2006)		Specific recommendation

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Non specific human immunoglobulin	Vivaglobin® 160	CSL Behring	3 months or until expiry date if earlier (do not re-refrigerate)	SmPCs (2008)		Specific recommendation
Gemtuzumab	Mylotarg® 5 mg vial	Wyeth Farma	90 days	Sala et al., 2004[5]		A
Glatiramer	Copaxone® 20 mg prefilled syringe	Sanofi-Aventis	7 days, 15–25 °C	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Silgado et al., 2006,[2] Sala et al., 2004[5]		B
Gonadotrophin	Gonal F® 300 IU 22 mcg/0.5 ml pref. pen	Serono Spain	3 months	Consult lab 21/12/09	917454400 (Merck)	A
Gonadotrophin	Gonal F® 450 IU 33 mcg/0.75 ml pref. pen	Serono Spain	3 months	Consult lab 21/12/09	917454400 (Merck)	A
Gonadotrophin	Ovitrelle® 250 mcg prefilled syringe	Serono Spain	30 days	Consult lab 21/12/09	917454400	A
Gonadotrophin	Puregon® 300 IU cassette 0.36 ml	Organon Spain	3 months at <25 °C, once open 1 month	Consult lab 05/03/09	915673000	A
Gonadotrophin	Puregon® 600 IU cassette 0.72 ml	Organon Spain	3 months at <25 °C, once open 1 month	Consult lab 05/03/09	915673000	A
Gonadotrophin	Puregon® 900 IU cassette 1.08 ml	Organon Spain	3 months at <25 °C, once open 1 month	Consult lab 05/03/09	915673000	A
Hyaluronate	Healon® ''5'' 23 mg/ml prefilled syringe	Panalab	30 days 25 °C	Cobos Campos et al., 2006[3]		A
Hemin	Normosang® 250 mg vial	Orphan Europe	1 week up to 26 °C	Silgado et al., 2006,[2] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		B
Infliximab	Remicade® 100 vial	Schering Plough	12 months	Cobos Campos et al., 2006[3]		A
C1 esterase inhibitor	Berinert® 500 IU vial	Csl Behring	Stable, can be stored at temps up to 25 °C	SmPCs (review year not available)		A

Insulin	Insuman infusat® 100 U	Sanofi-Aventis	Storage: no information available Once in use: 4 weeks	Consult lab 21/12/09	934859400	Specific recommendation
Insulin glargine	Lantus® 100 U/ml solostar	Sanofi-Aventis	4 weeks at <30 °C (including usage time)	Bovaira García et al., 2004[4]		A
Insulin aspart	Novorapid flexpen® 100 U/ml pens	Novo Nordisk Pharma	Storage: 24 h at 25 °C. Once in use: 4 weeks	Bovaira García et al., 2004[4]		D
Insulin aspart-protamine	Novomix 30 flexpen® 100 U/ml pref. pens	Novo Nordisk Pharma	Storage: 24 h at 25 °C. Once in use: 4 weeks	Bovaira García et al., 2004[4]		D
Insulin detemir	Levemir® 100 U/ml	Novo Nordisk Pharma	Once in use: 6 weeks (do not re-refrigerate once open or if carried as a spare)	SmPCs (review year not available)		Specific recommendation
Insulin glulisine	Apidra® 100 U/ml solostar	Sanofi-Aventis	4 weeks (including administration time)	SmPCs (review year not available)		Specific recommendation
Insulin regular	Actrapid® 100 IU/ml vial	Novo Nordisk Pharma	Storage: 24 h at 9–25 °C Once in use: 6 weeks	Cobos Campos et al., 2006,[3] Consult lab 25/08/09	913349800	D
Insulin regular	Actrapid innolet® 100 IU/ml pref. pen	Novo Nordisk Pharma	Storage: 24 h at 9–25 °C Once in use: 4 weeks	Cobos Campos et al., 2006,[3] Consult lab 25/08/09	913349800	D
Insulin protamine	Insulatard® 100 IU/ml vial	Novo Nordisk Pharma	Storage: 24 h at 9–25 °C. Once in use: 4 weeks	Cobos Campos et al., 2006[3]		D
Insulin protamine	Insulatard flexpen® 100 IU/ml pref. pen	Novo Nordisk Pharma				D
Insulin protamine	Insulatard innolet® 100 IU/ml	Novo Nordisk Pharma				D
Insulin regular-isophane	Humulina® 20:80 pen 100 U/ml	Lilly	Storage: 4 days (20 °C), 48 h (25 °C), 24 h (30 °C), 12 h (35 °C). Once in use: 28 days (25 °C)	Bovaira García et al., 2004[4]		C

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Insulin regular-isophane	Humulina® 30:70 pen 100 U/ml	Lilly	Storage: 4 days (20 °C), 48 h (25 °C), 24 h (30 °C), 12 h (35 °C). Once in use: 28 days (25 °C)	Bovaira García et al., 2004[4]		C
Insulin regular-protamine	Mixtard 20 innolet® 100 IU/ml	Novo Nordisk Pharma	Storage: 24 h at 9–25 °C. Once in use: 4 weeks	Cobos Campos et al., 2006[3]		D
Insulin regular-protamine	Mixtard 30 innolet® 100 IU/ml	Novo Nordisk Pharma	Storage: 24 h at 9–25 °C. Once in use: 4 weeks	Cobos Campos et al., 2006[3]		D
Insulin lispro	Humalog® 100 IU/ml vial	Lilly	Storage: 7 days (20 °C), 48 h (25 °C), 24 h (30 °C), 12 h (35 °C). Once in use: 28 days (25 °C)	Cobos Campos et al., 2006,[3] SmPCs (review year not available)		C
Insulin lispro	Humalog humaject® 100 U/ml pref. pen	Lilly	Storage: 7 days (20 °C), 48 h (25 °C), 24 h (30 °C), 12 h (35 °C). Once in use: 28 days (25 °C)	Cobos Campos et al., 2006,[3] SmPCs (review year not available)		C
Insulin lispro	Humalog pen® 100 U/ml pref. pen	Lilly	Storage: 7 days (20 °C), 48 h (25 °C), 24 h (30 °C), 12 h (35 °C). Once in use: 28 days (25 °C)	Cobos Campos et al., 2006,[3] SmPCs (review year not available)		C
Insulin lispro-protamine	Humalog MIX25 pen® 100 IU/ml pref. pen	Lilly	Storage: 7 days (20 °C), 48 h (25 °C), 24 h (30 °C), 12 h (35 °C). Once in use: 28 days (25 °C)	Cobos Campos et al., 2006,[3] SmPCs (review year not available)		C
Insulin zinc	Monotard® 100 IU/ml vial	Novo Nordisk Pharma	Storage: 24 h at 25 °C. Once in use: 6 weeks	Cobos Campos et al., 2006[3]		D
Interferon 2A	Intron A® 10 MIU vial solution	Schering-Plough	7 days	Cobos Campos et al., 2006,[3] Bovaira García et al., 2004,[4] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		B

Interferon 2A	Intron A® 18 MIU pen	Schering-Plough	48 h at 25 °C	Bovaira García et al., 2004,[4] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		C
Interferon 2A	Intron A® 60 MIU pen	Schering-Plough	48 h at 25 °C	Bovaira García et al., 2004,[4] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		C
Interferon B-1A	Rebif® 22 mcg prefilled syringe	Serono Spain	Storage: 6 days 25 °C. Once in use: 1 month	Silgado et al., 2006,[2] Cobos Campos et al., 2006,[3] Bovaira García et al., 2004,[4] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		C
Interferon B-1A	Rebif® 44 mcg prefilled syringe	Serono Spain	Storage: 6 days 25 °C. Once in use: 1 month	Silgado et al., 2006,[2] Cobos Campos et al., 2006,[3] Bovaira García et al., 2004,[4] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		C
Isoprenaline	Aleudrina® 0.2 mg vial	Reig Jofre	6 months at 25 °C (at this temperature, reduce expiry 3 months)	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Bovaira García et al., 2004[4]		Specific recommendation
Lactobacilli	Casenfilus®	Casen Fleet	24 h	Silgado et al., 2006[2]		D
Laronidase	Aldurazyme® 500 IU vial	Genzyme	6 months at 25 °C	Consult lab 26/02/09	916591670	A
Latanoprost	Xalatan® eye drops	Pfizer	1 month at 25 °C	SmPCs, Bovaira García et al., 2004[4]		A
Latanoprost + timolol	Xalocom® eye drops	Pfizer	1 month at 25 °C	SmPCs, Bovaira García et al., 2004[4]		A
Leuprolide	Eligard®	Astellas Pharma	14 days at room temperature before use	Consult lab 21/12/09	914952700	B
Levosimendan	Simdax® 2.5 mg/ml	Orion Corporation	Storage time (contact laboratory if exceeded): >25 °C: not acceptable 15–25 °C: 2–3 days 8–15 °C: 1 week 0–2 °C: 1 week <0 °C: 1 week	Consult lab 21/12/09	915030252	F

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
LHRH	LHRH®	Ferring	15 days at 25 °C	Consult lab 16/02/09	917994780	B
Organ preservation fluid	Viaspan®	Bristol Myers	Use not recommended 12–24 h after breaking chain	Consult lab 18/02/09	914565300	D
Lopinavir + ritonavir	Kaletra® oral solution 60 ml	Abbott Laboratories	42 days	SmPCs, Silgado et al., 2006,[2] Cobos Campos et al., 2006[3]		A
Tetryzoline + medroxyprogesterone + chloramphenicol	Colircusi medrivas®	Alcon Cusi	Storage: 15 days 25 °C. Once in use: 1 month	Consult lab 20/2/09, Bovaira García et al., 2004[4]	934977000	B
Melphalan	Melfalan® 2 mg tablets	Lilly	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 21/12/09	916635000	F
Methylergometrine	Methergin® 0.2 mg/ml	Novartis Farmaceutica	2 weeks	Cobos Campos et al., 2006,[3] Silgado et al., 2006[2]		B
Methoxy peg epoetin beta	Mircera® 100 mcg/0.3 ml prefilled syringe	Roche Farma	1 month at ≤30 °C. Do not re-refrigerate	Consult lab 21/12/09	913248100	Specific recommendation
Methoxy peg epoetin beta	Mircera® 150 mcg/0.3 ml prefilled syringe	Roche Farma	1 month at ≤30 °C. Do not re-refrigerate	Consult lab 21/12/09	913248100	Specific recommendation
Methoxy peg epoetin beta	Mircera® 200 mcg/0.3 ml prefilled syringe	Roche Farma	1 month at ≤30 °C. Do not re-refrigerate	Consult lab 21/12/09	913248100	Specific recommendation
Methoxy peg epoetin beta	Mircera® 250 mcg/0.3 ml prefilled syringe	Roche Farma	1 month at ≤30 °C. Do not re-refrigerate	Consult lab 21/12/09	913248100	Specific recommendation
Methoxy peg epoetin beta	Mircera® 50 mcg/0.3 ml prefilled syringe	Roche Farma	1 month at ≤30 °C. Do not re-refrigerate	Consult lab 21/12/09	913248100	Specific recommendation
Methoxy peg epoetin beta	Mircera® 75 mcg/0.3 ml prefilled syringe	Roche Farma	1 month at ≤30 °C. Do not re-refrigerate	Consult lab 21/12/09	913248100	Specific recommendation

Muromonab	Orthodone® OKT3	CILAG Gmbh	1 week at 30 °C if at least 6 months of expiry period is left. 48 h at 25 °C if 3 months of expiry period is left	Cuervas-Mons et al., 2004[6]		C
Natalizumab	Tysabri® 300 mg 1 vial perfusion	Elan Farma	No information available	Consult lab 06/03/09	935677880	F
Nonacog alfa	Benefix® 500 IU/1000 IU	Baxter	1 month at ≤25 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		A
Octreotide	Sandostatin® 0.05 mg/ml	Novartis Farmaceutica	14 days at <30 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		B
Octreotide	Sandostatin® 0.1 mg/ml	Novartis Farmaceutica	14 days at <30 °C	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004[6]		B
Omalizumab	Xolair® 150 mg vial	Novartis Farmaceutica	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 18/02/09	933064200	F
Oxytocin	Syntocinón® 10 IU/ml	Defiante Farmaceutica Lda	3 months at <30 °C	Cobos Campos et al., 2006[3]		A
Oxytocin	Syntocinon® 10 IU/ml	Defiante Farmaceutica Lda	3 months at <30 °C	Cobos Campos et al., 2006[3]		A
Palivizumab	Synagis® 100	Abbott Laboratories	2 weeks at <25 °C	Silgado et al., 2006,[2] Sala et al., 2004[5]		B
Palivizumab	Synagis® 50	Abbott Laboratories	2 weeks	Sala et al., 2004[5]		B
Panitumumab	Vectibix® 100 mg vial	Amgen	24 h at 25 °C	Consult lab 20/2/09	936001900	D
Panitumumab	Vectibix® 400 mg vial	Amgen	24 h at 25 °C	Consult lab 16/02/09	936001900	D

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Pegaptanib sodium	Macugen® 0.3 prefilled syringe	Pfizer	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 04/03/09	932213366	F
Pegfilgrastim	Neulasta® 6 mg prefilled syringe	Amgen	72 h at <30 °C	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		C
Peginterferon alpha 2a	Pegasys® 135 mcg prefilled syringe	Roche Farma	7 days	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		B
Peginterferon alpha 2a	Pegasys® 180 mcg prefilled syringe	Roche Farma	7 days	Cuervas-Mons et al., 2004,[6] Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Bovaira García et al., 2004[4]		B
Peginterferon alpha 2b	Pegintron® 100 mcg pref. pen	Schering-Plough	18 months at <25 °C	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		A
Peginterferon alpha 2b	Pegintron® 120 mcg pref. pen	Schering-Plough	18 months at <25 °C	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		A
Peginterferon alpha 2b	Pegintron® 150 mcg pref. pen	Schering-Plough	18 months at <5 °C	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		A
Peginterferon alpha 2b	Pegintron® 50 mcg pref. pen	Schering-Plough	18 months at <5 °C	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		A
Peginterferon alpha 2b	Pegintron® 80 mcg pref. pen	Schering-Plough	18 months at <25 °C	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		A

Protamine	Protamina® Rovi 50 mg vial	Rovi	48 h at 25 °C – 1 week	Cobos Campos et al., 2006,[3] Sala et al., 2004[5]		C
Prothrombin	Prothromplex Inmuno® Tim4 600 IU	Baxter	6 months	Sala et al., 2004[5]		A
Ranibizumab	Lucentis® 10 mg vial	Novartis Farmaceutica	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 16/02/09	933064200	F
Rasburicase	Fasturtec® 1.5 mg vial	Sanofi-Aventis	15 days at 25 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		B
Risperidone	Risperdal® 25 mg	Janssen-Cilag	7 days	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		B
Risperidone	Risperdal® 37.5 mg	Janssen-Cilag	7 days	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		B
Risperidone	Risperdal® 50 mg	Janssen-Cilag	7 days	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Sala et al., 2004[5]		B
Ritonavir	Norvir® 100 mg soft capsules	Abbott Laboratories	1 month at <25 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Sala et al., 2004,[5] Bovaira García et al., 2004[4]		A
Rituximab	Mabthera® 100 mg vial	Roche Farma	18 days at <30 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		B

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Rituximab	Mabthera® 500 mg vial	Roche Farma	18 days at <30 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		B
Rocuronium	Esmeron® 100 mg vial	Organon Spain	12 weeks at <30 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Sala et al., 2004,[5] Bovaira García et al., 2004[4]		A
Rotigotine	Neupro® patches	Ucb Pharma	7 days at 25 °C	Consult lab 25/08/09	915703444	B
Measles-Mumps-Rubella	Vacuna® MSD triple	Sanofi Pasteur MSD	7 days at 25 °C	Cobos Campos et al., 2006[3]		B
Secretin	Secrelux®	Sanochemia	3 weeks at 25 °C	Bovaira García et al., 2004,[4] García Vázquez et al., 1997[7]		B
Sirolimus	Rapamune® 1 mg tablets	Wyeth Farma	24 h at 25 °C	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Sala et al., 2004,[5] Bovaira García et al., 2004[4]		D
Somatrophin	Zomacton® 4 mg	Ferring	24–48 h	Consult lab 16/02/09	917994780	D
Somatrophin	Genotonorm kabipen® 12 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 0.2 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 0.4 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation

Somatrophin	Genotonorm miniquick® 0.6 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 0.8 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 1 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 1.2 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 1.4 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 1.6 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 1.8 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Genotonorm miniquick® 2 mg vial	Pfizer	6 months at 25 °C (including use). Do not re-refrigerate	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		Specific recommendation
Somatrophin	Humatrope® 12 mg cassette	Lilly	6 days at 8–25 °C, 72 h at 25–30 °C, 24 h at 30–40 °C	Bovaira García et al., 2004[4]		C
Somatrophin	Humatrope® 24 mg cassette	Lilly	6 days at 8–25 °C, 72 h at 25–30 °C, 24 h at 30–40 °C	Bovaira García et al., 2004[4]		C
Somatrophin	Humatrope® 6 mg cassette	Lilly	6 days at 8–25 °C, 72 h at 25–30 °C, 24 h at 30–40 °C	Bovaira García et al., 2004[4]		C
Somatrophin	Norditropin® simplexx 10 mg	Novo Nordisk Pharma	24 h at <25 °C	Consult lab 05/03/09, Bovaira García et al., 2004[4]	913349800	D

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Somatrophin	Norditropin® simplexx 15 mg	Novo Nordisk Pharma	24 h at <25 °C	Consult lab 05/03/09, Bovaira García et al., 2004[4]	913349800	D
Somatrophin	Norditropin® simplexx 5 mg	Novo Nordisk Pharma	24 h at <25 °C	Consult lab 05/03/09, Bovaira García et al., 2004[4]	913349800	D
Somatrophin	Nutropin® AQ 10 mg (30 IU) cassette	Ipsen Farma	Discard (no information available)	Consult lab 21/12/09	936858100	E
Somatrophin	Omnitrope® 3.3 mg/ml vial	Sandoz Farmaceutica	1 day at 25 °C and 15 days at 15 °C, 2 weeks at 0 °C or between −2 °C and −5 °C	Consult lab 23/3/09	917401280	D
Pulmonary surfactant	Curosurf® 120	Chiesi Spain	24 h at <25 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Bovaira García et al., 2004,[4] Consult lab 17/02/09	934948000	D
Pulmonary surfactant	Curosurf® 240	Chiesi Spain	24 h at <25 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Bovaira García et al., 2004,[4] Consult lab 17/02/09	934948000	D
Suxamethonium	Anectine® 100 mg vial	Glaxo SmithKline	2 weeks at 25 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Bovaira García et al., 2004,[4] Cuervas-Mons et al., 2004,[6] García et al., 2004[4]		B
Temsirolimus	Torisel® 25 mg vial	Wyeth Farma	24 h at 25 °C; note batch no., expiry, temperature, exposure time and contact laboratory. (cadena_de_frio@wyeth.com)	Consult lab 20/2/09	913346400	F
Tetracosactide	Nuvacthen Depot®	Defiante Farmaceutica	1–3 months at <25 °C	García Vázquez et al., 1997,[7] Sala et al., 2004[5]		A

Tetracosactide	Synacthen®	Novartis Farmaceutica	3–4 h at <25 °C	Silgado et al., 2006,[2] Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004[6]		D
Thymoglobulin	Timoglobulina® 25 mg vial	Genzyme	24 h at <37 °C	Silgado et al., 2006[2]		D
Thiotepa	Tioplex® 15 mg vial	Addiene	3 months at 25 °C (Oncothiotepa)	Silgado et al., 2006[2]		A
Tipranavir	Aptivus® 250 mg soft capsules	Boehringer Ingelheim Spain	Storage: 60 days, 15–30 °C. Once in use: 60 days at <25 °C	Consult lab 21/12/09	934045100	A
Thyrotropin alpha	Thyrogen® 0.9 mg vial	Genzyme	1–2 years	Cuervas-Mons et al., 2004,[6] Cobos Campos et al., 2006,[3] Sala et al., 2004,[5] Silgado et al., 2006,[2] Bovaira García et al., 2004[4]		A
Tobramycin	Tobi® 300 mg 56 amp. 5 ml	Chiron Iberia	1 month at 25 °C	Cuervas-Mons et al., 2004,[6] Silgado et al., 2006,[2] Bovaira García et al., 2004,[4] Sala et al., 2004[5]		A
Topotecan	Hycamtin® 0.25 mg capsules	Glaxo SmithKline	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 20/02/09	918070301	F
Topotecan	Hycamtin® 1 mg capsules	Glaxo SmithKline	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 20/02/09	918070301	F
Toxin A, Cl. botulinum	Dysport® 500 IU vial	Ipsen Pharma	3 days	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Arrixaca, Sala et al., 2004[5]		C
Botulinum toxin	Botox® 100 U	Allergan Sau	14 days at 25 °C; 7 days at 30 °C	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		B
Botulinum toxin	Botulismus-antitoxin Behring®	Esteve	1 week at 37 °C	Bovaira García et al., 2004[4]		B
Trabectedin	Yondelis® 0.25 mg vial	Pharmamar	72 h at 25 °C	Consult lab 25/10/07	918466000	C

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Trabectedin	Yondelis® 1 mg vial	Pharmamar	72 h at 25 °C	Consult lab 25/10/07	918466000	C
Trastuzumab	Herceptin® 150 mg vial	Roche Farma	30 days at 40 °C, 3 days at 50 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Arrixaca		A
Trientine hydrochloride	Syprine®	Merck Sharp Dohme	7 days	García Vázquez et al., 1997[7]		B
Tuberculin	Tuberculina® PPD	Ucb Pharma	6 months at 25 °C, 2 weeks at 35 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006[2]		A
Meningococcal C vaccine	Meningitec® prefilled syringe	Wyeth Farma	24 h at <25 °C	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Bovaira García et al., 2004[4]		D
Diphtheria, tetanus, pertussis vaccine	Boostrix® 0.5 ml syringe	Glaxo SmithKline	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 25/08/09	918070467	F
DTP and hepatitis B vaccine	Tritanrix®	Glaxo SmithKline	2 weeks at 21 °C; 1 week at 37 °C. Although, as it is a vaccine, it is recommended to be discarded	Bovaira García et al., 2004[4]		E
DtaP vaccine	Infanrix®	Glaxo SmithKline	2 weeks at 21 °C; 1 week at 37 °C. Although, as it is a vaccine, it is recommended to be discarded	Cobos Campos et al., 2006,[3] Silgado et al., 2006,[2] Bovaira García et al., 2004[4]		E
Haemophilus influenzae b vaccine	Hiberix®	Glaxo SmithKline	2 weeks at 21 °C; 1 week at 37 °C. Although, as it is a vaccine, it is recommended to be discarded	Silgado et al., 2006[2], Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		E
Hepatitis B vaccine	Twinrix® adult prefilled syringe	Glaxo SmithKline	Note batch no., expiry, temperature, exposure time and contact laboratory	Consult lab 25/08/09	918070467	F
Pneumococcal conjugate vaccine	Prevenar® prefilled syringe	Wyeth Farma	24 h at ≤25 °C. Although, as it is a vaccine, it is recommended to be discarded	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		E

Rabies vaccine	Rabipur®	Novartis Farmaceutica	1 year at 25 °C; 3 months at >37 °C; 1 month at >55 °C. Although, as it is a vaccine, it is recommended to be discarded	Consult lab 01/04/06	933064200	E
Varicella vaccine	Varilrix®	Glaxo SmithKline	1 week at 21 °C. Although, as it is a vaccine, it is recommended to be discarded	Bovaria García et al., 2004,[4] Silgado et al., 2006[2]		E
Hepatitis A vaccine	Havrix® 1440	Glaxo SmithKline	2 weeks at 21 °C; 1 week at 37 °C. Although, as it is a vaccine, it is recommended to be discarded	Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		E
Hepatitis A vaccine	Havrix® 720	Glaxo SmithKline	2 weeks at 21 °C; 1 week at 37 °C. Although, as it is a vaccine, it is recommended to be discarded	Silgado et al., 2006,[2] Cuervas-Mons et al., 2004,[6] Bovaira García et al., 2004[4]		E
Meningococcal C vaccine	Menjugate®	Esteve	6 months at 30 °C, 1 week at 40 °C (without reducing expiry period). Although, as it is a vaccine, it is recommended to be discarded	Cobos Campos et al., 2006,[3] Bovaira García et al., 2004[4]		A
Hepatitis B vaccine	Engerix-B® 10 mcg	Glaxo SmithKline	2 weeks 21 °C, 1 week 37 °C	Cobos Campos et al., 2006[3]		B
Hepatitis B vaccine	Engerix-B® 20 mcg	Glaxo SmithKline	3 weeks 21 °C, 1 week 37 °C	Cobos Campos et al., 2006[3]		B
Tetanus and diphtheria vaccine	Diftavax® 40/4 IU adult	Sanofi Pasteur Msd	14 days at 25 °C	Silgado et al., 2006[2]		B

Table 2 (*Continued*)

Active Ingredient	Drug Product	Manufacturing Laboratory	Stability at Room Temperature (22–25 °C)	Reference	Contact Telephone No.	Category
Tetanus and diphtheria vaccine	Ditanrix® 20/2 IU adult	Glaxo Smithk	2 weeks at 21 °C, 1 week at 37 °C	Cobos Campos et al., 2006[3]		B
Inactivated polio vaccine	Vacuna Poliomelitica Berna®	Berna Biotech Spain	Temperature ≤25 °C: <24 h: reduce expiry period by 2 months >24 h and <72 h: reduce expiry period by 4 months >72 h and <120 h: reduce expiry period by 6 months >120 h: discard	Cobos Campos et al., 2006[3]		D
Vinblastine	Vinblastina® 10 mg vial	Stada	21 days at 15 °C and 14 days at 25 °C	Consult lab 20/2/09	934738889	B
Vincristine	Vincristina® 2 mg vial	Pfizer	24 h at 25 °C	Cobos Campos et al., 2006,[3] Cuervas-Mons et al., 2004[6]		D
Vinorelbine	Navelbine® 20 mg capsules	Pierre Fabre Iberica	1 month at <25 °C, 15 days at <30 °C, can be frozen	Consult lab 20/2/09, Silgado et al., 2006,[2] Bovaira García et al., 2004[4]	934833000	A
Vinorelbine	Navelbine® 30 mg capsules	Pierre Fabre Iberica	1 month at <25 °C, 15 days at <30 °C, can be frozen	Consult lab 20/2/09, Silgado et al., 2006,[2] Bovaira García et al., 2004[4]	934833000	A
Vinorelbine	Navelbine® 50 mg vial	Pierre Fabre Iberica	1 month at <25 °C, 15 days at <30 °C, <48 h at >30 °C or exposed to the light. Can be frozen	Cuervas-Mons et al., 2004,[6] Silgado et al., 2006[2]		A
Voriconazole	Vfend® 40 mg/ml oral suspension	Pfizer	30 days at 25 °C (temperature excursions are cumulative, so contact the laboratory for an individual evaluation)	Consult lab 21/12/09	914909900	A
Hyaluronic acid viscoelastic	Provisc®	Alcon Cusi	12 h at 25 °C	Consult lab 26/08/09	934977000	D

Govern de les Illes Balears
Hospital Universitari Son Dureta
Pharmacy department

BREAK IN THE COLD CHAIN
STANDARD OPERATING PROCEDURE

Date issued 01/01/10
Valid until 01/01/11

All refrigerators must have a temperature sensor or a temperature control probe.

The refrigerator temperatures must be checked at 8am every day by a pharmacy assistant.

If temperature is >8°C, inform the pharmacist who will download the temperature monitoring and assess the incident.

If the temperature has been between 8-12ºC for a period <8 hours, no action must be taken.

If the period is >8 hours or the refrigerator temperature has exceeded 12ºC, the following steps must be taken:

1. Record the incident, indicating the temperature reached and time.
2. Make a list of the drugs, the quantity and withdraw the affected packages.
3. Review of stability of each of them.
4. Label all category A, B and C medications affected as follows:

Safety Notice
This medicine was outside of the refrigerator for ... (hours) on.... (day).
It can still be used

5. Evaluate category D drugs according to specific information and type of medication.
6. Dispose of category E medications. Vaccines are always disposed of, whatever their stability.
7. Contact the laboratory if a batch-dependent drug is affected.

Category	Stability >8°C	Action
A	Stable ≥ 1 month (28 days) at 25°C	Label
B	Stable ≥ 1 week (7 days) at 25°C	Label
C	Stable ≥ 48h at 25°C	Label
D	Stable < 48h at 25°C	Evaluate individually
E	Not stable outside the fridge (>8°C)	Discard
F	Stability depends on the batch	Consult laboratory

8. Breaks in the cold chain have a cumulative effect on the drug. If a drug has been affected by a previous cold chain break, consult the manufacturing laboratory.

Figure 1 Standard operating procedure for a break in the cold chain.

Finally, agreement was reached within the pharmacy department on a standard operating procedure (SOP) for any break in the cold chain, which sorted the drugs into 6 categories based on the time they were stable outside of the refrigerator (Table 1).

Results

A total of 254 medicinal products corresponding to 162 active ingredients were reviewed (Table 2).

The number of drugs in each classification was as follows: (A) 65, (B) 47, (C) 30, (D) 47, (E) 12, and (F) 22. There were also specific recommendations for each category, as follows, provided that the time and temperature limits stipulated for each category were not exceeded:

- A, B, and C: Establish a control and monitoring system by labelling (Fig. 1).
- D: Continue in use if it was a one-off break in the cold chain and did not exceed the established maximum time. Otherwise, dispose of or return the drug to the laboratory.
- E: Dispose of or return the drug to the laboratory.

There were 31 drugs that could not be included in any category, so it is recommended to check the specific information regarding room temperature stability in Table 2.

The information obtained is available on the hospital intranet, in the ''*manuales de procedimiento*'' section of the pharmacotherapy portal. There is also a version on the Internet, in the free access pharmacy department portal (see URL at the end of the article).[11]

Discussion and Conclusions

The methodology used to conduct this review was similar to that used in the aforementioned studies.[2–10] However, there are differences in the information given by certain pharmaceutical laboratories. This may be because the drug companies involved have carried out further stability studies during the time between the completions of both reviews.

One problem found was the differences in stability data for the same active ingredient, depending on the laboratory that undertook the study. We agree with Cobos Campos et al.[3] who suggested that laboratories should conduct their stability studies under the same temperature conditions to standardise them and facilitate comparison. However, it is important to consult the information available at each centre for the drug product in question.

It was deemed necessary to have stability data for all drugs to be incorporated in the hospital guide upon inclusion, and for the laboratory to provide degradation tables, as a query made when the chain is broken is urgent, and the laboratory cannot guarantee a drug outside its recommended conditions.

When returning drugs to the laboratories, an agreement can be reached with the manufacturing laboratory, especially when the drug cost is high. The manufacturing cost is often significantly less than the most expensive selling price, and in our experience the contribution of the industry in these cases has been very adequate.

One limitation of this review is that the majority of the data found do not specify the possibility of re-refrigerating after breaking the cold chain, or whether these data are valid if there is a second break in the cold chain. For such a case, the manufacturing laboratory should be consulted.

Another limitation is that action has been formalised only for exceeding the maximum proper conservation temperature, but not for freezing.

Lastly, it is important to note that the information contained in this paper is intended as a reference tool for rapid action in those special situations when the cold chain is broken and it is necessary to know whether a drug may be used or not. If in doubt, we recommend contacting the manufacturing laboratory specifying the concrete conditions to which the product has been subjected. Due to the importance of establishing the period of time the drugs have been out of the recommended temperature range and the temperature reached, this information should not be given to other hospital departments, so as to prevent any bad conservation practice. However, it was considered appropriate to have access to it in the ''*manuales de procedimiento*'' section of the pharmacotherapy department portal and to inform other pharmacy departments to facilitate action in the case of a break in the cold chain.To summarise, one of the priority functions of a pharmacist is to ensure the correct storage of medicines.[12] This requires the availability of updated information on the validity times of thermolabile drugs when the cold chain is broken. It is the responsibility of the pharmacist to establish guidelines for action when incidents occur. This information must be available and updated in the hospital pharmacy department to ensure that appropriate measures are taken.

Conflicts of Interest

The authors affirm they have no conflict of interest.

References

1. Steffen WH, Newton DW, Miller KW. Room temperature and drug stability. Am J Hosp Pharm. 1994;51:406–9.
2. Silgado R, Jiménez MJ, Ferrari JM, Herreros de Tejada A. Desviaciones máximas de las temperaturas permisibles para medicamentos termolábiles. Ars Pharm. 2006;47:173–83.
3. Cobos Campos R, Salvador Collado P, Gómez Gener A, Boj Borbones M. Estabilidad máxima de los medicamentos termolábiles fuera de nevera. Farm Hosp. 2006;30:33–43.
4. Bovaira García MJ, Lorente Fernández L, de la Rubia Nieto MA, San Miguel Zamora MA. Conservación de medicamentos termolábiles [s.n.]. Murcia: Hospital Universitario Virgen de la Arrixaca; 2004.
5. Sala F, Juarez JC, Tomás E, Monterde J. Estabilidad de las especialidades farmacéuticas termolábiles en distintas condiciones de temperatura: actualización. El Farmacéutico Hospitales. 2004;160:5–16.
6. Cuervas-Mons Vendrell M, Fernández Prieto M, Sánchez Sánchez MT, Maestre Fullana MA, Abad Lecha E, Salvador Palacios A, et al. Posible validez de medicamentos termolábiles fuera de las condiciones de conservación recomendadas por el fabricante. Farm Hosp. 2004;28:440–4.
7. García Vázquez N, Ruano Encimar M, García López A, Arenós Monzó C, Larrubia O, Jiménez Caballero E. Estabilidad de medicamentos termolábiles a temperatura ambiente. Farm Hosp. 1997;21:283–8.
8. Cohen V, Jellinek S, Teperikidis L, Berkovits E, Goldman W. Room-temperature storage of medications labeled for refrigeration. Am J Health-Syst Pharm. 2007;64:1711–5.
9. de la Rubia A. Conservación de medicamentos termolábiles [editorial]. Farm Hosp. 2006;30:1–3.
10. Rivero Cava MS. Medicamentos termolábiles. Boletín de Noticias Farmacoterapéuticas del centro de información de medicamentos y servicio de atención farmacéutica especializada de la gerencia de área de salud de Badajoz. 2009;1:1–4.
11. Medicamentos termolábiles pauta actuación HUSD 2009 [quoted 2010 Apr 20]. El comprimido. Available from: http://www.elcomprimido.com/FARHSD/MP_MedicamentosTermolabilesPautaActuacionHUSD2009.doc.
12. Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios. BOE núm. 178, de 27 de julio de 2006.