

5º CUERPO

22707-11-1



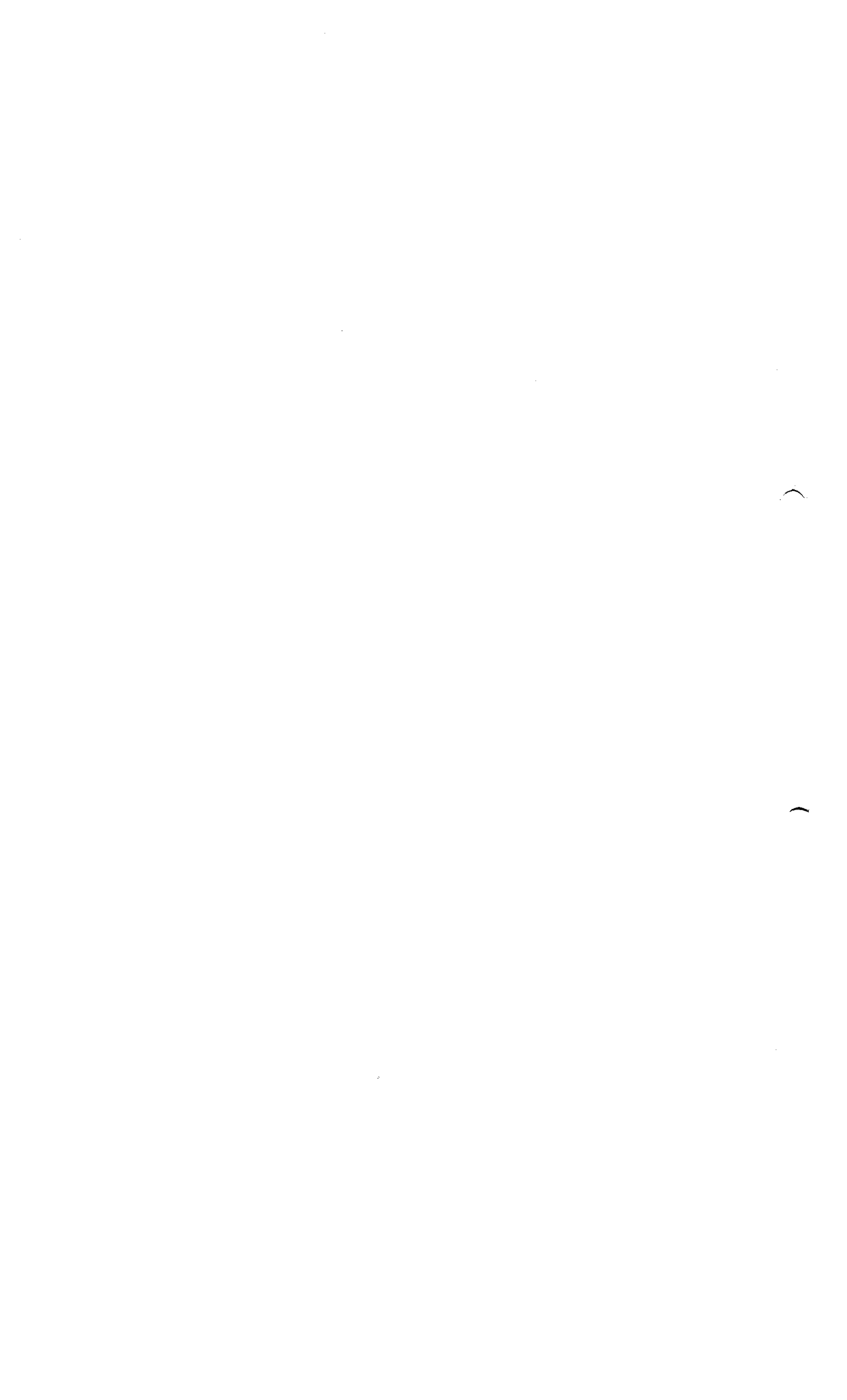
U0129866774

CLIENTE

748

DOGADEA

221776





CORP	Requirement	Document Number GQ_000863
Previous Doc. Number N/A		Version Number 4.0
		Level N/A
<b>Storage and Distribution</b>		

Department: sanofi pasteur Quality Operations

Section:

Additional Information:

Section	Reason for Revision (include reason on page 2 where applicable)

Approval Name	Title	Date	Signature
Author PREVILLE Odile	RESPONSABLE DEPARTEMENT	04 Dec 2010 14:36:49	I am approving this document
Approver AITCHISON Bill	SENIOR VICE-PRESIDENT	15 Dec 2010 12:28:27	I am approving this document
Quality Approver HANSELAER Johan	VP of Global Quality Operations	15 Dec 2010 13:30:48	I am approving this document

29 Dec 2010

Effective date:

First Review			
Second Review			

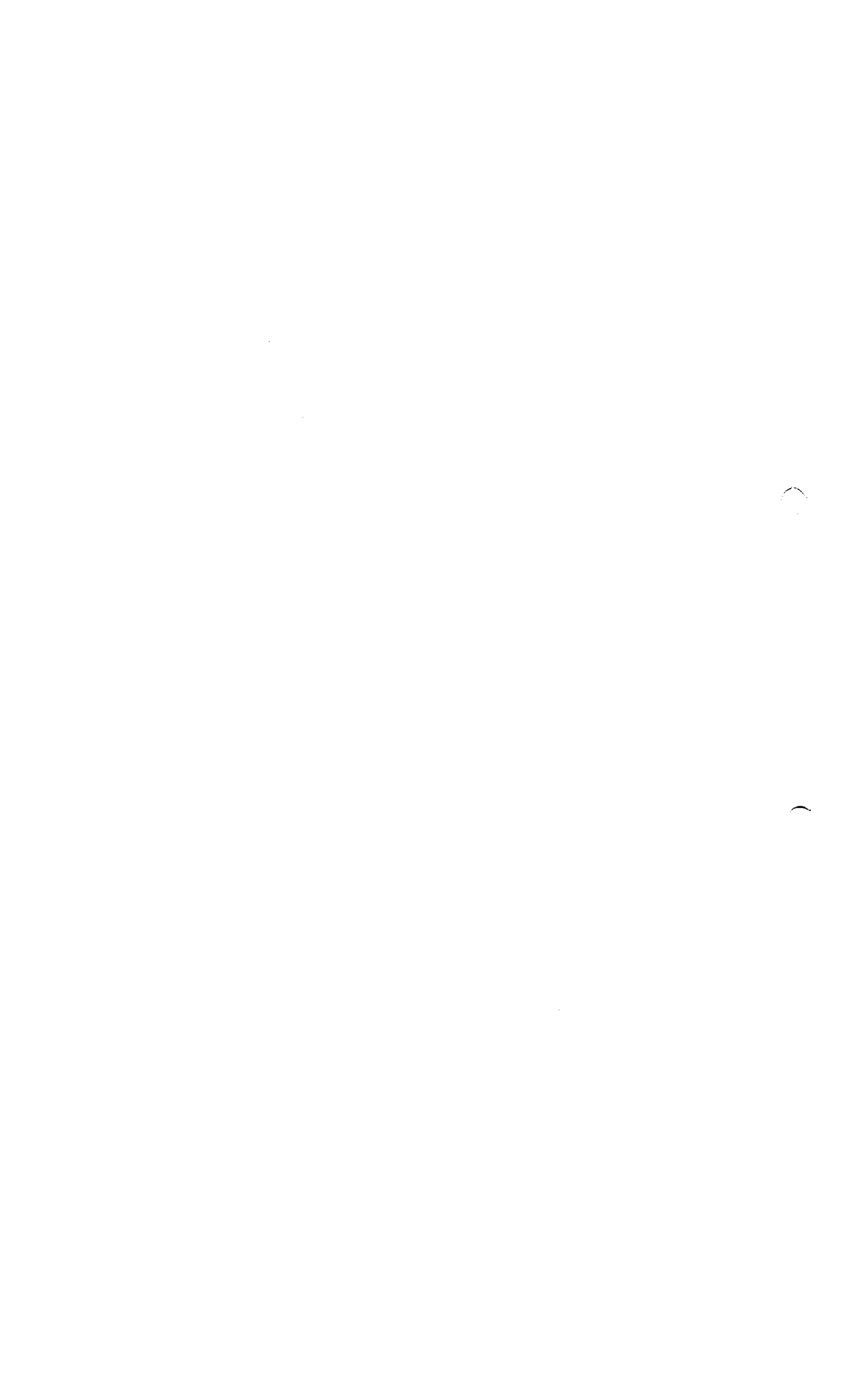
ROXANA MONTEMILONE DIRECTORA TÉCNICA  
  
 CHRISTIAN DOMÍNGUEZ COORDINADOR

**Confidential/Proprietary Information**  
 SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.

Status: Effective  
Justification: Intranet export

On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations

Exported by HICKS Katherine  
To Katherine Hicks







Reason for Revision	
Section	Revisions (include reason where applicable)
Entire Document	Administrative Change: Removed all directive references and replaced with Corporate Quality Requirement (CQR)
Entire Document	Administrative Change: Removed all Global references and replaced with sanofi pasteur

Status: Effective  
Justification: Intranet export

On 1/3/2011 21:37:56  
Title/Org: Sanofi Pasteur Quality Operations

  
 ROXANA MONTEMILONE  
 DIRECTORA TÉCNICA  
 SANOFI PASTEUR S.A.

  
 CHRISTIAN DOMINGUE  
 VICEPRESIDENTE  
 SANOFI PASTEUR S.A.

Exported by HICKS Katherine  
To Katherine Hicks

Confidential/Proprietary Information  
Page 2 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

0

1

## Table of Contents

List of Appendices .....	4
1 PURPOSE AND OBJECTIVES .....	5
2 SCOPE.....	5
3 GLOSSARY AND REFERENCES .....	6
3.1 Glossary .....	6
3.2 References .....	9
4 RESPONSIBILITIES .....	10
5 REQUIREMENTS.....	11
5.1 Process mapping .....	11
5.2 Specifications development .....	13
5.3 Temperature monitoring .....	20
5.4 Validation & Qualification .....	22
5.5 Returns management, including recalls .....	30

Status: Effective  
Justification: Intranet export

On 1/3/2011 21:37:56  
Title/Org.: Sanofi Pasteur Quality Operations

ROXANA MONTEMILONE DIRECTORA TÉCNICA  
SANOFI PASTEUR S.A.  
CHRISTIAN DOMINGUEZ  
SANOFI PASTEUR S.A.

Expended by HICKS Katherine  
To Katherine Hicks

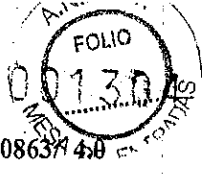
Confidential/Proprietary Information

Page 3 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

(


)




## List of Appendices

Appendix 1: Cold Chain Break Deviation Management..... 31

On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations  
Status: Effective  
Justification: Intranet export

  
ROXANA MONTEMILONE  
DIRECTORA TÉCNICA  
SANOFI PASTEUR S.A.

  
CHRISTIAN DOMÍNGUEZ  
COORDINADOR  
SANOFI PASTEUR S.A.

Exported by: HICKS Katherine  
To: Katherine Hicks

Confidential/Proprietary Information

Page 4 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.



# 1 PURPOSE AND OBJECTIVES

For many pharmaceutical products storage and transportation conditions especially temperature (under standard pressure), are a significant factor in maintaining their quality throughout the shipments operations.

The objective is to provide directions on how to store and transport materials and products so as to maintain the quality level of products during storage / or transport from sanofi pasteur manufacturing /or distribution site to their point of receipt.

Temperature sensitive goods are usually regarded as those requiring a storage temperature of +2°C (35.6°F) to +8°C (46.4°F) or freezing e.g. -20°C (-4°F), however, goods requiring other storage temperature ranges may also be sensitive to temperature extremes, which may have an adverse effect on their physical and / or chemical properties, and should also be regarded when necessary (diluent such as Water For Injection, Sodium Chloride at different concentrations and all the adjuvant solutions).

Temperature deviations during storage or shipping operations may generate Time Out of Refrigeration (TOR). Refer to the CQR "TOR" GQ\_000848.

# 2 SCOPE

This Corporate Quality Requirement (CQR) applies to all sanofi pasteur manufacturing sites and all sanofi pasteur distribution centers and distribution subcontractors at the 1st level, with regard to flows:

- Between IO sites (transfers) or contractors/distributors hired to perform packaging or distribution activities on behalf of sanofi pasteur
- Toward external customers (delivery)

It describes common processes / or practices used at several products steps (from concentrated antigen to final packed products) and different activities (RA, R&D for Clinical Trial Materials from phase 3 of trials, IO / or Commercial Operations for Interco shipments & external distribution).

It does not apply to 2<sup>nd</sup> level manufacturing or distribution subcontractors nor beyond 1<sup>st</sup> customer in case of delivery.

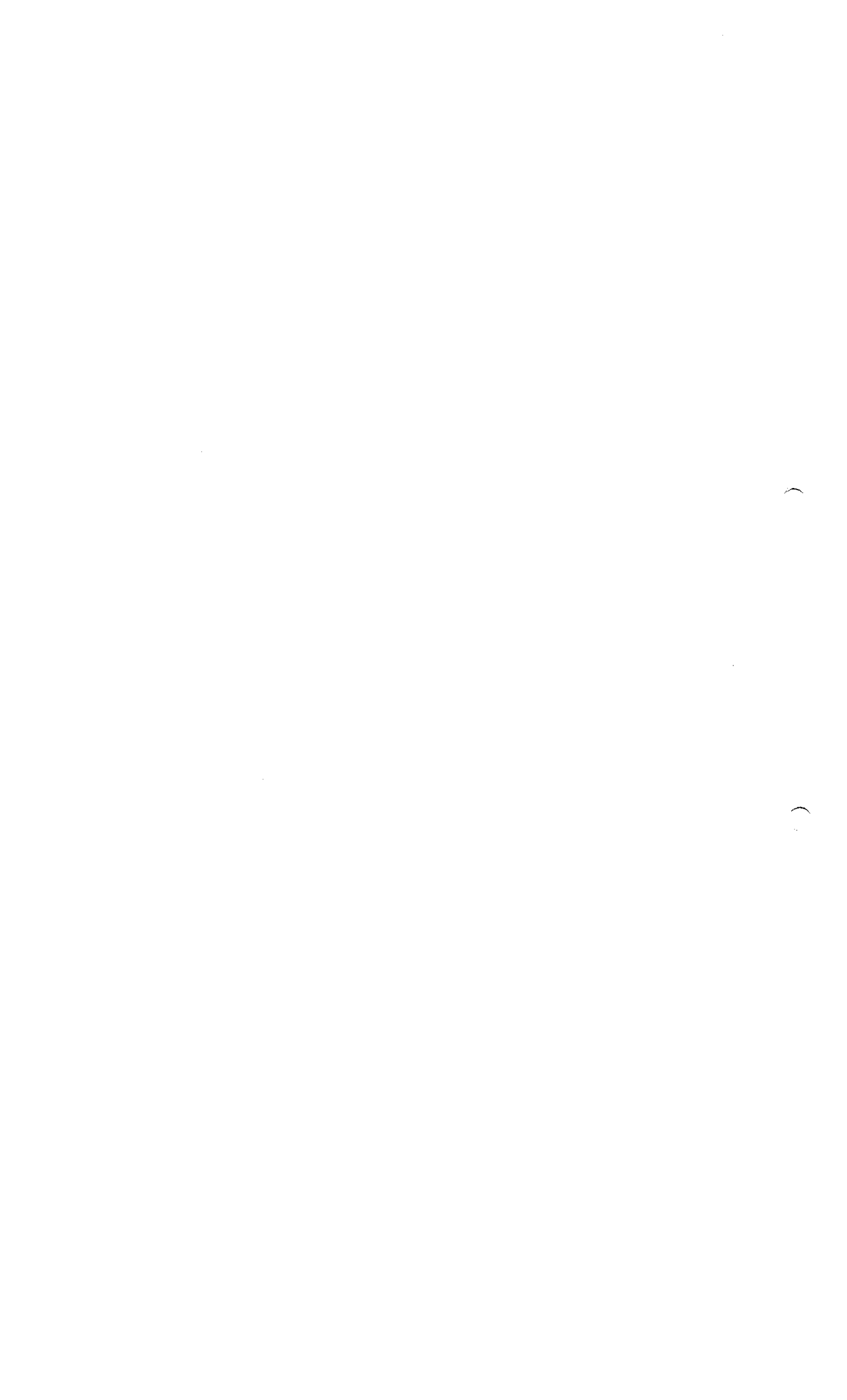
  
ROXANA MONTEMILONE  
DIRECTORA TÉCNICA  
SANOFI PASTEUR S.A.

  
CHRISTIAN DOMÍNGUEZ  
GERENTE  
SANOFI PASTEUR S.A.

Confidential/Proprietary Information  
Page 5 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Stans: Effective  
Justification: Intranet export  
On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations  
Exported by HICKS Katherine  
To: Katherine Hicks



The following materials are covered:

- Finished products (manufactured by sanofi pasteur or outsourced), including samples for clinical trials
- Intermediates and bulk sold or shipped as finished products (filled containers, bulk in vessels, intermediate products and concentrated antigens)

It does not include raw materials nor other manufacturing components (e.g. medical devices such as droppers, needles, etc. produced for sanofi pasteur).

The following processes are covered:

- Storage at the distribution centers before shipping of goods by carriers
- Inter companies and inter sites shipments / or transfers
- Distribution (commercial shipments and deliveries to external customers).

Note: Returned / or recalled materials are part of the covered flows as long as they remain property of the company. This CQR is not applicable when neither shipment is managed by external customer nor if products have to be destroyed (i.e. recall situation).

### 3 GLOSSARY AND REFERENCES

#### 3.1 Glossary

It covers products, process, devices & equipments, logistics and qualification & validation concept applied to cold chain.

##### 3.1.1 Product related definitions

Potency - Ability to give protection against disease

Stability study - Simulation generally established on the basis of predefined limits (e.g. 5°C (41°F), 20°C (68°F), 25°C (77°F), 37°C (98.6°F) + possibly others) that makes it possible to determine the maximum shelf life during which the product continues to comply with its initial specifications. In some cases, the product may be subjected to variable temperature cycles (e.g.: successive freeze-thaw cycles) if this is likely to have an effect on its quality. Freezing temperature value can be part of the stability study.

ROXANA MONTEMILONE DIRECTORA TÉCNICA SANOFI PASTEUR S.A.  
CHRISTIAN DOMINIQUEZ GERENTE SANOFI PASTEUR S.A.

Confidential/Proprietary Information

Page 6 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Status: Effective  
Justification: Intranet export

On: 13/2011 21:37:36  
Title: Org: Sanofi Pasteur Quality Operations

Exported by: HICKS Katherine  
To: Katherine Hicks



### 3.1.2 Process related definitions

1st level distribution contractor - External provider handling as consignee with SP owned products and in charge of storage and distribution operations.

2nd level distribution contractor - External provider handling as distributor of SP products after property transfer.

Cold Chain - Processes involved in logistics from receiving till shipping that maintains temperature sensitive products within approved temperature specifications.

Primary stores - Intermediate storage facilities after manufacturing or first distribution step, where SP products are still under consignment (before property transfer).

Temperature profiles - Studies performed seasonally to capture actual temperature conditions within the distribution network (based on the seasonal temperature shipping profile)

Worst case - Determination of the most unfavorable conditions in terms of storage locations, times, breaks in transit and weather conditions that makes it possible to reduce the impact of uncontrolled parameters.

Process Capability - In worst case conditions, ability to produce results within 6 sigma's range around average specification (defined vs. upper & lower specifications limits). Capability is usually good (within 6 sigma) in controlled environment (e.g. internal storage) but might be poorer (outside 6 sigma) for subcontracted external operations (e.g. transportation can not be validated).

Time Out of Refrigeration (TOR) - Time during which the products are outside the cold room or a qualified shipping container, during the whole process of handling, preparation of orders, loading, transport and during transfers (including the air transport). Storage and distribution TOR is part of the global TOR cumulative calculation covering also manufacturing steps (filling, packaging and associated transfers). Regarding Clinical Trial Material, TOR is calculated for phase 3 only.

Note: associated with the available stability data, TOR is the basis for a decision on the fate of the product in case of deviation (risk analysis of potency loss).

### 3.1.3 Devices & equipments related definitions

#### 3.1.3.1 Temperature monitoring tools

Indicator - Single use device. Display is based on chemical / or physical reactions (e.g. color change, solid melting / or liquid freezing, etc.), leading to definitive visible modification / or alteration (e.g. colored spot, ink stain / or migration on scale, breaks / or burst out, etc.). It turns on according to defined conditions of temperature time combination or single temperature value (threshold effect).

ROXANA MONTEMILONE CHRISTIAN DOMINIQUE  
DIRECTORA TÉCNICA GERENTE  
SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.

Confidential/Proprietary Information  
Page 7 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Status: Effective  
Justification: Intranet export

On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations

Exported by HICKS Katherine  
To: Katherine Hicks



Tracer - Generally single use device featuring temperature sensitive electronic probe (thermistor), Central Processing Unit (chip), Liquid Crystal Display (reading) and Memory (archive) enabling to display value (min-max) or cumulated time regarding defined threshold. Tracers can be also designated by "Tags".

Data logger - Generally single or multiple use programmable device featuring temperature sensitive probe (bi-metallic coil or thermistor), enabling to read sampled values during a period of time. Either mechanical or electronic loggers are available. Probe can be either internal or external and multi channels devices are generally connected to a computerized system and to a printer through wire or radio frequency link. Loggers can be also designated by "Recorders".

Vaccine Vial Monitor (VVM) - Indicator featuring circle with a small square inside it, be printed on a product label. Inner square of the VVM is made of heat sensitive material that is light at the starting point and becomes darker with exposure to heat, gradually and irreversibly. A direct relationship exists between the rate of color change and temperature. VVM can be directly applied on filled products labels and requires no activation.

### 3.1.3.2 Equipment

Cold room - A purpose made insulated enclosure fitted with refrigeration equipment which maintains a set temperature of +2°C (35.6°F) to +8°C (46.4°F). A fridge is assimilated to a very small cold room and must be equally qualified.

Freezer room - A purpose made insulated enclosure fitted with refrigeration equipment which maintains a set temperature of -20°C (-4°F) or below. A freezer is assimilated to a very small freezer room and must be equally qualified.

### 3.1.4 Logistics related definitions

Shipper - An individual or company who tenders (pharmaceutical) products for transportation by land, sea or air from one site to another.

Service Agreement - A contractual agreement, which describes the legal, logistical, technical and quality terms or contractual arrangements between shippers and transport service providers. It must be established as a common document gathering "Quality Agreements" + "supply agreement" + "legal & commercial contract".

Transit time - Interval between exit of goods from departure from the premises until delivery to customer by the carrier.

Packing list - Document featuring detailed content of parcel (e.g. item identification, batch n°, expiry date, etc.).

Manifest of transport - Transportation document for road, sea (e.g. bill of lading), or air (e.g. Air Way Bill = AWB).

ROXANA MONTEMILONE CHRISTIAN DOMINIQUE  
DIRECTORA TÉCNICA GERENTE

Confidential/Proprietary Information SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.

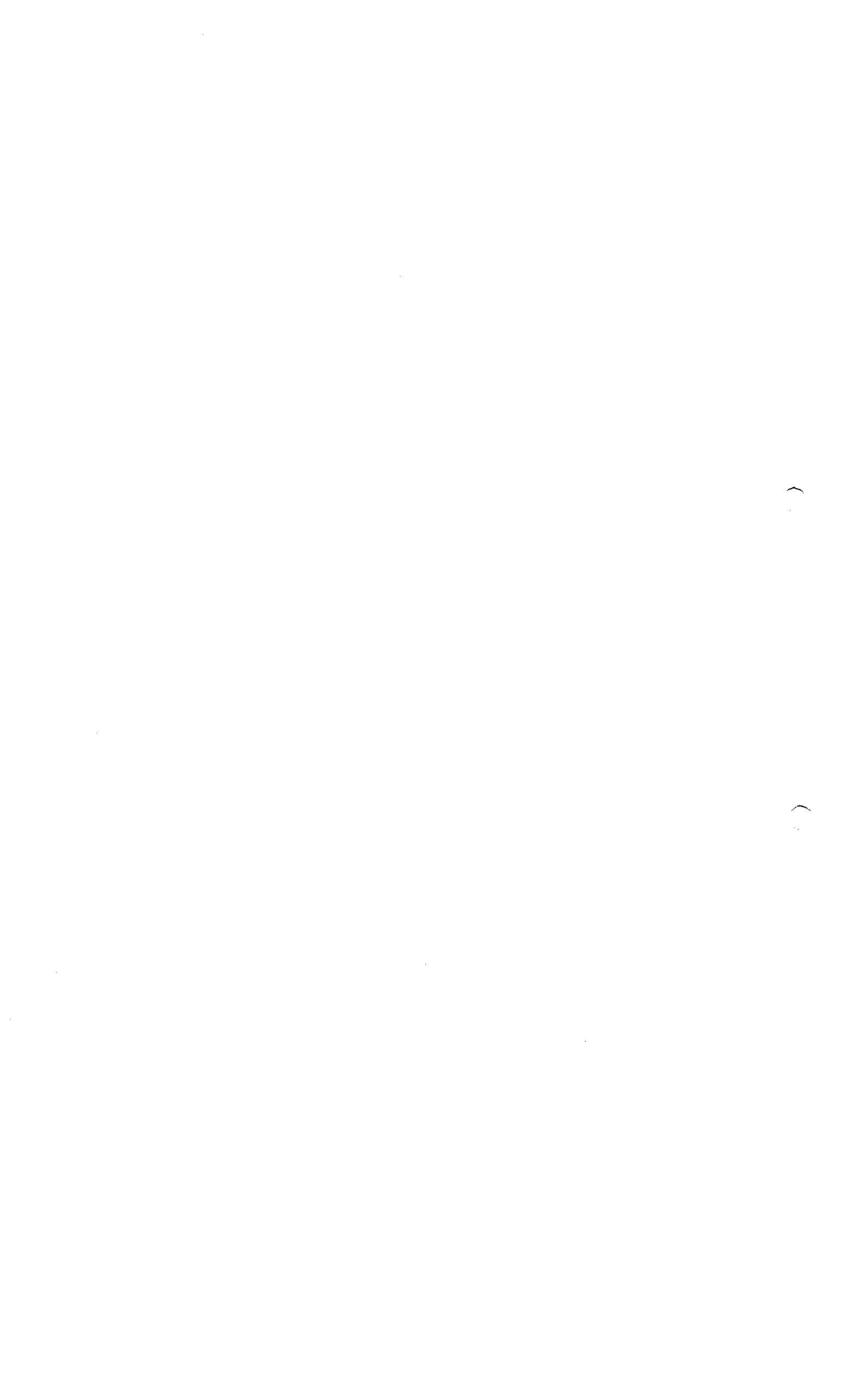
Page 8 of 31

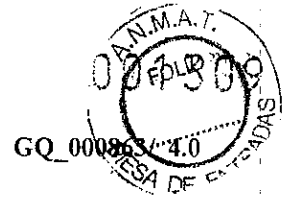
Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Status: Effective  
Justification: Intranet export

On 1/5/2011 21:37:36  
Title/Orig: Sanofi Pasteur Quality Operations

Exported by HUCKS Katherine  
To Katherine Hucks





Truck Load (TL) - Maximum volume (usually calculated in m3) to optimize transport utilisation (e.g.: 48 pallets fitting in a trailer).

INCOTERM - International COmmercial TERMinology defining each other responsibility, title pass between vendor and purchaser for goods and insurance from point of dispatch to point of delivery.

Shipping qualification (SQ) - Performance qualification applied to transport in determined conditions (which might not be repeatable) and establishing confidence that shipping process meets acceptance criteria based on chamber study or field study.

## 3.2 References

### 3.2.1 cGxPs



Good Distribution Practices EU N° 2000/9 bis  
Good Manufacturing Practices (European)  
Code of Federal regulations #21 (USA) § 211.xx

### 3.2.2 Sanofi-aventis IQC Directives (D) & Guides (G)

D (SA)-E-05-26-01-01 Transport of materials, products and medical devices  
D (SA)-E-01-03-01-02 Warehousing and Good Distribution Practices  
G (SA)-E-05-26-01-01 Validation of Transport of Materials, Products and Medical Devices  
G (SA)-E-05-26-03-01 Storage and transport of temperature sensitive goods

### 3.2.3 Sanofi pasteur Corporate Quality Requirements

Material Identification, Quality Status, and Status Labeling, GQ\_000502  
Failure Investigations Management, GQ\_000506  
Calibration, GQ\_000544  
Preventive Maintenance, GQ\_000547  
Time Out of Refrigeration, GQ\_000848  
Management of Technical Complaints, GQ\_000868

  
ROXANA MONTEMILONE DIRECTORA TÉCNICA  
  
CHRISTIAN DOMÍNGUEZ SECRETARIO  
SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.

Confidential/Proprietary Information  
Page 9 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Status: Effective  
Justification: Intranet export  
On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations  
Exported by: HICKS Katherine  
To: Katherine Hicks



### 3.2.4 Others

USP General Chapter <1079> Good Storage and Shipping Practice

PDA Technical Report No. 39 Cold Chain Guidance for Medicinal Products

WHO guidelines:

- WHO/V&B/02 for storage facilities
- WHO/V&B/99.15 for temperature monitoring
- WHO/GPV/98.07 for thermo stability of vaccines
- WHO/IVB/05 for packaging & shipping of vaccines
- Equipment performance specifications and test procedures => E1: Cold rooms and freezer rooms; E4&E11: insulated containers
- Overcoming freezing in the cold chain (25 February 2003, WHO Geneva)

GUIDE-0069 "Guideline for Temperature Control of Drug Products during Storage and Transportation" Health Canada (HPFB Inspectorate)

The American Society for Testing and Materials document, "Standard Practice for Performance Testing of Shipping Containers and Systems" (ASTM D4169-01)

## 4 RESPONSIBILITIES

Distribution centers management, transportation and customs compliance management or delegations appointed by them in IO / or Commercial Operations organizations are responsible for the following:

- Ensuring application of this CQR in local procedures
- Training personnel in the application of derived local procedures
- Running or sub-contracting qualification / validation processes in their respective areas
- Performing risk analysis regarding logistics decisions
- Evaluating the impact of any change to the process on the cold chain qualification / validation within the framework of change control
- Reporting deviations to Quality Operations

ROXANA MONTEMILONE DIRECTORA TÉCNICA  
SANOFI PASTEUR S.A.  
CHRISTIAN DOMINGUEZ  
SANOFI PASTEUR S.A.

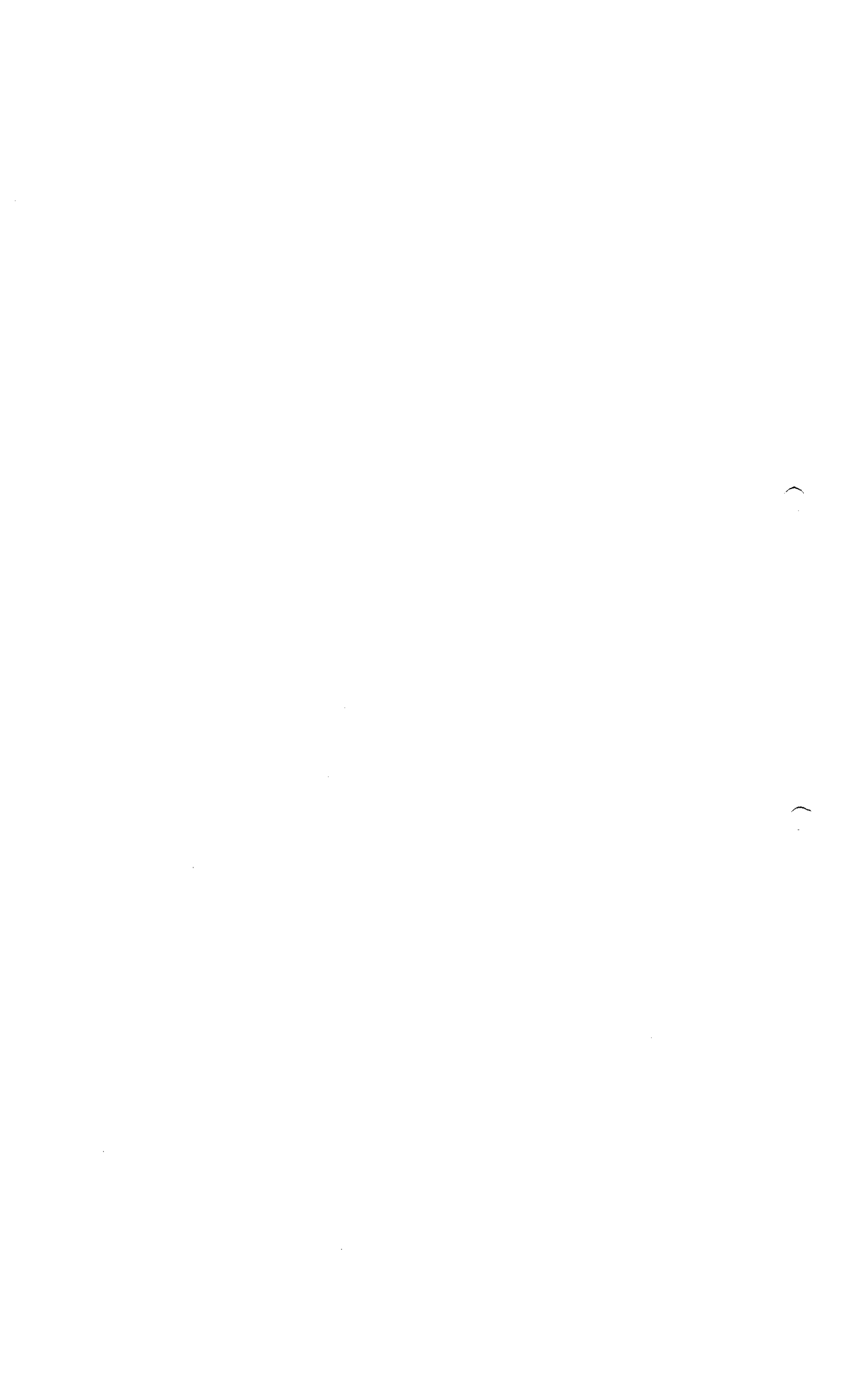
Confidential/Proprietary Information  
Page 10 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Status: Effective  
Justification: Intranet export

On 13/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations

Exported by HICKS Katherine  
To Katherine Hicks



Quality Operation managers are responsible for the following:

- Ensuring application of this CQR in local procedures
- Approving SOPs and qualification / validation documents
- Evaluating and validate the change controls made to storage and distribution management on each site
- Managing the deviations and are responsible for decision about product fate (destruction or return to inventory)

Note: if the local regulation imposes requirements not mentioned in these reference frames, they must be reported to the Quality Operations.

## 5 REQUIREMENTS

### 5.1 Process mapping

The aim is to ensure that process mapping is properly completed and in compliance with all local storage & distribution SOPs.

#### 5.1.1 Products data

Storage or distribution sites must:

- Apply labeled storage conditions (temperature and others) for each product they handle (item or family)
- Have available and documented data regarding authorized TOR for "post manufacturing" operations (storage, picking & packing, shipping) within allocated time frame
- Remaining tolerances in case of deviations based on stability studies rationale.

#### 5.1.2 Storage

Storage or distribution sites must have updated list of qualified building / or equipments used to keep the products in cold room / freezing rooms or fridges / or freezers.

Vendor's and / or contractor's primary stores qualification must be included in Service Agreement.

Warehouse activities include receipt operations, orders preparations and shipping activities that must be covered by SOPs.

ROXANA MONTEMILONE CHRISTIAN DOMINGUEZ  
DIRECTORA TÉCNICA GERENTE  
SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.

Confidential/Proprietary Information

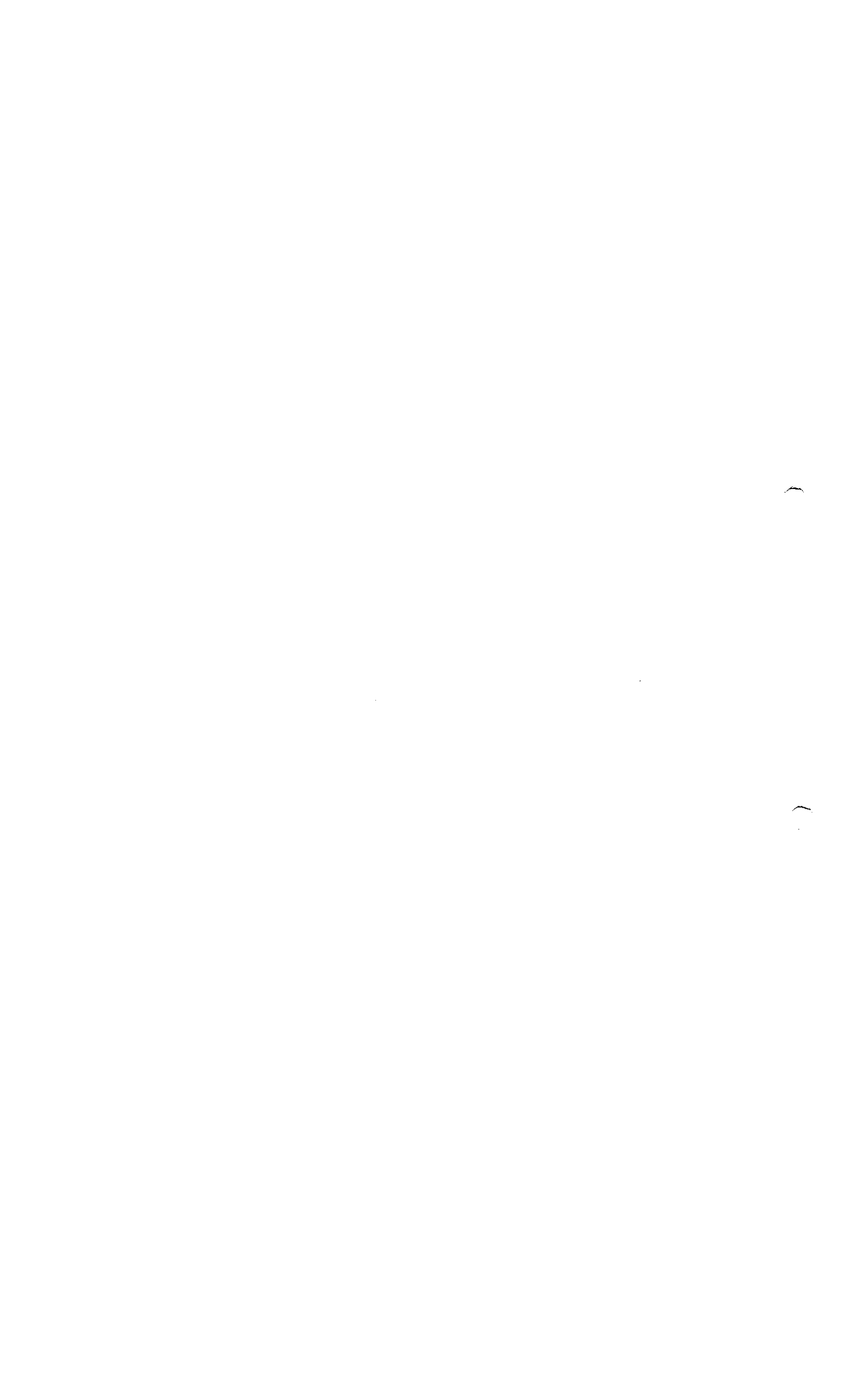
Page 11 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Status: Effective  
Justification: Intranet export

On 1/3/2011 21:57:36  
Title/Org: Sanofi Pasteur Quality Operations

Exported by: HICKS Katherine  
To: Katherine Hicks



### 5.1.2.1 Receipt checks

Goods characteristics such as identity, quantity, batch, etc. must be checked against reference document (e.g. order, procurement requisition, manifest of transport).

Potential visible damages or recorded temperature deviations must be reported through deviation systems according to local SOPs. Product in question must be stored appropriately and quarantined.

### 5.1.2.2 Storage / or handling operations

Items must be clearly identified and managed through the defined local rules to guaranty safety (labelled conditions, batch status, shelf life, etc.) and accuracy (counting, easy access, etc.).

### 5.1.2.3 Orders preparation & shipment

Process mapping should highlight the following points:

- Distribution network design = description of authorized primary storage facilities and of the supply lines connecting them with travel distances.
- Route definition = description for each destination of what method of transport is used and whether the transport is currently serviceable or not (taking into account maintenance availability) studying alternative arrangements based on different linkages between existing facilities as well as alternatives (contingency planning, intermediate stores at convenient places between 2 sets of points, etc.).
- Selection of the carrier = sourcing based on several criteria involving logistics, purchasing, legal affairs and quality operations to achieve the Service Agreement.
- Tracking of shipped goods = reporting through transmission systems (e.g. Electronic Data Interchange, web site, faxes / or e-mails, satellite GPS, etc.) about shipment position, delays, temperature or any incidents till final delivery.

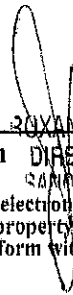

Status: Effective  
Justification: Intranet export

On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations

Exported by HICKS Katherine  
To Katherine Hicks

Confidential/Proprietary Information

Page 12 of 31

ROXANA MONTEMILONE DIRECTORA TÉCNICA  
SANOFI PASTEUR S.A.    
CHRISTIANO DOMINGUEZ GERENTE  
SANOFI PASTEUR S.A.

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.





## 5.2 Specifications development

### 5.2.1 Storage

#### 5.2.1.1 Sites, facilities & equipment layout

##### 5.2.1.1.1 General specifications

The storage and / or distribution centers must have the adequate authorizations according to their activities and the nature of the distributed products (all operations performed in warehouses or distribution centers must be covered under the authorization license).

The distributed products are authorized in accordance with the regulation in force (must adhere to all applicable licensing requirements).

The premises must be designed to ensure the safety, security and proper storage conditions of products and be and monitored (e.g. security personnel on site or remote alarm report, fire protection system, backup power supply for cold rooms) 24 hours a day.

Facilities layout must be designed to prevent contamination by outside elements (e.g. litter, dust, pests, etc.), mix-up or cross-contamination during receipt, storage, sampling and distribution. Then, capacity must be sufficient to allow distinct areas (e.g. receipt, storage, preparation, shipment) and storage in good conditions.

The conditions of lighting, temperature and humidity (e.g. the condensate from the chiller units must not be collected inside the cold store in an open vessel) must be suitable to allow storage meeting label requirements.

The control and / or measuring apparatus having a demonstrated impact on quality (e.g. temperature recording devices, balances, bar code readers involved in ) must be initially qualified and calibrated then checked periodically through routine utilisation or periodical retest.

Ancillary areas (e.g. rest rooms, cafeteria, cloakrooms, maintenance, etc.) must be separated from the process area.

Equipment (e.g. forklift trucks), must be designed, installed and maintained in order to ensure safety of personnel and quality of products. Refer to the CQR Calibration, GQ\_000544.

##### 5.2.1.1.2 Cold / or freeze rooms specifications

The internal layout of the cold storage area must ensure that the product is only stored in areas shown by temperature mapping to provide adequate temperature control (e.g. auto defrost must be available and the temperature within the unit must not be affected during the defrost cycle).

Security systems covering temperature alarms and safety systems (emergency exit doors for people working inside, fire detection and extinguishers / or sprinklers, etc.) must be in place and

ROXANA MONTEMILONE CHRISTIAN DOMINGUE  
DIRECTORA TÉCNICA DIRECTOR TÉCNICO  
SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.

Confidential/Proprietary Information

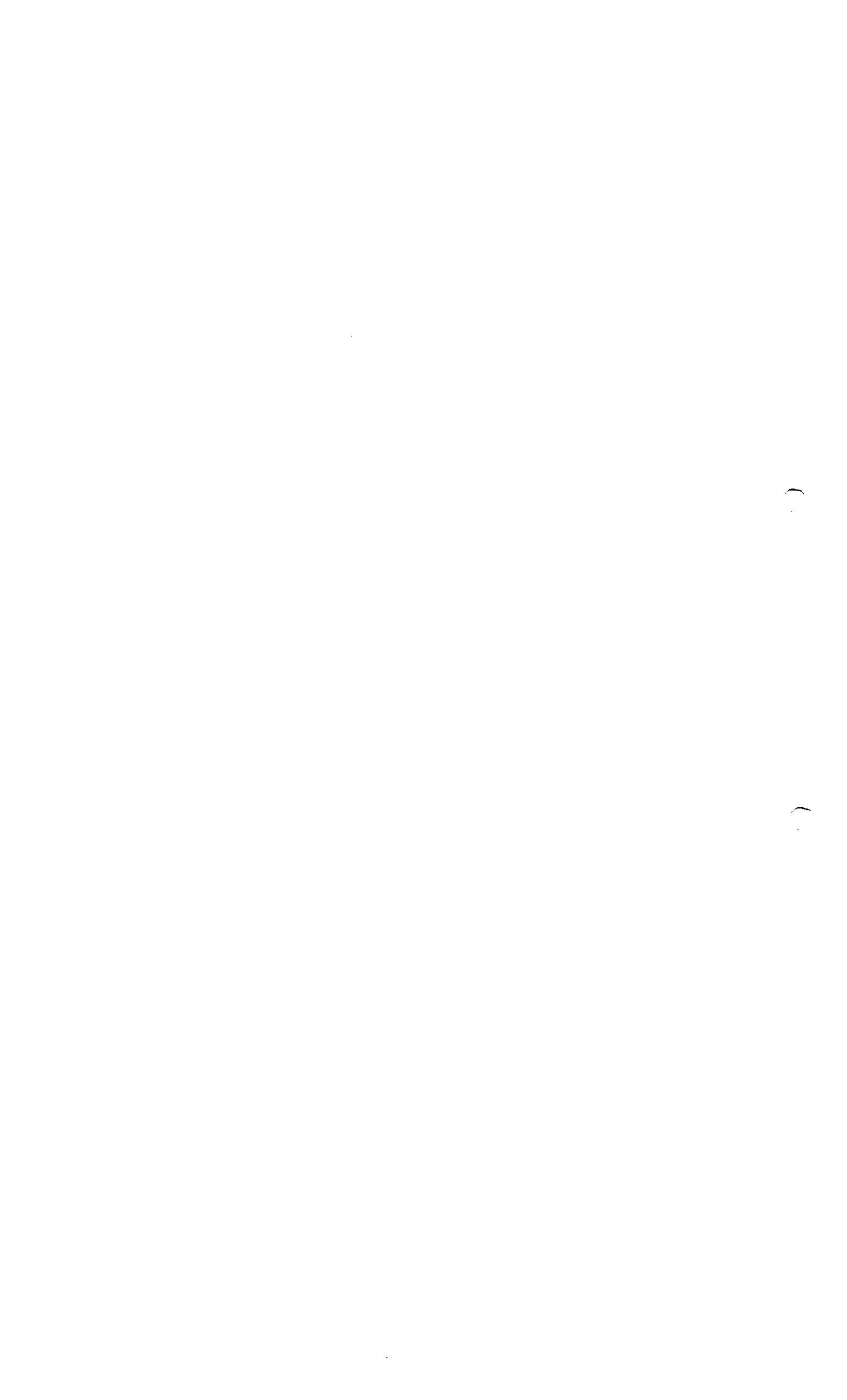
Page 13 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Status: Effective  
Justification: Intranet export

On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations

Exported by HICKS Katherine  
To Katherine Hicks



covered by local specific SOPs. Critical monitoring / or alarm systems must be redundant / or backed up and rescued in case of power failure.

The maintenance of cooling equipment must be covered by procedures / or contracts and include annual preventive maintenance planning (e.g. Technical Service Dpt). Refer to the CQR Preventive Maintenance, GQ\_000547.

### 5.2.1.2 Stock keeping and inventory management

#### 5.2.1.2.1 Integrity and shelf life

The products to be distributed must have a sufficient remaining shelf life (compatible with future usage) and available stock must be free of expired, rejected or spoiled products. Any damaged items or items with broken seals must be identified, quarantined and removed.

Products subjected to specific conditions of storage (e.g., hazardous materials, controlled substances, returned products, out-of-date, deteriorated, flammable products, temperature controlled products) must be identified and stored in compliance with legal requirements. Storage of products directly on the ground is prohibited.

Temperature sensitive products must be immediately stored in the cold room after receiving.

Cleaning and maintenance must be performed according to written procedures, without any impact for stored products.

**Note:** if batches are not directly selected by the picking instruction, it is strongly recommended to apply the earliest-expiry-first-out (EEFO) / or first-expired-first-out (FEFO) handling rule.

#### 5.2.1.2.2 Batch status and traceability

Except in case of very specific procedures (e.g. Clinical Trial Materials), batch status management system (quarantine) must segregate and prevent shipping any unreleased product to external customers.

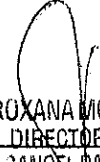
Secured, segregated areas must be provided for quarantine, unless an automated warehouse employing a validated "electronic quarantine" controlled system is used.


Returned, recovered, recalled or rejected products by quality decisions must always be stored in physically separated closed and locked area (e.g., "jail" for rejected goods).

A system of rapid traceability must be in place to ensure:

- A quick access for sampling purpose
- The efficiency of withdrawal / or effective recall procedure.

To prevent mix up risk, each handling unit must contain only 1 batch of a determined product.

  
ROXANA MONTEMILONE  
DIRECTORA TÉCNICA  
SANOFI PASTEUR S.A.

  
CHRISTIAN DOMINGUEZ  
GERENTE GENERAL  
SANOFI PASTEUR S.A.

Confidential/Proprietary Information

Page 14 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations  
Status: Effective  
Justification: Intranet export

Exported by HICKS Katherine  
To Katherine Hicks



Periodical physical inspections of the warehouse will guaranty clearly defined locations (either fixed or floating), no stacking of non protected pallets, free aisles between racks and accessibility to the retrieved products.

### 5.2.1.3 Orders preparation (picking & packing)

#### 5.2.1.3.1 Picking operations

The picking operations must guaranty the identity of the products (item, batch number), the required quantity (traceability and stock accuracy impact) as well as packaging integrity.

#### 5.2.1.3.2 Packing operations

The packing operations must guaranty that, products will be transported under conditions ensuring precautions against breakage, theft, diversion, tampering, excessive conditions of temperature / or humidity and pests.

Tamper evidence devices must be used (e.g. special printed tape, strapping, sealing, etc.) to preserve product integrity.

Over packaging (e.g. cardboard corners, shrinking film wrapped around, carton top, etc.) is recommended to reinforce mechanical resistance during transport, especially when goods overlap the pallet size / or when stacking cannot be avoided. It must preserve clear identification of the shipper and the consignee as well as specific labelling regarding content (e.g. hazardous materials, etc.) and specific transport conditions.

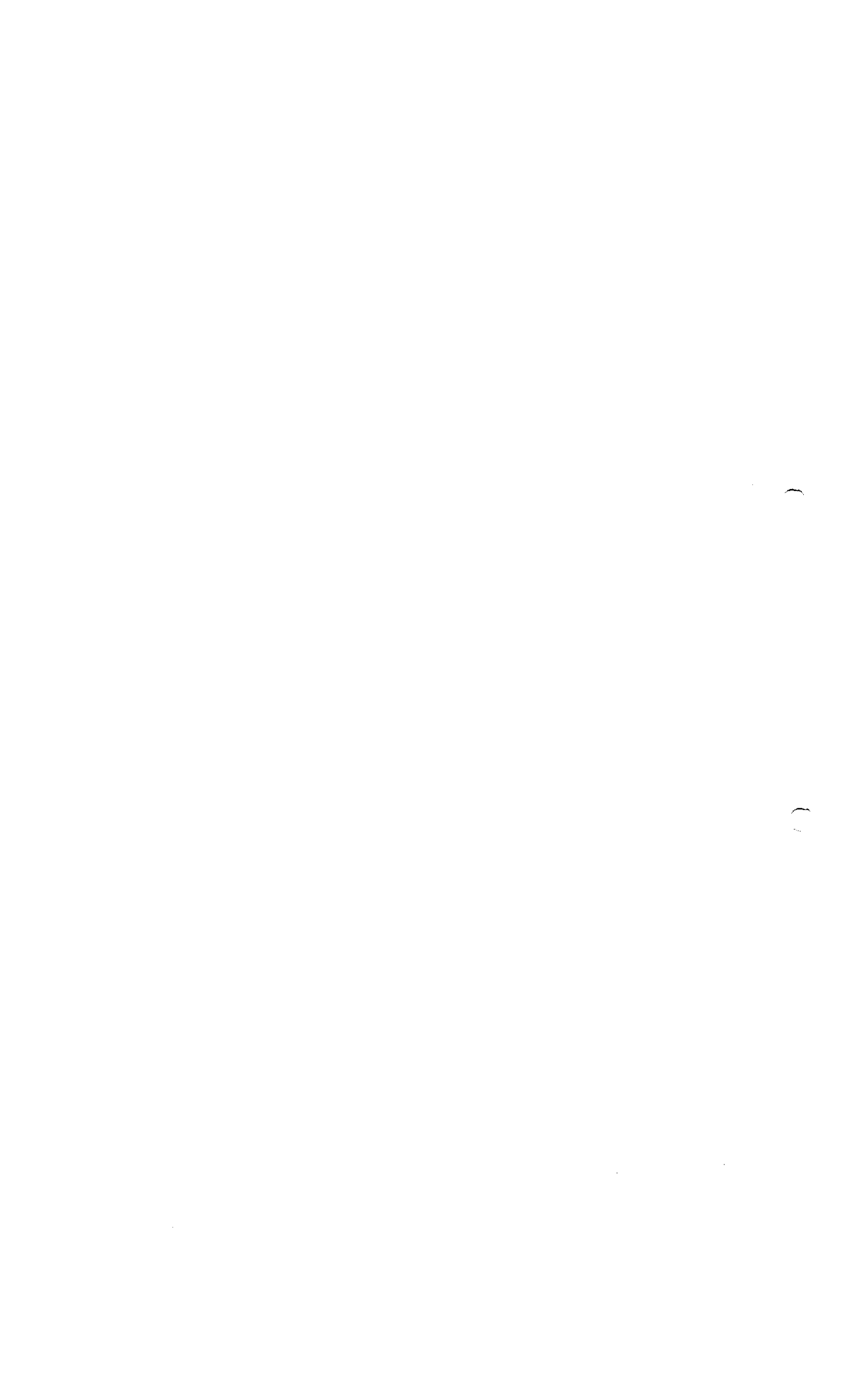
Packed orders may contain several different batches and items gathered inside same boxes stacked on pallets (the storage rule : "1 batch per location" does not apply any longer at this stage).

A packing list must be issued for each order (not for each parcel or box) and enclosed to the products or transmitted separately:

- To support checks at receipt and customs clearance + invoicing processes if exportation
- And archived to trace and record order preparation (paper / or computer)

 ROXANA MONTEMILONE  
DIRECTORA TÉCNICA  
SANOFI PASTEUR S.A.

 CHRISTIAN DOMINICO  
GERENTE  
SANOFI PASTEUR S.A.



## 5.2.2 Shipment

### 5.2.2.1 Principles & methods

Optimization of delivery time and temperature must be based on following criteria:

- Reliability (including supplier qualification or certification and partnership)
- Acceptable delivery time (e.g. airplane vs. sea freight)
- Distance, geography (e.g. overseas) and category of delivery target (e.g. forwarding agent, wholesaler, retailer, healthcare center, doctor, patient, etc.)
- Ensuring temperature required conditions are met (e.g. frozen, refrigerated, ambient, etc.)
- Minimize intermodal shipment
- Minimize transfer locations
- Use one carrier for shipment when possible
- Based on the shipment size and service requirement the appropriate refrigerated truck or qualified shipping container will be selected.



#### 5.2.2.1.1 Refrigerated Transportation

When it is possible, large volumes of temperature sensitive goods should preferably be transported in temperature-regulated vehicles or special containers.

The truck /container load will be considered as a whole transportation batch.

Service Agreement used for refrigerated transport by road must mention:

- Compatibility problems if not fully dedicated transport (e.g. untransformed food products such as meat carcasses, fish, etc. within specialized networks for food industry)
- The service agreement must specify the steps and conditions that can lead to loading or unloading of the product (breaks in transit must be minimized)
- Temperature setting instruction and authorized range (e.g. continuous setting vs. cycle setting to avoid experiencing the defrost cycle)
- Carrier maintenance and calibration records for temperature monitors must be readily available.

  
ROXANA MONTEMILONE DIRECTORA TÉCNICA  
  
CHRISTIAN DOMINGUEZ GERENTE  
SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.

Confidential/Proprietary Information

On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations  
Status: Effective  
Justification: Intranet export

Exported by HICKS Katherine  
To Katherine Hicks



### 5.2.2.1.2 Insulated containers

Insulated containers can be single or multiple use models.

Multiple use models require inspection and damage repair prior to re-use (i.e. cleaning, drying to prevent mold, cooling elements regeneration, check of packaging functions and re-labelling).

#### 5.2.2.1.2.1 Functions

Packaging function must ensure:

- Products protection from outside ambient conditions: temperature, humidity, vibrations, shocks or drops (cf. WHO / or ASTM specifications)
- Shipment identification during transport (including customs clearance if export) and warning messages when applicable (e.g. "cold chain" / or "hazardous materials" labels as appropriate to the country of destination)
- Tampering evidence to track security checks or customs inspections at airports (e.g. seals, security tape, etc.)

Note1: given that adequate protection is afforded by primary packaging materials, effects of high humidity on the products is relatively insignificant, however, it can have a deleterious effect on the strength of third level cardboard packaging, especially when stacked (cartons may become softened and collapse, exposing their contents to risk of damage from physical shock).

Note2: fragility problems are very critical because they can lead to a wide range of defects (e.g. visible breakage or spoilage but also invisible leaks or cracks) and must be prevented by relevant packaging means (e.g. placing filling or shock absorbent material between the contents and in the void spaces; keeping isolated large-volume liquid containers; anchoring the load to avoid shift, etc.).

Insulating function is based on a combination of variable density and wall thickness of insulating material (e.g. Expanded PolyStyren/Ethylen, Polyurethane foam, Vacuum Insulated Panels, etc.) with cooling elements (e.g. frozen / or refrigerated water, eutectic solution, dry ice, non toxic gels, etc.) absorbing energy variations (e.g. endothermic or exothermic reactions of state change).

The cooling autonomy depends both of initial packaging configuration and temperature profiles met during transit time.

The expected result of insulated packaging is the limitation of calorimetric exchanges by :

- Convection (e.g. storage near heating device or cold room)
- Radiation (e.g. exposure to sunlight)
- Conduction (e.g. contact with cold or hot floor and walls)

Caution: for the single use packaging configuration, cooling elements must not contain any toxic substance which could be ingested afterwards (e.g. further miss use out of sanofi pasteur control) and hence following rules have to be strictly applied :

ROXANA MONTEMILONE CHRISTIAN DOMINGUEZ  
DIRECTORA TÉCNICA GERENTE  
SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.

Confidential/Proprietary Information

Page 17 of 31

Printed documents are uncontrolled copies and must be checked against the current effective electronic version prior to use to ensure version control. All or part of the information contained in this document must be treated as the confidential property of sanofi pasteur or its affiliates. It cannot be published or divulged for whatever purpose to unauthorized persons, or third parties, in any form without the prior written consent of sanofi pasteur.

Status: Effective  
Justification: Intranet export

On 1/3/2011 21:37:36  
Title/Org: Sanofi Pasteur Quality Operations

Exp. by HICKS Katherine  
To Katherine Hicks

