Technical Report No. 39 Revised 2007 Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment

PDA Journal of Pharmaceutical Science and Technology

2007

Supplement

Volume 61

No. S-2

PDA Technical Report No. 39 Revised 2007 PDA第39号技术报告（2007年修订版）

Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment
温度受控的药品的指南：通过运输环境保持温度敏感药品的质量

Temperature-Controlled Pharmaceuticals Group (TPG)—Harmonization Task Force

Rafik H. Bishara, Ph.D., Eli Lilly and Company –ret. (chair and contact person)

Detlef Dichte, Eli Lilly and Company
Shirley-Ann Feld, Sanofi-Aventis
Janne Grusgaard, Novo Nordisk
David Patrick, Johnson & Johnson
Bob Seevers, Ph.D., Eli Lilly and Company
Edward J. Smith, Ph.D., Wyeth
David Ulrich, Abbott Laboratories
Wigand Weirich, Ph.D., Roche
Karl Womastek, Baxter

PDA Technical Report No. 39 PDA第39号技术报告

Cold Chain Guidance for Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment
温度受控的药品的指南：通过运输环境保持温度敏感药品的质量

PDA Cold Chain Management Task Force

Rafik H. Bishara, Ph.D., Eli Lilly and Company –ret. (chair and contact person)

Jim Antonopoulos, Sanofi-Pasteur
Mari Bakken, Abbott Laboratories
Daniel Colton, Genentech Inc.
Laura Fontan, Human Genome Sciences
Derrik Gallagher, Sanofi-Aventis
Paul Harber, Eli Lilly and Company
Kelly Klien, Wyeth
Landauer, Amgen Inc.
Teresa Lucas, Eli Lilly and Company
Sarvang Mishra, Wyeth
Kevin O'Donnell, Abbott Laboratories
Oumer Salim, Wyeth
Jeff Seeley, Merck & Co., Inc
Bob Seevers, Ph.D., Eli Lilly and Company
Edward J. Smith, Ph.D., Wyeth
Douglas Staruk, Wyeth **Chris**
Donald Wilson, Amgen Inc.

Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment

温度受控药品的指导原则：在运输环境下保持温度敏感产品的质量

Technical Report No. 39 (Revised 2007) Supplement
Vol. 61, No. S-2
2007

Table of Contents 目录

This document is a guidance to help minimize the risk to temperature-sensitive medicinal products during transport. It is not intended to establish any mandatory or implied standard. The original version was published in 2005. This is a revised version to harmonize with European Union (EU) regulatory expectations.
本文件是一个帮助最小化温度敏感药品运输风险的指南。其目的不是为了建立强制或隐含的标准。其原版本发布于 2005 年。此版本是为了与欧盟药监部门期望保持一致的修订版。

1.0 Introduction 介绍

Some medicinal products require storage under controlled temperature in order to maintain product quality. In addition to those labeled for refrigerator or freezer storage, some products are stable at controlled room temperature but may suffer degradation at temperatures of 30 ℃ or above or at temperatures below 0 ℃ due to freezing. Such products, where a limited temperature range is necessary to maintain quality, may be termed temperature-controlled pharmaceuticals (TCP). All such products requiring special temperature handling should be transported by appropriately specialized means to ensure product quality is not adversely affected during transport. These products may be shipped outside of their respective label storage conditions provided stability data or scientific/technical justifications exist demonstrating that product quality is not affected and meets the national and international requirements.
为了保持产品质量有些药品需要控制温度储存。除了那些标注了冷藏或冷冻储存的以外，有些产品在控制室温时是稳定的但是在 30 ℃ 或 30 ℃ 以上或者低于 0 ℃ 结冻时可能经受降解。此类产品，何处限定温度范围对保持质量有必要，可以被叫做温度受控药品（TCP）。所有这类需要特殊温度处理的产品应以适当专业的方法运输以确保产品质量在运输中不受不利影响。这些产品也许会在超出其各自标识的储存条件下运送，只要有稳定性数据或科学/技术理由可以证明不影响产品质量并且符合国内外的要求。
This document presents an approach to develop and implement specialized packages and systems that will protect temperature-sensitive products during transport. The design approach is comprised of three elements. These elements are (1) Identification of Requirements, (2) Development, and (3) Implementation.
此文件介绍了一个开发和实施用于在运输中保护温度敏感产品的专业包装和系统的方法。设计方法由三个要素组成，这些要素是（1）基本要求的识别，（2）开发，和（3）实施。
The distribution environment can vary greatly, especially when transporting medicinal products between climatic zones. Seasonal changes, mode of transportation, and regional regulations and capabilities are also variables that must be considered within the transportation environment. These variables should be evaluated on a case-by-case basis.
药品分销环境可能变化很大，尤其当在不同气候分区之间运输药品时。季节变换、运输方式和地区性法规和能力也是在运输环境里必须考虑的变数。这些变数应逐一评估。
Global regulatory expectations, guidelines (e.g., Good Distribution Practices) and compendial standards (e.g., USP <1079>) regarding good storage and transportation practices, and the use of time, temperature, and humidity monitoring devices have been put forth by the World Health Organization (WHO), EU, Canada, Ireland, Australia, Brazil, United States Pharmacopeia (USP), and other government and non-government organizations.
世界卫生组织（WHO）、欧盟（EU）、加拿大、爱尔兰、澳大利亚、巴西、美国药典和其他政府和非政府组织已提出了关于良好的储存和运输规范的国际法规期望、指导原则（如良好配送规范）和药典标准（如 USP<1079>）以及计时、温度和湿度监测设备的要求。

1.1 Purpose 目的

The purpose of this document is to provide guidance to industry on the essential principles and practices of transporting temperature-sensitive medicinal products through the transportation environment. This process is commonly referred to as “temperature-controlled”. This guidance has necessarily been written at a high level. As befits a guidance document, it enunciates the what without providing prescriptive detail on the how. Quality systems should be developed by pharmaceutical companies and extended into the supply chain where appropriate.
此文件的目的是为制药行业在通过运输环境运输温度敏感药品的基本原则和规范上提供指导。此过程通常被叫做“温度受控”。此指南必然已经在一个高水平上编写。如指导性文件该做的那样，它阐明了做什么但没有详细规定怎么做。制药公司应开发质量体系，在适当情况下质量体系应延伸至供应链。

1.2 Scope 范围

The process defined in this document is for temperature-controlled transportation of medicinal products. The same principles may also be applicable for investigational medicinal products, intermediates, excipients, active pharmaceutical ingredients (APIs), and diagnostic products that require temperature-controlled transportation.
此文中确定的过程用于药品温度受控的运输。同样的原则也可用于需要温度受控运输的研究用药物、中间产品、

辅料、原料药和诊断产品。

The level of guidance provided herein should allow firms to develop their own processes and also be aligned with the Center for Drug Evaluation and Research (CDER) Guideline on **General Principles of Process Validation** as adapted in this guidance. Generally speaking, the supply chain cannot be "validated"; however, the principles can be used to qualify portions of the supply chain. Where qualification does not add value, change control can be utilized:

在此提供的指导水平应允许企业去开发其自己的工艺也应与药品评估和研究中心（CDER）的指导原则"**工艺验证的基本原则"**相匹配。总的来说，供应链无法被"验证"；但是这些原则可以用来确认部分的供应链。在确认不增加价值的地方，可以利用变更：

- **Component/System Qualification (CQ; later referred to as Design Qualification, DQ)**

部件/系统确认（CQ；随后被叫做设计确认，DQ）

— Establishing confidence that ancillary component systems are capable of consistently operating within established limits and tolerances

建立辅助组件系统在建立的限度和允许偏差内能够始终地操作的信心。

- **Operating Qualification (OQ) 运行确认（OQ）**

— Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges

安装或改造的设备或系统如期在预期的操作范围内如期执行的具有文件证明的核实。

- **Performance Qualification (PQ) 性能确认（PQ）**

— Documented verification that the equipment and ancilary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications

连接在一起的设备和辅助系统可以基于批准的工艺方法和标准有效并重复地运转的具有文件证明的确认。

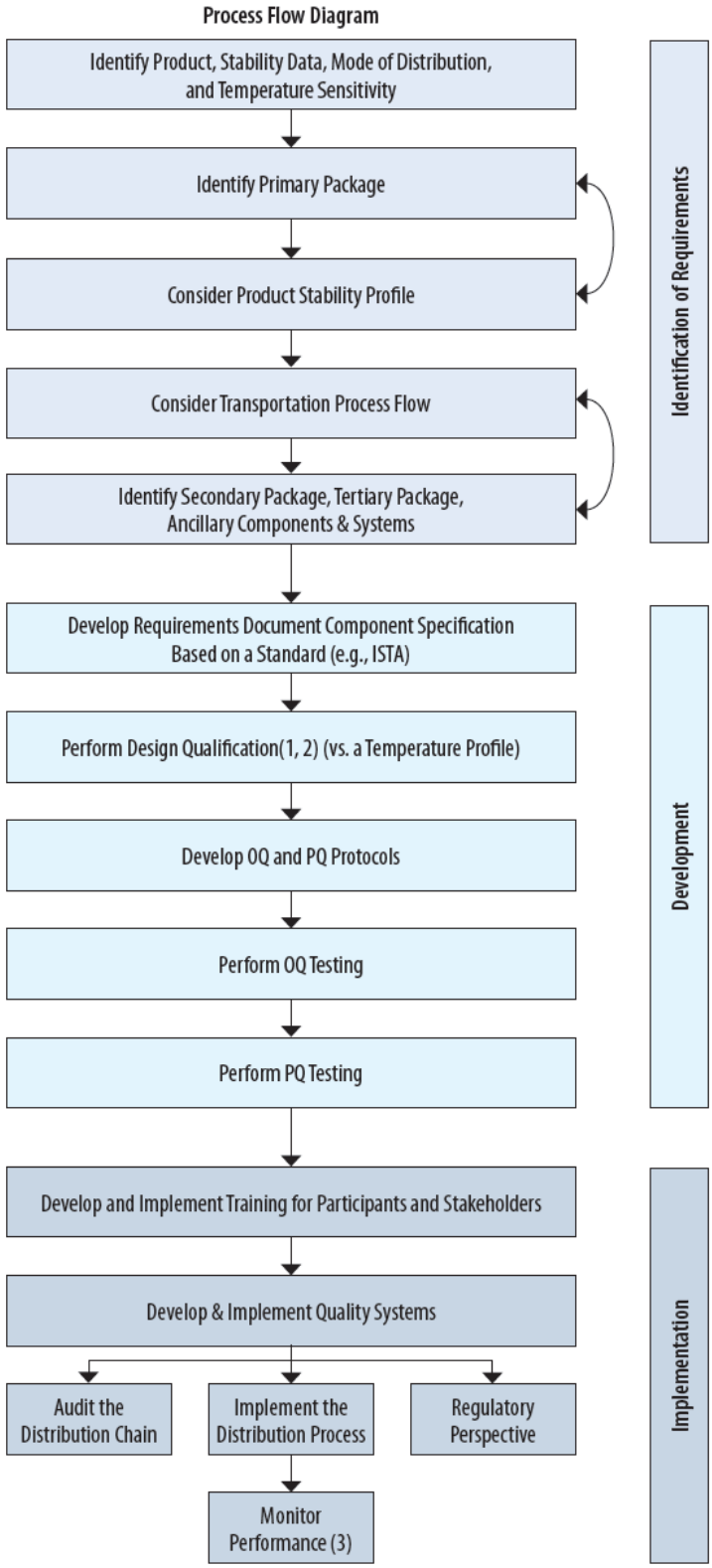
The above principles may be used to reliably qualify the temperature-controlled distribution process. Even a qualified process is subject to change over time. Therefore, periodic and appropriate monitoring is recommended. The frequency and type of monitoring will be based on the specific conditions of a given distribution process. While the qualification process is a typical quality system for manufacturing, it should be noted that it may be a relatively new concept for logistics service providers, e.g. distributors, wholesalers, transportation companies, etc.).

上述原则可用于可靠地确认温度受控的配送过程。实际上已确认的过程会随时间变化。所以建议定期和适当的监控。监控的频次和类型要基于配送过程的特定条件。当确认过程是生产商的典型质量体系时，需要指出的是它可能相对于物流服务商（比如配送商、批发商、运输公司等）而言是一个新的理念

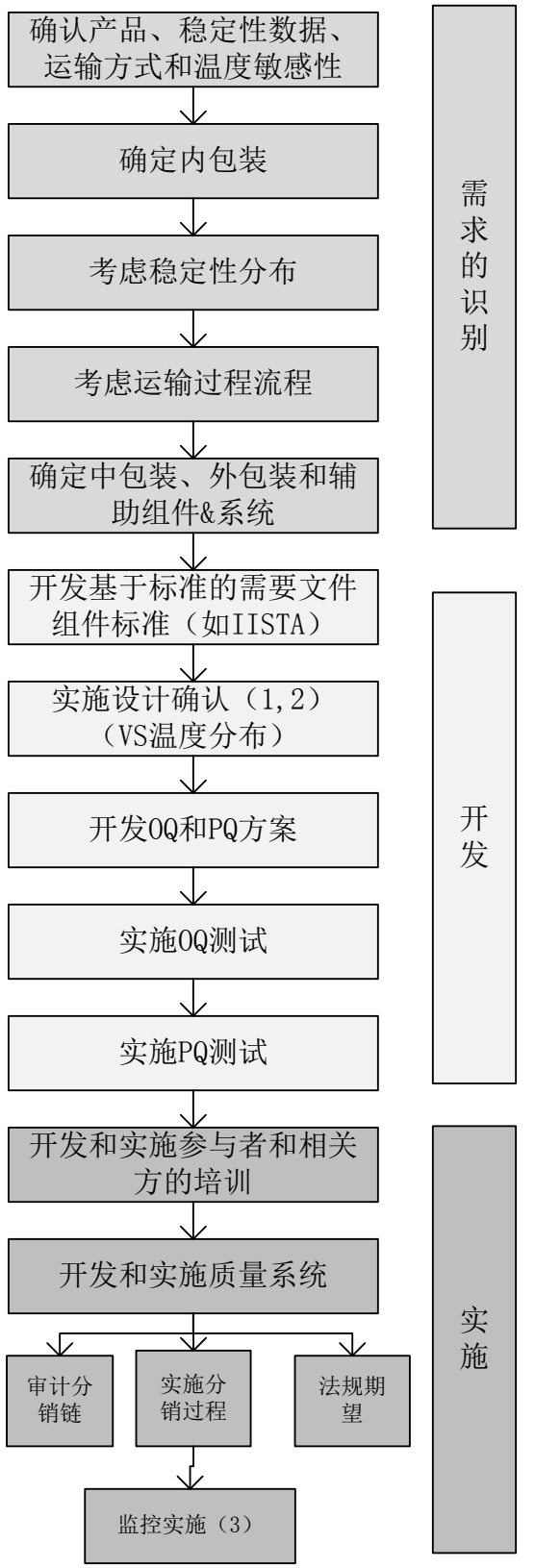
The diagram in **Figure 1** shows an overview of the medicinal temperature-controlled management process flow.

图 1 的示意图展示了整个药品温度受控管理流程。

Figure 1.2-1 ■ Process flow diagram.



Note 1: Temperature profiles should be reviewed periodically and updated as seen appropriate.
Note 2: If a vendor is used, the vendor should be part of the firm supplier audit program.
Note 3: A quality system including change control should be used on the implemented process.



注释 1：温度概况应定期回顾并视情况更新。
注释 2：如果使用供应商，供应商应成为公司供应商审计项目的一部分。
注释 3：包含变更控制的质量体系应在实施的过程中使用。

2.0 Glossary of Terms 术语表

Active Systems: Systems with active temperature control (e.g., air/sea freight containers, refrigerated trucks/cars).
主动系统：带有主动温度控制的系统（比如空运/海运集装箱，冷藏车）
Ancillary Packaging Components/Systems: Additional means used in combination with the basic transportation unit to maintain the required temperature during transport. Examples include active systems and passive systems.
辅助包装组件/系统：为了在运输中维持需要的温度用于与基本运输单元结合的附加手段。实例包括主动系统和被动系统。
API: Active pharmaceutical ingredient.
API：活性药物成分。
Bulk Packaged Product: Consists of solid, liquid, or frozen product in a bulk container configuration such as a bag, tank, or drum. The product may be in these container configurations between process steps or prior to filling into vials, ampoules, cartridges, or syringes.
大包装产品：用大包装配置比如袋子、罐或桶里装的固体、液体或冷冻产品。产品可以在工艺步骤之间或灌装进玻璃瓶、安瓿瓶、、或注射器之前的容器配置里。
Change control: The processes and procedures to manage changes being made.
变更控制：管理变更的过程和程序。
Critical Quality Attributes: Attributes that describe a parameter or item that must be controlled within predetermined criteria to ensure that the medicinal product meets its specification (ICH Q7A).
关键质量属性：为了确保药品符合其质量标准必须在预先确定的标准内描述一个参数或项目的属性（ICH Q7A）。
Design Qualification (DQ): Documented verification that the proposed design of the systems is suitable for the intended purpose. Also establishing confidence that ancillary component systems are capable of consistently operating within established limits and tolerances.
设计确认（DQ）：系统提出的设计适合于预期目的的具有文件证明的核实。也建立辅助部件系统能够始终在已建立的限度和允许偏差范围内操作的信心。
Distribution: Transport of a medicinal product from a drug manufacturer's warehouse/storage facility to distribution centers, commercial customers, or clinical facilities. Subsequent distribution may also occur.
分销（配送）：从药品生产商的仓库/储存设施运输药品至配送中心、商业客户或临床设施。随后的配送也会发生。
Distribution Temperature: The temperature range, supported by stability studies, within which a medicinal product can be transported for a short duration of time without adverse effect on quality parameters.
配送温度：药品可以在短时间内运输不会对质量参数有不利影响的由稳定性考察支持的温度范围。
Intermediate: Material resulting from a pre-step in the manufacture of an active pharmaceutical ingredient (API).
中间体：产生于在一个活性药物成分（API）的生产的前一个步骤的物料。
ISTA: International Safe Transit Association. World-wide organization that supports its membership in designing and developing effective pre-shipment packaging performance standards, guides, and best practices that for product distribution.
ISTA：国际安全运输协会。协助会员设计和开发用于产品配送的有效的转运前包装性能标准、指南和最佳方法的全球性组织。
Market Package: The package presentation intended for the end user (e.g., bottle + cap liner + screw cap + label + dose cup + carton; may contain multiple units of product) but not including packaging used solely for transportation (e.g., corrugated boxes or insulated containers).
市售包装：用于终端用户的包装展示（例如瓶+瓶盖垫+螺旋盖+标签+计量杯+纸盒；可以包含多个产品单元）但是不包含仅仅用于运输的包装（例如瓦楞纸箱或保温箱）。
Medicinal Product: Any product intended for the diagnosis, treatment, or prevention of disease.
药品：用于疾病诊断、质量或预防的产品。
Operational Qualification (OQ): Transport tests that are conducted in a temperature-controlled chamber or by other simulated test protocols. Generally, simulated testing is conducted using a temperature profile that contains the anticipated extremes for the transportation duration and temperature.
运行确认（OQ）：在温度控制箱内或使用其他模拟试验方案进行的运输试验。模拟试验通常是为运输时限和温度所进行的使用包含了预期极限条件的温度概况的试验。
Passive Systems: Systems without active temperature control (e.g., insulated containers with or without refrigerants).
被动系统：没有主动温度控制的系统（如带有或带有制冷剂的保温箱）。
Performance Qualification (PQ): Transport tests of product or representative product that is conducted during actual transportation or distribution.
性能确认（PQ）：在实际运输或配送期间进行的产品或产品替代品的运输试验。

Primary Packaging Component: A component that is (or may be) in direct contact with the dosage form. Some examples of primary components are glass vials, syringe barrels, bottles, rubber closures, and container or closure liners.
内包装：会（或可能会）直接接触剂型（药品）的组件。内包装的例子有玻璃注射剂瓶、注射器筒、瓶子、橡胶塞和容器或密封垫。
Qualification: Documented testing that demonstrates with a high degree of assurance that a specific process will meet its pre-determined acceptance criteria.
确认：用高度保证证明特定工艺将符合其之前确定的合格标准的的具有文件证明的试验。
Quality Management (QM) System for Transport 运输的质量管理（QM）系统
Service Providers: A QM system that may cover topics such as, but not limited to
服务提供商（者）：可以包含但不限以下主题的质量管理系统：
- GMP/GDP-relevant processes identified and described in standard procedures
在标准程序中确认和描述的 GMP/GDP-相关的过程
- A procedure to identify the main functions of individuals, roles and responsibilities, and contact information of relevant individuals in the case of a deviation
确认人员主要职能、角色和职责以及在偏差出现情况时相关人员联系方式的程序。
- An adequate change control system
完善的变更控制系统
- An adequate deviation management system, including procedures for corrective actions
包含了纠正措施程序的完善的偏差管理系统。

Secondary Packaging Component: A component is not nor will not be in direct contact with the drug product (e.g., vial seals, overwraps, container labels). The purpose of secondary packaging is to identify, protect, market, and communicate information about the product. Examples of secondary packaging include labels, cartons/folding boxes, and leaflets.
中包装组件：不是也不会直接与药品接触的组件（如**瓶子封条**、外包装纸、容器标示）。中包装的目的是辨别、保护、销售产品和交流产品信息。中包装的例子包括标签、纸盒/可折叠内盒和说明书。
Shipper: An individual or company who tenders products for transportation.
货主：为运输提供产品的个人或公司。
Shipping: The transit of any material by land, sea, or from one site to another. This may include intra-plant movements.
装运：通过陆地、海上或从一个地点到另一个地点的任何物资的运送。这个包括工厂内部的运转。
Stability: The capacity of a drug substance or a drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the retest period or expiration dating period, as appropriate.
稳定性：一个原料药或药品在整个复验期或有效期内视情况保持在质量标准内以保证其鉴别、效力、质量和纯度的能力。
Stability Profile: The physical, chemical, biological, and microbiological behavior of a drug substance or drug product as a function of time when stored under the defined environmental conditions of an approved protocol.
稳定性概况：当储存在已批准方案中确定的环境条件下作为时间的函数的原料药或药品的物理、化学、生物和微生物性能。
Storage Temperature: The temperature range listed on the medicinal product label specified for long-term storage.
储存温度：列在药品标签上规定的长期储存的温度范围。
Sub-Contractor: An individual or company hired by the transport service provider to perform the actual shipment. The shipper and the sub-contractor do not necessarily have a contractual agreement.
分包商：被承运商雇用的执行实际运输的个人或公司。货主和配送商不一定有合同。
Supply Chain: The process by which a drug product is shipped and distributed from the manufacturer to the end user.
供应链：药品从生产商运输和配送至终端用户的过程。
Transportation Study: Study performed to generate data to evaluate the effect of temperature variation on the product during transportation on product quality. Other tests, such as vibration, pressure, and drop tests, may also be considered.
运输研究：为了生成评估产品运输过程中温度变化对产品的影响的数据实施的研究。也可以考虑其他试验，比如用振动、加压或跌落试验。
T**emperature-Controlled:** The sequence of transportation events, from the manufacture of the API up to the receipt of the final packaged product by the end-user, which maintains temperature-sensitive products within approved temperature specifications. Maintaining temperature control during these transportation events assures that product quality is maintained.
温度受控：从原料药的生产一直到终端用户接收最终包装好的产品保持温度敏感产品在批准的温度标准内的一系列运输事件。确保保持产品质量的这些运输事件中的维持温度的控制方式。

Temperature Excursion: Any event in which product is exposed to temperatures outside of the recommended storage and/or transport temperature range.
温度偏移：产品暴露在温度超出建议的储存和/或运输温度范围的所有事件。
Temperature-Sensitive Products: Products whose quality may be adversely affected by temperature extremes (e.g., frozen, refrigerated, and certain controlled room temperature products).
温度敏感产品：温度极限条件可能会对质量产生不利影响的产品（比如冷冻、冷藏和某些控制室温产品）。
Tertiary Packaging Component: A component that air is used to assemble secondary or primary packages in the form of the basic transportation unit and to provide protection against mechanical impact. Examples are corrugated cardboard boxes, but corresponding plastic boxes/containers are also used.
外包装部件：以基本运输单元形式体现的用于装配中包装或内包装的并针对机械影响提供保护的接触空气的部件。例子是瓦楞纸箱，但也可以使用对应的塑料盒/箱。
Transportation: Movement of medicinal product within a designated supply chain including activities from preparation for shipment up to the point of receiving at the final destination.
运输：药品在指定供应链之内的运转包括从准备装运一直到在最终目的地的接收。
Transport Duration: The time from preparing goods for transport until receipt of goods. This includes, but is not limited to
运输时限：从运输备货一直到货物接收的时间。这个包括但不限于：

- Preparation 备货
- Loading 装货
- Transit 运送
- Intermediate storage 中间储存
- Unloading 卸货

Transport Service Provider: Contracting party who mediates or executes the transportation of medicinal products on behalf of the shipper.
承运商：代表货主斡旋或执行药品运输的承包方。
Transport Service Agreement: A contractual agreement that describes the legal, logistical, technical and quality terms or contractual arrangements between shippers and transport service providers. Different names might be used for this type of agreement in different companies.
运输服务协议：描述货主与承运商之间法律、物流、技术和质量条款或合同约定的合同协议。不同公司这类协议可能使用不同的名称。
Temperature Profile: Anticipated ambient temperature variation and duration to which product may be exposed during transportation.
温度概况：在运输期间产品可能暴露的预期的环境温度变化和持续时间。
Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting pre-determined acceptance criteria.
验证：证明工艺、方法和系统始终能够得到符合预先确定的标准的在高度控制条件下完成的具有文件证明的测试。

3.0 Principles of Qualification for Transport 运输确认原则

The principles of qualification for the transport of temperature-sensitive medicinal products closely follow established guidelines and regulations for qualifying the manufacture of these same products. These include
温度敏感药品运输确认原则密切遵循确认同一产品的生产已建立的指导原则和法规，这些包括：

- Development of specifications, processes, systems, and components 标准、工艺、系统和组件的开发
- Written procedures 书面的程序
- Approved protocols and reports 批准的方案和报告
- Justified test methods and acceptance criteria 经证明的测试方法及其合格的标准
- Qualification testing that challenges “anticipated extremes”挑战“预期最恶劣的条件”的确认试验
- Ongoing monitoring and/or periodic evaluation 持续的监测和/或定期评估
- Change control 变更控制

Medicinal products are transported in a commercial environment as opposed to a controlled laboratory environment. Therefore, factors such as unforeseen transport events and the weather affect the actual conditions a specific shipment may encounter. These factors should be considered when designing test protocols and in understanding “anticipated extreme” challenges. Utilizing this type of information (typical transportation extremes) to support widening shipping specification versus label claim storage conditions is beneficial, if supported by product stability data.
药品在商业环境运输与受控试验室环境截然不同。所以比如无法预见的运输事件和天气等因素都会影响特定货物遇到的实际情况。当设计试验方案和理解“预期最恶劣的条件”挑战时应该考虑这些因素。如果产品稳定性数据支持，有利于使用此类信息（典型的运输最恶劣的条件）去支持相比标示要求的储存条件扩大的运输标准。

4.0 Product Stability Profile 产品稳定性概况

Medicinal products must be transported in a manner that ensures products will be maintained within an acceptable temperature range. The acceptable temperature range may differ from the conditions specified for long-term storage and is determined by performing product temperature-excursion studies. These products may be shipped outside of their respective label storage conditions (example: 0–15 ℃ for product with storage conditions of 2–8 ℃, mean kinetic temperature no greater than 8 ℃, per USP controlled cold temperature guidelines) provided stability data or scientific/technical justification exists demonstrating that product quality is not affected and that the data or justification meets the applicable national and international requirements.

药品必须以可以确保产品保持在合格温度范围内的方式运输。合格温度范围可以不同于为长期储存规定的条件并通过实施产品温度偏移研究确定。只要存在证明产品质量没有被影响的稳定性数据或科学/技术理由和数据或证据符合适用的国家和国际要求，这些产品就可以在超过其各自标示的储存条件下运输（例如储存条件 2~8 ℃的产品 0~15 ℃ ，平均动力学温度不高于 8 ℃，按照美国药典 USP 低温受控指导原则）

When product is exposed to temperature excursions during shipping, an investigation should occur and stability data or technical justification should be used to support the quality of the product.

当产品在运输中暴露在温度偏移环境下时，调查应该发生，应使用稳定性数据或技术理由去支持产品的质量。

The objective of this section is to outline studies for evaluating the impact of temperature excursions on product stability that may occur during transport of medicinal products.

本节的目标是概述了为了评估在药品运输过程中可能发生的温度偏移现象对产品稳定性的影响进行的研究。

Figure 2 shows the basic principles of the proposed product stability studies.

图 2 指出了建议的产品稳定性考察的基本原则。

Figure 4.0-1 ■ The basic principles of the proposed product stability studies.

Principle	Reference
Long-term and accelerated stability studies are run on final formulation in final primary package	ICH Q1A
Transportation studies designed to include anticipated ambient temperature variation and duration are run when primary stability studies are initiated	Company Decision
Upon completion of transportation study, samples may be placed on long-term-stability testing conditions	Company Decision
Note: Generally speaking, it is acceptable to ship controlled room temperature (CRT) products at refrigerated conditions. The pharmaceutical company should assemble the appropriate technical justification or stability data to support this practice.	

图表 4.0-1 建议的产品稳定性考察的基本原则

基本原则	参考文件
长期和加速稳定性考察基于最终制剂步骤以最终内包装形式进行。	ICH Q1A
当主要的稳定性考察开始后，应进行设计为包括预期环境温度变化及其持续时间的运输研究。	公司决策
基于完成的运输研究，样品应该放在长期稳定性测试条件下。	公司决策
备注：总的来说，在冷藏条件下运输控制在室温条件下（CRT）的产品是可接受的。制药企业应该收集技术理由或稳定性数据来支持此活动。	

These studies (temperature cycling studies or temperature excursion studies) will expose medicinal products to temperature conditions outside of the long-term storage conditions submitted for approval. The main purpose of these studies is to demonstrate the "robustness" of a product versus typical temperature excursions seen in the supply chain. (See **Section 14.0, Tables 1–4: Long-term stability study—ICH Q1A; Accelerated stability study—ICH Q1A; Temperature excursion study; Thermal Cycling Study**.)

这些研究（温度循环研究或温度偏移研究）将使药品暴露在超出呈请批准的长期储存条件的温度条件下。这些研究主要目的是为了证明产品对供应链中发现的典型温度偏移条件的耐受性。（**见 14.0 节，表 1~4:长期稳定性考察-ICH Q1A；加速稳定性考察—ICH Q1A；温度偏移研究；温度循环研究**）

The idea is to evaluate stability data from long-term and accelerated stability studies, temperature-excursion studies, and/or temperature cycling studies to predict the impact of temperature excursions on medicinal product quality during the transportation process. An example of a comprehensive study design for a refrigerated product to generate sufficient stability data to determine the potential effect of temperature excursion on product quality is presented in Table 14.0-5. In this example, the product has three strengths; in addition to long-term and accelerated stability data, a bracketing approach is used in which the high and low strengths are also tested under freezing conditions, at 40 ℃, and under

temperature cycling conditions. Other study designs may be used as appropriate.

此理念是通过评估长期和加速稳定研究、温度偏移研究和/或温度循环研究来预测在运输过程中温度偏移对产品质量的影响。一个设计用来通过生成有效稳定数据以确定温度偏移对冷藏产品质量的潜在影响的的综合研究的例子列举在表 14.0-5 中。在这个例子中，产品有三个强度；除长期和加速稳定性数据外，归类法被用在冷冻条件下测试哪一点最高和最低点以及在温度循环条件下的 40 ℃。可以酌情使用其他研究设计。

Table 14.0-6 is an example of compiling the results of the stability studies from the example protocol shown in **Table 14.0-5**. This then would serve as a guide to the type and extent of temperature excursions that would be supported by the stability data for this example product. Transportation study results from **Table 14.0-5** have been used to write the Transportation Control Strategy document shown in **Table 14.0-6**. The stability data support the temperature excursions for the time periods indicated.

表 14.0-6 是一个收集来自于**表 14.0-5** 给出的示例方案的稳定性考察结果的示例。然后此示例对由此示例产品稳定性数据来支持的温度偏移类型和范围将起到一个指南的作用。从**表 14.0-5** 中得出的运输研究的结果已经被用于编写在**表 14.0-6** 中给出的运输控制策略文件。稳定性考察数据支持显示时间期间的温度偏移情况。

Note: A table such as **Table 14.0-5** should be constructed for each product based on product-specific stability data.

备注：应该基于特定产品的稳定性数据为每个产品建立类似**表 14.0-5** 的表格。

The process described covers newer products for which International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) stability data are available. Pre-ICH guidance products will need to be assessed on a case-by-case basis.

上面描述的过程覆盖已有 ICH 稳定性数据的新产品。在 ICH 指南之前的产品也需要逐一进行评估。

A Note on Storage Temperature versus Distribution Temperature: Storage temperatures of drug products are relatively constant, and stability studies intended to support storage conditions take into account expected variations of storage temperatures; thus drug products intended for storage at 20 ℃ may usually be stored at 25 ℃. It is not possible to control the temperature of product in the same way during the distribution process; therefore additional studies at anticipated extreme temperatures (e.g., elevated or freezing temperatures) should be performed. Long-term storage or label storage temperatures may be different from short-term shipping/distribution temperatures.

储存温度与配送温度的一点注释：药品的储存温度是相对恒定的，旨在支持储存条件的稳定性考察考虑了储存条件下的预期变化；因此用来储存在 20 ℃ 的药品可能常常存放在 25 ℃。但在配送过程中使用同样的方式控制产品的温度是不可能的；因此应实施在预期极端温度（如高温或冷冻温度）下的附加研究。长期储存或标示的储存温度可能不同于短期运输/配送的温度。

5.0 Transportation Process Flow Considerations 运输工序流程注意事项

5.1 Development of Temperature Profiles for Use in Qualification Studies 用于确认研究的温度概况的开发

In order to perform qualification studies of shipping systems, which have to maintain a defined temperature range during transport, it is typically necessary to conduct laboratory testing to thermally challenge the packages and systems. These tests should be conducted using environmental temperature profiles (also termed “ambient profiles”) that are typical of the conditions that the package will encounter during a shipment. In order to develop the testing profiles, the shipper should consider a number of factors, including but not limited to

为了实施确认运输系统必须在运输过程中保持已确定的温度范围的研究，通常需要进行针对包装和系统的温度挑战的实验室测试。这些测试应使用包装在运输过程中会遇到的典型条件下的环境温度概况来进行（也称作“周围环境概况”）。为了开发测试概况，货主应考虑许多因素，包括但不限于以下因素：

- Temperature conditions at origin, destination points, and throughout the complete route

出发地、目的地和整个运输路线的温度条件

- Seasonal temperatures (winter versus summer)

季节性气温（冬季与夏季）

- Transport routes and modes (overnight air, ground, international, etc.)

运输路线和方式（通宵空运、地面运输、国际运输等）

- Total duration of transit

运输整个持续时间

- Duration, temperature, and location of various handling/stopover points along routes

沿着运输路线的各种各样处理/中途停留点的持续时间、温度和地点

- Product handling at various handling/stopover points along routes

沿着运输路线的各种各样处理/中途停留点的产品处理

Sound rationale should be provided for the process used in developing temperature profiles used in transport qualification testing.

应为开发用在运输确认测试中的温度概况的过程提供合理论据。

Environmental profiles should be based on realistic expectations of transport temperatures, which are developed using scientifically sound criteria. This may be done using field-testing (monitoring) of actual shipments, review of historical environmental data, review of published standards (i.e., ISTA 7D, USP <1079>, etc.), or by other means. Profiles should include anticipated extreme conditions in order to challenge the effectiveness of the temperature-controlled package or system, whenever possible.

环境概况应该基于对运输温度的实际期望，并使用科学合理的标准进行开发。这个可以使用实际运输的实地测试（监控）、历史环境数据的回顾、已发布标准的回顾（如 ISTA 7D、USP<1079>等）或其他方式来完成。只要可能，为了挑战温度受控包装或系统的有效性概况应该包含预期的最恶劣的条件。

Anticipated extremes in ambient temperatures to which the product may be exposed are sometimes referred to as “summer” and “winter” or “hot” and “cold” temperature profiles. Where actual historical temperature data in transportation is not available, the scenarios may be defined by calendar months or actual temperatures at product origin, product destination, along the transport route, and at transportation hubs (as applicable).

产品可能暴露在环境温度下预期最恶劣的条件有时会涉及到如“冬天”和“夏天”或“热”和“冷”温度概况。如果没有运输过程中实际历史温度数据，可以通过产品发运点、产品目的地、整个运输路线和交通枢纽（如果适用的话）的日历月份或实际的温度来确定场景。

5.2 Packaging (Passive) and Transportation (Active) Systems 包装（被动的）和运输（主动）系统

Shipment under temperature-controlled conditions may be required for investigational medicinal products as well as market packages and any precursors to the market package such as APIs, intermediates, excipients, bulk-packaged drug products, or packages of multiple units of the labeled or unlabeled drug product in its primary package (e.g., vial or syringes).

温度受控条件下的运输即可研究用药品要求也可已对市场包装及其市场包装的任一前体比如原料药、中间体、辅料、大包装药品或在其内包装（比如小瓶或注射器）标识或不标识为药品的多单元包装。

Packaging must be identified to determine the amount of thermal mass that must be temperature-controlled. The greater the thermal mass, the less reactive it is to ambient temperature variation.

包装必须被确认以确定必须进行温度受控的蓄热量的数量。蓄热量越大，其对环境温度变化的反应越小。

5.2.1 Packages/Components/Systems 包装/部件/系统

Components that need to be identified are divided into primary, secondary, tertiary, and ancillary packaging components. Primary/secondary/tertiary packages or packaging components are part of standard packaging processing steps, independent of whether or not temperature control is required. Ancillary packaging components or systems are to maintain the required temperature during transport.

需要确认的部件被分为内包、中包、外包和辅助包装部件。内包装/中包装/外包装或包装组件均是标准包装工艺步骤的一部分，不依赖于是否需要温度控制。辅助包装组件或系统是为了在运输中保持要求的温度。

- A primary packaging component is one that is or may be in direct contact with the dosage form. Some examples of primary components are glass vials, syringe barrels, bottles, rubber closures, and container or closure liners.

内包装组件是或可能与制剂产品直接接触的部件。主要部件比如玻璃小瓶、注射器筒、瓶、橡胶塞和容器或密封垫。

- A secondary packaging component is one that is not, nor will be, in direct contact with the dosage form. The purpose of secondary packaging is to identify, protect, market, and communicate information about the product. Examples of secondary packaging include labels, cartons/folding boxes, and leaflets. The materials and components selected for the secondary package may affect the design of the transportation container and/or system. The secondary package must be identified to determine the minimum and maximum product loads that can be placed within the transportation container/tertiary package. The secondary package also determines the number of primary packages that can be placed within it.

中包装部件是现在和将来都不会直接接触制剂产品的部件。中包装的目的是为了鉴定、保护、销售产品和交流产品信息。中包装的例子包括标签、纸箱/折叠内盒和说明书。选择的中包装的材质和部件可能影响运输容器和/或系统的设计。中包装必须被确认以确定可以放置在运输容器/外包装内的最小和最大产品装载量。中包装也决定了可以装载在其中的内包装的数量。

- A tertiary packaging component is one used to assemble secondary or primary packages in form of the basic transportation unit and to provide protection against mechanical impact for the medicinal product during handling and transport. Examples are corrugated cardboard boxes, but corresponding rigid plastic boxes/containers are also used.

外包装部件是用于装配中或内包装以基本运输单元形式体现的可以针对药品在处理和运输的机械影响提供保护的部件。实例有瓦楞纸板箱，但也使用相当的硬质塑料箱/容器。

The assembly of primary and/or secondary packages with tertiary packaging components in the form of the basic transportation unit is the overall thermal mass that must be temperature-controlled.

内包装和/或中包装与外包装部件以基础运输单元的形式组合在一起就是必须进行温度受控的全部蓄热量。

- Ancillary packaging components/systems are additional means used in combination with the basic transportation unit to maintain the required temperature during transport. Examples are

辅助包装部件/系统是为了保持运输过程中要求的温度与基础运输单元联合使用的附加手段。例子有：

— Active systems: Systems with active temperature control, for example, air/sea freight containers, refrigerated trucks/cars

主动系统：带着主动温度控制的系统，例如空运/海运集装箱、冷藏车

— Passive systems: Systems without active temperature control, for example, insulated containers (made of expanded poly-styrene or poly-urethane) with or without refrigerants

被动系统：没有主动温度控制的系统，例如带或不带制冷剂的保温箱（由聚苯乙烯或聚氨基甲酸酯泡沫做成的）

— All practical combinations thereof 所有实际它们的组合

6.0. Design and Development 设计和开发

6.1 Functional Requirements Document 功能要求文件

The functional requirements document is the summary of the Identification of Requirements process step. The purpose of this step is to document the critical parameters of the product, packaging, and transport system previously identified in Sections 1.0 through 4.0. Critical parameters can include

功能要求文件是识别要求过程步骤的总结。此步骤的目的是文件化前面在 1.0 节至 4.0 节中识别的产品、包装和运输系统的关键参数。关键参数可能包括：

- Transportation (e.g., duration, mode(s), route(s))运输参数（如时限、模式、路线）
- Product stability (e.g., temperature range established)产品稳定性（如已建立的温度范围）
- Packaging 包装
- Minimum/maximum expected shipping volumes 预期最大/最小装运容积
- Minimum/maximum thermal mass 最大/最小蓄热量
- Expected ambient profiles 预期的环境温度分布图
- Material requirements/restrictions 物料要求/限制条件
- Marketing requirements 市场要求
- User requirements 用户要求

6.2. Component/System Specification (CS) 部件/系统标准

This section of the guidance outlines general principles that apply to the ancillary packaging components and systems for the transport process. Product temperature-impact components/systems are those that may reasonably be expected to have a direct effect on the temperature performance of a transportation system. Examples of product temperature-impact components include insulated containers and refrigerants. The CS establishes confidence that components/systems are capable of consistently performing within established limits and tolerances.

本节指导原则概括了应用于运输过程中的辅助包装部件和系统的基本原则。产品温度影响部件/系统是那些可以被合理期望对运输系统的温度特性有直接影响的部件/系统。产品温度影响部件的实例包括保温箱和制冷剂。部件/系统标准建立了对部件/系统能够在已建立的限度和允许偏差内可以持续执行的信心。

A specification should be generated to outline component/system requirements as applicable. This specification may include, but is not limited to

应该生成一个标准以概述同样适用的部件/系统要求。此标准可以包括但不限于以下内容：

- Material requirements 物料要求
- Mechanical requirements 机械要求
- Dimensional requirements 尺寸（空间）要求
- Printing requirements 印刷要求
- Storage requirements 储存要求
- Sampling requirements 取样要求
- Weight requirements 称量要求
- Calibration limits 校准范围
- Fragility limits 易碎限制
- Shock and vibration limits 冲击和振动限制
- Insulation requirements 保温要求
- Proposals for re-usability & environmental considerations 重复使用&环境考虑的建议
- Non-toxic and non-hazardous materials 无毒无害材料
- Recommendations on the dimensions 外形尺寸方面的推荐

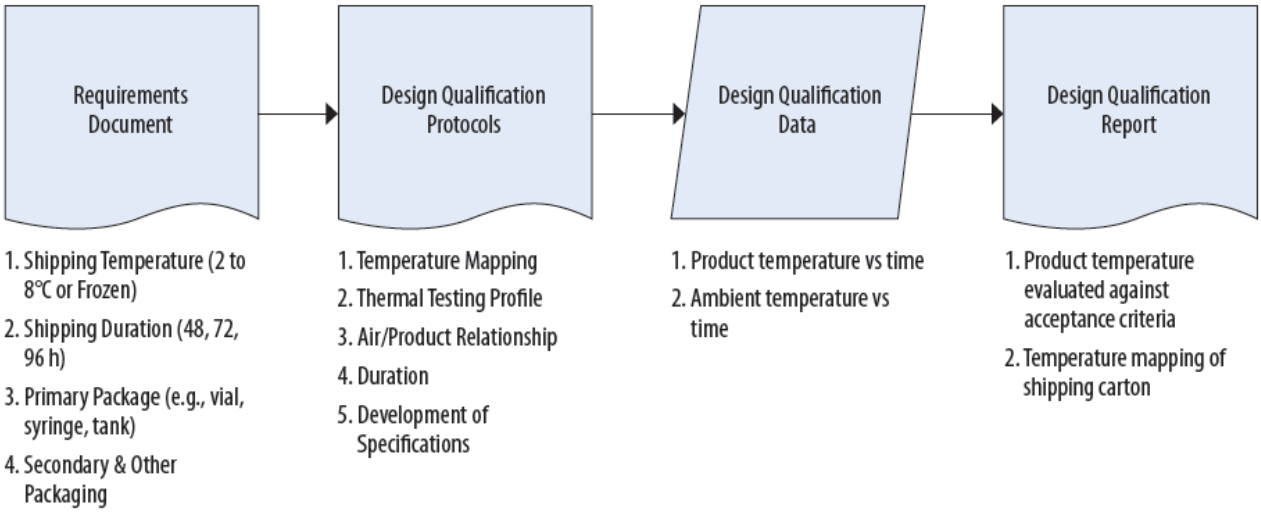
6.3 Design Qualification (DQ) 设计确认（DQ）

Design qualification should be performed prior to operational qualification (OQ) and performance qualification (PQ). DQ is performed to ensure that functional requirements are met by the proposed package or system. DQ process parameters typically include, but are not limited to
设计确认应在运行确认（OQ）和性能确认（PQ）前实施。实施 DQ 以确保通过推荐的包装或系统来满足功能要求。DQ 过程参数典型包含但不限于

- Process duration 过程持续时间
- A defined ambient temperature profile 确定的环境温度概况
- Quantity, temperature conditioning, and location of refrigerant or air conditioning system 数量、温度条件和制冷剂或空调系统的位置
- Product shipping configuration and temperature monitoring device location 产品装运结构和温度监控设备位置
- Type of insulating material/air conditioning system 保温材料/空调系统的类型
- Minimum and maximum thermal mass/loads 最小和最大蓄热量/装载量
- Location of the thermocouples 热电偶的位置

The outcome of successful DQ assures a high confidence for successful operational qualification (OQ) of a specific package or system. The results of DQ should be formally documented in a report. DQ is illustrated in **Figure 3**.
成功 DQ 的结果高度确保特定包装或系统成功的运行确认。DQ 的结果应该以报告的形式正式地文件化。DQ 在图 3 中举例说明。

Figure 6.3-1 ■ A design qualification (DQ) process.



需求文件	设计确认方案	设计确认数据	设计确认报告
1、运输温度（2 到 8 度或冷冻） 2、运输时限（48、72、96 小时） 3、内包装（比如小瓶、注射器、罐） 4、中包装&其他包装	1、温度分布图 2、热测试分布 3、空气/产品之间关系 4、时限 5、标准的开发	1、产品温度 vs 时间 2、环境温度 vs 时间	1、针对合格标准评估的产品温度 2、运输外箱的温度分布图

7.0 Operational and Performance Qualification Testing 运行和性能确认测试

A Note on Qualification versus Validation: Qualification is documented testing that demonstrates with a high degree of assurance that a specific process will meet its pre-determined acceptance criteria. Validation is documented testing, performed under highly controlled conditions, that demonstrates that a process consistently produces a result meeting pre-determined acceptance criteria. Furthermore, validation is used to test processes, methods, and systems for which conditions can be controlled in the real world (i.e., after completion of testing, when the process is in use).
关于确认与验证的注释：确认是为了证明可以高度确保特定工艺将符合其预定合格标准的具有文件证明的测试。验证是在高度控制条件下实施的具有文件证明的测试，证明工艺始终可产生符合预定合格标准的结果。此外，验证用于测试过程、方法和系统以确定哪些条件在现实世界（比如完成测试后，当工艺在使用中时）可以被控制。
Therefore, transportation processes can be qualified rather than validated, as it is not possible to control, in the real world, all the parameters that could affect the transportation process (e.g., weather, customs and traffic delays, mechanical failures, etc.). A qualified process may change over time. Therefore, periodic and appropriate monitoring is recommended. The frequency and type of monitoring will be based on the specific conditions of a given distribution process.
因此运输过程可以确认而不是被验证，因为它不可能在现实中控制所有可能影响运输过程的参数（比如气候、客户和交通延误、机械故障等）。一个经确认的过程可能会随时间而改变。因此建议使用定期和适当的监控。监控的频率和类型将基于给出的配送过程的特定条件。

OQ/PQ should be performed using the designated transport configuration to provide assurance that product quality is maintained during transport. Qualification testing and results should be documented in a formal report.
应使用指定的运输结构实施 OQ/PQ 以为在运输中保持产品质量提供保证。确认测试及其结果应该以正式报告的形式形成文件。
The OQ and PQ protocols, test plans, and procedures should contain at a minimum the
OQ 和 PQ 方案、测试计划和程序应该至少包含以下内容

- Testing objective 测试目的
- Scope 范围
- Materials description 物料描述
- Equipment description and calibration information 设备描述和校准信息
- Critical quality attributes 关键质量属性
- Critical performance parameters 关键性能参数
- Test methods and rationale 测试方法及原理
- Acceptance criteria 合格标准

7.1 Qualification Protocol 确认方案

Qualification testing should always be performed under a pre-approved protocol, test plan, or procedure. Testing typically consists of OQ and PQ.
确认测试应始终在预批准的方案、测试计划或程序下实施。测试通常包含 OQ 和 PQ。

7.1.1 OQ Testing OQ 测试

Testing may be performed using temperature-controlled environments (i.e., temperature chambers) or actual shipments at ambient temperatures (i.e., field testing) as appropriate, based on the projected transportation channel. The testing should reflect actual transportation load conditions and configurations.
测试基于计划的运输通道可以使用温度受控环境（如恒温槽）或视情况在环境温度（实地测试）的实际运输情况进行。测试应反映实际运输的装载条件和结构。
Product or approved representative material may be used in qualification testing. Rationale for using approved representative material should be included in the qualification protocol.
确认测试可以使用产品或批准的替代物。使用批准的替代物的原因应包含在确认方案中。
All packaging components used in testing should be approved for use.
所有用在测试中的包装部件应经过批准才能使用。
Calibrated temperature data loggers should be placed directly in contact with the product or representative product, if possible, to collect temperature data. Sufficient positions within the load should be monitored to get representative temperature data on variances that may be inherent to the load packing, load configuration, or manner of transport.

如果可能，经过校准的温度数据记录仪应该直接放置在与产品或替代产品接触的位置以收集温度数据。应该在装载内监测足够的点以获取装载包装、装载结构或运输方式内在变化的有代表性的温度数据。

OQ testing should include but is not limited to OQ 测试应该包括但不限于以下内容：

- Use of temperature profiles designated according to Section IV 根据 IV 节指定的温度概况的使用
- Duration beyond what is anticipated for the transport process 超过运输过程期望的时限
- Minimum and maximum transportation load configurations 最小和最大运输装载结构
- Defined packing configuration(s) 确定的包装结构
- Calibrated temperature monitors 经过校准的温度监控器
- A sufficient number of tests to assure reliable results 确保可靠结果的足够的测试数量
- Identification of temperature-monitoring locations for PQ 为 PQ 识别温度监控点

7.1.2 PQ Testing PQ 测试

PQ testing consists of consecutive, replicate field transportation tests to demonstrate that the process is effective and reproducible.

PQ 测试由连续重复的现场运输测试组成以证明过程是有效和可重复的。

Testing is performed using typical load configurations. Sound rationale to justify the test methods, number of tests, and load configurations (as applicable) should be stated in the protocol.

使用典型的装载结构实施测试。应该在方案中规定证明测试方法的合理原理、测试数量和装载结构（如果适用的话）。

PQ testing should be executed according to approved standard operating procedures (SOPs) and include

应该按照批准的标准操作规程（SOPs）实施 PQ 测试，包括

- Actual ambient temperature variances, including seasonal changes customary in transportation

实际的环境温度变化，包括在运输中习惯的季节变化

- Representative transportation load configurations 典型的运输装载结构
- Defined packing configuration(s) 确定的包装结构
- Calibrated temperature monitors 经过校准的温度监控器
- A sufficient number of tests to assure reliable results 确保可靠结果的足够数量的测试

8.0 Process Implementation and Training 过程实施及培训

The specific transport systems and temperature-controlled packaging systems are confirmed during qualification. Transfer of the qualified process to the operational areas is formally accomplished by means of approved procedures that will implement the controls of critical process parameters which will result in repeatable, successful transport of medicinal products. The written, approved procedures should be in place and responsible personnel should be trained prior to implementation of the process. Consideration should be given to the attachment of procedures used in the PQ report.

特定运输系统和温度受控的包装系统在确认过程中被确认。已确认的过程转换至操作区域通过批准的程序的方式正式完成，此程序将执行对可带来可重复并成功运输药品的关键工艺参数的控制。书面的并经过批准的程序应在现场，负责人员在过程实施前应已经过培训。应考虑放在用在 PQ 报告中的程序附件中。

Training should provide instruction to relevant personnel and organizations participating in the temperature-controlled process (i.e., process stakeholders) concerning the principles of packaging, qualifying, and transporting temperature-sensitive medicinal products.

培训应为参与温度受控过程（如过程相关方）的相关人员和组织提供包装原则、确认和运输温度敏感药品相关的指导。

9.0 Quality Systems 质量体系

Regulated good distribution processes and systems used for transportation of temperature-sensitive medicinal products require a foundation of quality systems to support their use. These systems provide a high degree of assurance that the qualified transportation system will continue to perform as intended.

需要建立质量体系来支持在温度敏感药品运输中使用法规规定的良好分销过程和系统。这些系统将高度保证经过确认的运输系统将如预期一样继续实施。

The quality systems should include the following, as applicable:

如果适用，质量体系应包含以下内容：

- Approved written procedures and specifications 批准的书面程序和标准
- Calibration program 校准项目
- Stability program 稳定性项目
- Qualification program 确认项目
- Deviation and investigation program 偏差及调查项目
- Corrective and preventive action (CAPA) program 纠正预防措施项目
- Training program 培训项目
- Audit program 审计项目
- Periodic temperature-controlled process assessment 定期温度控制过程评估
- Change control program 变更控制项目
- Management controls 管理控制

10.0 Handling 处理

This section provides guidance for shippers and transport service providers involved in the transportation of medicinal products. The purpose is to ensure that the integrity of the transport chain for medicinal products as conducted by shippers, transport service providers, and their sub-contractors is maintained.
此节为药品运输中涉及的货主和承运商提供指导。目的是确保由货主、承运商及其分包商实施的药品运输链的完整性被保持。

10.1 Scope 范围

This guidance applies to all transportation methods and to all parties involved in the transportation of medicinal products and the related activities, such as (but not limited to)
此指南适用于所有运输方法和涉及药品运输的各方及相关活动比如（但不限于）

- Preparing the goods for transport 为运输备货
- Loading/unloading goods into shipping equipment 从运输设备上装卸货物
- Loading/unloading from one shipping equipment to another 从一个运输设备装卸到另一个运输设备
- Receipt of goods 收货
- Handling between transportation (e.g., airport transit, harbor transit) 在运输方式之间处理（比如空运，海运）

10.2 Responsibilities 职责

10.2.1 Shipper's Obligations 货主职责

- The shipper should have a transport service agreement with the transport service provider.
货主与承运商有运输服务协议。
- The shipper should audit the transport service provider on a predefined basis.
货主应审计预先确定的承运商。
- The shipper should instruct the transport service provider on the characteristics of the medicinal product and the handling requirements of the shipment.
货主应该在药品的特征和运输的处理要求方面指导承运商。
- Detailed instructions on transportation and handling conditions should be integrated into the shipping documents. Markings on the shipment should clearly indicate the temperature range within which the shipment must be handled.
运输和装卸条件的详细说明应整合到运输文件中。运输标记应清晰地指示装运必须在那个温度范围内进行。
- Transportation of medicinal products should be qualified to the extent possible.
药品运输应该确认至可达到的程度。
- Where appropriate, and preferably if no transportation qualification has taken place, a continuous temperature monitoring system should be in place during transportation.
在适当情况下，如果没有进行运输确认，更好的方式是在运输过程中现场安装一个连续的温度监测系统。

10.2.2 Transport Service Provider's Obligations 承运商的职责

- A quality management system should be in place at the transport service provider with a designated individual responsible for quality management.
应该在承运商现场以制定质量管理责任人的方式设置质量管理体系。
- A tracking & tracing system should be used throughout the transportation process.
应该在整个运输过程中使用跟踪&追踪系统。
- The shipper's approval should be obtained prior to changes potentially affecting good distribution practices (GDP) or product quality.
在进行潜在影响良好分销规范或产品质量的变更前应获得货主的批准。
- Regular, periodic training of transport service provider personnel as well as sub-contractor personnel should be carried out. Training should be documented.
应对承运商和分包商处人员实施经常、定期的培训。培训应该有文件证明。
- When subcontracting takes place, the transport service provider should have a transport service agreement with all sub-contractors. Its conditions should correspond to the transport service agreement between the transport service provider and the shipper.
当存在转包时，承运商应和分包商有运输服务协议。其条件应符合承运商和货主的运输服务协议。
- The same quality management rules should apply for the transport service provider and all its subcontractors.

同样的质量管理规定应该适用于承运商及其所有的分包商。

- The shipper has the right to audit subcontractors of transport service providers.

货主有权审计承运商的分包商。

10.3 Specific Aspects for Transportation in Vehicles/Containers Providing an Active Temperature-Controlled Environment 提供主动温度控制环境的运输车辆/容器的特殊要求

- Loading and clearance of vehicles should be carried out in an efficient manner especially when no insulated docking ramps are available and also when temperature-sensitive medicinal products have to pass areas which are not temperature-controlled.

车辆的装载和卸车应在以有效的方式进行尤其是当没有保温对接坡道可使用时，也当温度敏感药品必须穿过没有温度控制的区域时。

- Vehicles/containers should be pre-conditioned (depending on weather conditions) to the required temperature (e.g., between 2 and 8 ℃ for refrigerated products) prior to loading.

在装载之前车辆/容器应预处理（依赖于天气状况）到要求的温度（如对需要冷藏的产品在 2 到 8 ℃）

- Vehicles/containers for the transport of temperature-controlled medicinal products should be equipped with a cooling and/or heating device as well as a calibrated temperature-monitoring device.

温度受控药品的运输使用的车辆/容器应装备降温和/或加热设备，也应装备经过校准的温度监测设备。

- Studies regarding temperature mapping in the commonly used load schemes should be performed.

应按照经常使用的装载方式实施温度分布研究。

- Alarms should be set in such a way that deviations to the required temperature can be identified and corrective measures be implemented when possible. Deviations from the requested temperature range should be recorded and communicated to the shipper.

可能时通过设定报警这种方式来识别要求温度的偏差并实施纠正措施。超过要求的温度范围的偏差应被记录并与货主交流。

- Handling of active cooling containers should be carried out according to the supplier’s operating manuals.

应按照供应商的操作手册来进行主动冷却箱（冷藏箱）的操作。

- The service provider’s personnel should be familiar with the technology and the function of the active cooling containers. Through periodic training, personnel should be able to ensure proper handling of goods during all stages of the transportation process.

服务提供商的人员应熟悉主动冷却箱（冷藏箱）的技术和功能，人员应能保证在运输过程整个阶段的货物的妥善处置。

- Systems in use must be in a good working order, for example, regular maintenance should be performed to ensure the containers are functioning correctly.

在用的系统必须处于良好的状态，例如应实施经常的维护以确保冷藏箱运行正确。

10.4 Specific Aspects for Transportation in Passive Cooling Systems 被动冷却系统运输的特殊要求

- Handling of such containers should be done according to the instructions given by the shipper.

这些箱子的操作应该按照货主提供的说明进行。

- The containers should not be opened.箱子不能打开箱子。
- Insulated boxes should remain under controlled conditions as defined by the shipper. Exposure to extreme temperatures should be avoided or minimized as far as possible.

保温箱应该保持在由货主规定的控制条件下。在极端温度下的暴露应该避免或尽可能最少。

11.0 Conclusion 结论

Firms that manufacture and distribute medicinal products that require storage under controlled temperature can use the design approach presented in this document to evaluate and limit temperature excursion risks to these products. The recommendations presented here include

需要在控制温度下储存的药品的生产企业和配送企业可以使用在此文件中提出的设计方法并对这些产品温度偏移的风险进行限制。这里提出的建议包括：

- A qualification process for the distribution of these products covering package design and evaluation

涵盖包装设计和评估的这些产品配送的确认过程。

- Use of stability data for understanding the effect of temperature excursions

为了理解温度偏移影响的稳定性数据的使用。

- Assessment of routes and modes of transport

运输方式和路线的评估

The goal is to protect the product, minimize its exposure to temperature extremes, and understand the impact of such exposures, if they occur.

目的是保护产品、将其在温度最恶劣的条件下的暴露减小到最低限度并理解如果这些暴露发生时的影响。

The guidance presented here is consistent with current published regulatory expectations.

在这里提出的指南与现行已发布的法规期望是一致的。

12.0 Global Regulations and Phamacopoeial Standards 国际法规和药典标准

This section lists the global regulations and standards as known at the writing of this guidance (June 2007):

1. U.S. Food and Drug Administration (FDA) Federal Food, Drug and Cosmetic Act, Chapter V., Subchapter A, Sec. 501(a)(2)(B).
2. U.S. Food and Drug Administration (FDA) Federal Food, Drug and Cosmetic Act, Chapter III. Subchapter A, Sec. 301(a),(b),(c).
3. FDA Guideline on General Principles of Process Validation, 1987.
4. ICH Q1A(R2): Stability Testing of New Drug Substances and Products (Second Revision), 2003.
5. World Health Organization (WHO) Guidelines on the International Packaging and Shipping of Vaccines, December 2005.
6. Good Distribution Practices (GDP), WHO, Geneva, 2005.
7. General Chapter <1079> Good Storage and Shipping Practices, USP 30/NF 25.
8. General Chapter <1118> Monitoring Devices—Time, Temperature and Humidity, USP 30/NF 25.
9. Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUIDE-0069), Health Canada, October 2005.
10. Guidelines on Good Distribution Practice of Medicinal Product for Human Use (94/C63/03), European Union, 1994.
11. Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances, Irish Medicines Board, March 2006.
12. Australian Code of Good Wholesaling Practice for Therapeutic Goods for Human Use. Therapeutic Goods Administration, Commonwealth Department of Health, Housing and Community Services, November 1991.
13. Thermal Performance of Refrigerated Transport Equipment—Specification and Testing, AS 4982-2003, Standards Australia.
14. Good Wholesaling Practice for Wholesalers, Distributors, and Bonded Warehouses, Medicines Control Council, Department of Health, Republic of South Africa, June 2003.
15. Norms for the Good Distribution Practices of Medicines, Resolution by means of which the Good Distribution Practices of Medicines Is Issued, Ministry of Health and Social Development, No. 253, Bolivarian Republic of Venezuela, June 2004.
16. National Sanitary Surveillance Agency, resolution-RCD234, August 17, 2005, 3rd Article, Paragraph 5–7 and 7th Article, Paragraph 2, Brazilian Official Gazette, August 26, 2005.
17. Guidance Notes on Good Distribution practices, Health Science Authority, Center for Drug Administration, Ref. No. GUIDE-MQA-013-005, Singapore, 2005.
18. 479th Decree of the Federal Minister for Health and Women Concerning Companies which Manufacture Medicinal Products, Control Them or Put Them into Circulation. Federal Law Gazette for the Republic of Austria, 2005.
19. *Cold Chain Guidance for Medicinal Product: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment.* Technical Report No. 39. *PDA Journal of Pharmaceutical Science and Technology,* September-October 2005, Supplement Vol. 59, No. S3.
20. International Safe Transit Association (ISTA) Procedure 7D—*Thermal Controlled Transport Packaging for Parcel Delivery System Shipment*, 2002 ed., p. 5,
21. International Safe Transit Association (ISTA) Procedure 5B—*Focused Simulation Guide for Thermal Performance Testing of Temperature Controlled Transport Packaging*, 2002 ed., pp 1 and 4.
22. Decree on the Manufacture and Distribution of Pharmaceuticals, No. 411/2004, the Czech Republic, 21 June 2004.
23. China—Administrative Guidelines on Storage and Transport of Vaccines (Promulgated by the Ministry of Health and the State Food and Drug Administration, March 8, 2006).
24. South Korea—Good Distribution Practice for Pharmaceuticals, 8-Jun-2005.

13.0 Publications from Official Bodies 官方机构出版物

1. Okeke, C. C.; Bailey, L. C.; Medwick, T.; Grady, L. T. Temperature fluctuations during mail order shipment of pharmaceutical articles using mean kinetic temperature approach. *Pharmacopeial Forum* **1997**, *23* (3), 4155–4182.
2. Okeke, C. C.; Bailey, L. C.; Lindauer, R. F; Medwick, T.; Grady, L. T. Evaluation of the physical and chemical stability of some drugs when exposed to temperature fluctuations during shipment. *Pharmacopeial Forum* **1998**, *24* (5), 7064–7073.
3. Okeke, C. C.; Bailey, L. C.; Medwick, T.; Grady, L. T. Temperature and humidity conditions during shipment in international commerce. *Pharmacopeial Forum* **1999**, *25* (2), 7949–7959.
4. Okeke, C. C.; Watkins, J. W. III; Williams, W.; Medwick, T.; Bailey, L. C.; Grady, L. T. A study of the temperature and humidity variations in the shipping and distribution of Anthrax vaccines. *Pharmacopeial Forum* **2000**, *26* (3), 865–882.
5. "Drug product distribution chain" stimuli to the revision process. *Pharmacopeial Forum* **2003**, *29* (3), 864–875.
6. Taylor, J. New MHRA Regulatory Guidance, Practical Tools and Case Examples of Cold, Cool, Temperate and Subzero Temperature Range Pharmaceutical Products. Presented at the International Quality & Productivity Center Cool Chain 2006 Conference—Enhance the Integrity, Visibility and Validation of your Cool Chain to Ensure Safe and Effective Drugs are Distributed and Transported from Manufacturer to Patient, Brussels, Belgium, January 31 to February 1, 2006.
7. Taylor, J. Holloway, I, "Transportation of Biological Products: European Regulations and Guidance," *American Pharmaceutical Outsourcing*, May/June **2007**.

14.0 Tables 表格

Table 14.0-1 Long-Term Stability Study 长期稳定性考察

Storage Condition 储存条件	Testing Condition ICH Q1A ICH Q1A 测试条件	Testing Condition WHO Annex 5 WHO附录5测试条件
Controlled Room Temperature 20 to 25 ℃ 控制室温20~25 ℃	25 ℃/60% RH for 12 months 25 ℃/60% RH 12个月	30 ℃/65% RH or 30 ℃/75% RH for 12 months 30 ℃/65% RH 或30 ℃/75% RH 12个月
Refrigerated Condition 2 to 8 ℃ 冷藏条件2~8 ℃	5 ℃ for 12 months 5 ℃12个月	5 ℃ for 12 months 5 ℃12个月
Freezer Condition –20 to –10 ℃ 冷冻条件–20 ~–10 ℃	–20 ℃ for 12 months –20 ℃12个月	–20 ℃ for 12 months –20 ℃12个月
RH = relative humidity RH=相对湿度		

Table 14.0-2 Accelerated Stability Study加速稳定性考察

Storage Condition 储存条件	Testing Condition ICH Q1A ICH Q1A 测试条件	Testing Condition WHO Annex 5 WHO附录5测试条件
Controlled Room Temperature 20 to 25 ℃ 控制室温20~25 ℃	40 ℃/75% RH for 6 months 40 ℃/75% RH 6个月	40 ℃/75% RH for 12 months 40 ℃/75% RH 12个月
Refrigerated Condition 2 to 8 ℃ 冷藏条件2~8 ℃	25 ℃/60% RH for 6 months 25 ℃/60% RH6个月	----------
Freezer Condition –20 to –10 ℃ 冷冻条件–20 ~–10 ℃	5 ℃ for 6 months 5 ℃ 6个月	----------
RH = relative humidity RH=相对湿度		

Table 14.0-3 Temperature Excursion Study 温度偏移研究

Storage Condition 储存条件	Testing Condition ICH Q1A ICH Q1A 测试条件	Testing Condition WHO Annex 5 WHO附录5测试条件
Controlled Room Temperature 20 to 25 ℃ 控制室温20~25 ℃	1) –20 ℃ for 2 days –20 ℃ 2天 2) 60 ℃/75% RH for 2 days 60 ℃/75% RH 2天	----------
Refrigerated Condition 2 to 8 ℃ 冷藏条件2~8 ℃	1) –20 ℃ for 2 days –20 ℃ 2天 2) 40 ℃/75% RH for 2 days 40 ℃/75% 2天	----------
Freezer Condition –20 to –10 ℃ 冷冻条件–20 ~–10 ℃	1) 25 ℃/60% RH for 2 days 25 ℃/60% RH2天	----------
*Note: Testing conditions in Table III and Table IV may be adjusted to product-specific needs with reference to ICH Q1A for accelerated stability studies. Alternative study designs may be used as appropriate. *注释：在表III和表IV中的测试条件可以针对特定产品根据ICHQ1A加速稳定性考察的相关需要进行调整。适当情况下使用可替换的研究设计 RH = relative humidity RH=相对湿度		

Table14.0-4 Thermal Cycling Study 循环变温研究

Storage Condition 储存条件	Testing Condition ICH Q1A ICH Q1A 测试条件	Testing Condition WHO Annex 5 WHO附录5测试条件
Controlled Room Temperature 20 to 25 ℃ 控制室温20~25 ℃	–20 ℃ for 2 days followed by 40 ℃/75% RH for 2 days –20 ℃ 2天然后40 ℃/75% RH2天 Repeat for a total of 3 cycles 重复此过程三次	----------
Refrigerated Condition 2 to 8 ℃ 冷藏条件2~8 ℃	–20 ℃ for 2 days followed by 25 ℃/60% RH for 2 days –20 ℃ 2天然后25 ℃/60% RH2天 Repeat for a total of 3 cycles 重复此过程三次	----------
Freezer Condition –20 to –10 ℃ 冷冻条件–20 ~–10 ℃	–20 ℃ for 2 days followed by 5 ℃ for 2 days –20 ℃ 2天然后5 ℃2天 Repeat for a total of 3 cycles 重复此过程三次	----------
*Note: Testing conditions in Table III and Table IV may be adjusted to product-specific needs with reference to ICH Q1A for accelerated stability studies. Alternative study designs may be used as appropriate. *注释：在表III和表IV中的测试条件可以针对特定产品根据ICHQ1A加速稳定性考察的相关需要进行调整。适当情况下使用可替换的研究设计 RH = relative humidity RH=相对湿度		

Table 14.0-5 ■ Example of a Comprehensive Study Design for a Refrigerated Product

表14.0-5 冷藏产品综合研究设计的例子

Product Group 产品组	Item Code 项目代码	Description 描述	Storage Condition 储存条件	Routine 5 ℃ 日常5 ℃	Accelerated 25 ℃/60% RH 加速 25 ℃/60%RH	Excursions –20 ℃ 最差条件–20 ℃	Excursions 40 ℃/ 75% RH 最差条件 40 ℃/ 75% RH	Excursions Cycling* 最差条件 循环	Comments 备注
XXXX Vials XXXX瓶	VL123	5 mg	Refrigerated 冷藏	24 months 24个月	6 months 6个月	2 days 2天	2 days 2天	Cycling* 循环	Transportation Study Technical Report Tryyyy—Excursion TRzzzz—Cycling 运输研究技术报告 Tryyyy—最差条件 Trzzzz—循环
XXXX Vials XXXX瓶	VL456	10 mg	Refrigerated 冷藏	24 months 24个月	6 months 6个月				
XXXX Vials XXXX瓶	VL789	20 mg	Refrigerated 冷藏	24 months 24个月	6 months 6个月	2 days 2天	2 days 2天	Cycling* 循环	Transportation Study Technical Report Tryyyy—Excursion TRzzzz—Cycling 运输研究技术报告 Tryyyy—最差条件 Trzzzz—循环

*–20 ℃ for 2 days followed by 25 ℃/60% RH for 2 days (repeat for a total of 3 cycles) RH = relative humidity

*–20 ℃2天然后25 ℃/60% RH2天（重复3个循环）RH=相对湿度

Table 14.0-6 ■ Example of a Transportation Control Strategy Document Based On Product-Specific Stability Data To Determine the Effect of Temperature Excursions

表14.0-6 基于特定产品稳定性数据确定温度偏移效应的运输控制策略文件的例子

Storage Condition: Refrigerated Condition (2 to 8 ℃) 储存条件：冷藏条件（2~8 ℃）	
Temperature Range 温度范围	Time 时间
<–20 ℃ (<–4 ℉)	Do Not Use 不用
–20 to 2 ℃ (–4 to 36 ℉)	2 days 2天
2 to 8 ℃ (36 to 46 ℉)	Until Expiry 直到失效
8 to 25 ℃ (46 to 77 ℉)	6 days 6天
25 to 40 ℃ (77 to 104 ℉)	2 days 2天
>40 ℃ (104 ℉)	Do Not Use 不用
This table needs to be designed for every product and transportation route/method used. 此表格需要设计用于每个产品及其使用的运输路线/方法。	