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Review Article

Stability Studies Needed to Define the Handling and Transport Conditions of Sensitive Pharmaceutical or Biotechnological Products

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Abstract. Many pharmaceutical or biotechnological products require transport using temperature-controlled systems to keep their therapeutic properties. There are presently no official guidelines for testing pharmaceutical products in order to define suitable transport specifications. After reviewing the current guidance documents, this paper proposes a methodology for testing pharmaceutical products and defining appropriate transport conditions.

KEY WORDS: biotechnological products; distribution; pharmaceutical products; stability; temperature excursions; transport.

INTRODUCTION

It is considered good practice to test the stability of drug substances and drug products according to the International Conference on Harmonization (ICH) Q1A to Q1E (1–5), or Q5C (6) guidelines, or the World Health Organization (WHO) Technical Report Series, No. 953, 2009, Annex 2, "Stability testing of active pharmaceutical ingredients and finished pharmaceutical products" (7).

In a standard stability program, a stress study is first carried out to determine the drug substance's degradation path and to establish suitable analytical methods. Drug substance stability studies are then conducted to define stability under long-term and accelerated storage conditions. In the next phase of the development plan, the drug substance is formulated into a drug product and compatibility of the drug substance with excipients and container parts is then tested. When suitable conditions are determined, long-term and accelerated studies commence with the drug product. The data obtained from these studies are used to define the optimal storage conditions and corresponding retest dates for the drug substance or shelf-lives for drug product.

A major concern of the pharmaceutical industry and health authorities is to guarantee that drugs are delivered to patients without loss of therapeutic properties. An ever-increasing number of therapeutic products developed by the biotechnological or biologics (vaccines) industries require temperature-controlled distribution channels, and it is not infrequent that delays during transport put product quality at risk when transport times and temperature control cannot be maintained. In these cases, the drug may experience "temperature excursions".

Products sensitive to transport conditions need special care to ensure that their quality is not impaired by transport operations. When talking about sensitive products one usually thinks about products that are sensitive to temperature, but other environmental conditions should also be considered, including humidity, light, oxygen, shocks, pressure, vibrations and X-rays encountered during shipment by truck, train, boat, or plane.

Two points should be remembered before going any further. The first is that regulatory authorities require that the manufacturer ensures product quality not only during storage or transport but until it is used for patient treatment: "The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use." ICH Q1A 2.1.7 (1). This requirement is a challenge for the manufacturer, since it must be ensured even after controls by the manufacturer in the supply chain have ended. This is usually the case when the product is sold to pharmacists or hospitals for distribution to patients, and when patients store the product at home.

The second point is that the drug product manufacturer must decrease the risk of quality defects as much as possible. Quality defects might occur either if the temperature chosen for the transport of a temperature-sensitive product is outside the registered storage temperature range, or if the transport organization fails to maintain the planned transport conditions. Both will increase the degradation of the product, so the manufacturer must balance both situations and choose the best distribution plan. It might be suitable to transport a product at room temperature if the studies support this approach.

An additional, economic factor should be considered. The value of a product ready to be used by the patient has the highest cost along the whole supply chain. When a product is ready to be used, its value not only includes the aggregate cost of the drug substance, the drug product, storage and delivery, but also R&D, marketing, sales, taxes and other

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items. If the product is not properly stored during and after distribution, the loss can be major. Failing to address the distribution channel correctly may have negative consequences to patient health and harm the company's image, if a recall is mandated. Profits may also be impacted by a lack of drug availability.

There are no guidelines (such as those on storage stabilities) for testing to determine the suitability of transport conditions for sensitive products. After reviewing the status of the leading pharmaceutical associations' regulations and guidelines on transporting drugs, this paper will describe test program for determining optimal transport conditions that provide sufficient product protection, as well as satisfactory handling and distribution.

REGULATIONS AND GUIDANCE

Significant information on transporting medicinal products can be found in the publications issued by the regulatory authorities and pharmaceutical associations. This information is summarized below.

– ICH—WHO

ICH Q1A (2.1.2) (1)–WHO (2.1.2) (7) gives general guidance on how to perform stress tests. The results of such tests are essential to determine the sensitivity of a drug substance to temperature, humidity, oxidation, pH and light. The results of the stress tests are directly useful when it comes to transporting the drug substance, and will help to determine appropriate tests to control transport conditions for the drug product.

ICH Q1A also describes the recommended conditions for performing long-term and accelerated stability tests on drug substances and drug products (see Fig. 1), and gives useful guidelines on the temperature and humidity conditions for running these tests. Advice is provided to manufacturers for using these data:

– ICH Q1A; similar to WHO Glossary: Accelerated testing: "Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes."
– ICH Q1A chapter 2.1.7; similar to WHO 2.1.7: "Data from accelerated stability studies can be used to evaluate the effect of short term excursions higher or lower than the label storage conditions that may occur during the shipping of drug products."
– ICH Q1A chapter 2.1.7.3; identical to WHO 2.1.7.3: Drug substances intended for storage in a freezer: "…testing on a single batch at an elevated temperature (*e.g.*, 5°C±3°C or 25°C±2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition, *e.g.*, during shipping or handling."
– ICH Q1A chapter 2.2.7.5, similar to WHO 2.2.6.5:. Drug products intended for storage in a freezer "In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (*e.g.*, 5°C±3°C or 25°C±2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition."
– ICH Q5C (6): Stability of Biotechnological/Biological Products section 6.3. Accelerated and Stress Conditions: "Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (*e.g.*, during transportation) are deleterious to the product."

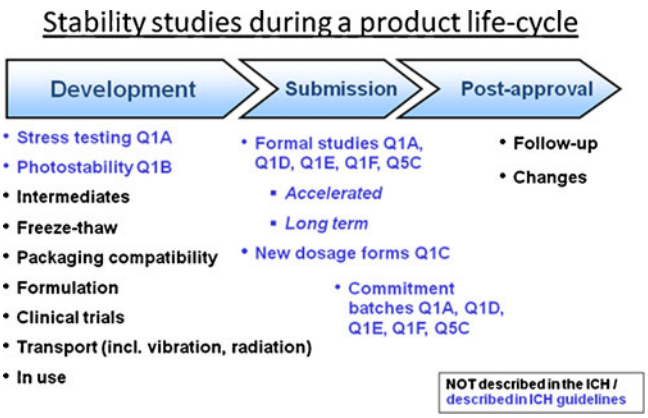

Fig. 1. Stability tests during the development of a drug product and those described in ICH guidelines

From these sections of the guidelines, it can be concluded that the manufacturer can use the accelerated stability data to assess the significance of temperature excursions outside the standard conditions during transport.

– United States Pharmacopoeia

United States Pharmacopoeia (8) has recently edited very interesting monographs on the programming of stability tests. Interested readers can find valuable information in the following documents:

– <795> Pharmaceutical Compounding—Nonsterile Preparations
– <797> Pharmaceutical Compounding—Sterile Preparations
– <1079> Good Storage and Shipping Practices
– <1118> Monitoring Devices—Time, Temperature, and Humidity
– <1191> Stability Considerations in Dispensing Practice

– Parenteral Drug Association Technical Report 39, Revised 2007 (9)

is certainly the best document to date for planning the testing of products under temperature cycling conditions and evaluating the impact of temperature excursions. Following

the proposed tests, the manufacturer can assess their product's sensitivity to temperature variations such as those that occur during transport. The chosen temperature should suit the specific situation.

– PDA Technical report 46, 2009 Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User (10)

provides practical guidance on how to transport products and includes a chapter on "stability data".

– Food and Drug Administration (FDA) (11,12)

The FDA has presented their view that transport conditions may differ from storage conditions, provided the manufacturer presents satisfactory supporting data.

– Others

Bishara and Seevers (13,14) have contributed significantly to the progress of the knowledge in this field by setting preliminary standards that are now included in the Parenteral Drug Association (PDA) documents. Temperature excursions and temperature cycling conditions are proposed. As stated in the summary "The effect of temperature excursions, outside of labeled storage conditions, can be evaluated on the basis of the stability analysis for that drug. Because the distribution environment is highly variable, a stability program should be established that provides stability profiles for each product. This article describes a stability program strategy designed on the basis of the information provided by the development and routine ICH Q1A stability programs."

No guideline is available on medicinal product sensitivity to vibrations, shocks, or X-rays. General testing methods for transport are described by organizations such as International Safe Transit Association (ISTA) (15) and American Society for Testing and Materials (ASTM) (16).

SETTING THE FRAMEWORK

Storage conditions are defined during stability studies in accordance with the ICH/WHO guidelines. However, a temperature-sensitive product may have issues associated with its manufacturing and transport that are not covered by the ICH/WHO conditions (see Fig. 1). One clear example is the filling and packaging of frozen products. According to the ICH/WHO, stability studies are limited to a −20°C long-term study without accelerated conditions. But these products have to be handled at temperatures which are not those of the long-term storage conditions if they have to be thawed in order to be poured into vials or syringes, or if they have to be brought to room temperature (or at least above 0°C) to allow for proper labeling.

Additional studies are necessary to complete the knowledge about a product's stability profile. Such studies should include the time needed to prepare the product (*e.g.*, filling, labeling, packaging, preparation for dispatch, transport, and receipt) and the consequences of deviations during these operations.

Three different development areas can be distinguished:

1. Studies on product storage (performed according to the ICH/WHO guidelines)
2. Studies on product handling according to internal SOPs for filling, labeling, distribution
3. Studies on managing unforeseen situations (*e.g.*, that occur during distribution).

The study plan will depend on the type of drug product. It has to consider the parameters that are critical to prevent product degradation, and should also evaluate the parameter limits within which the product can be handled safely.

DIFFERENT TYPES OF PRODUCTS

The stability program will depend largely on the product's sensitivity to environmental conditions. The product should be understood as the content AND the container, both of which determine final sensitivity.

Stable Products=products not sensitive to environmental changes (*e.g.*, products that are heat sterilized after production)

• These products will usually be stored at 25°C, and no extensive studies are needed to define the transport conditions. The environment-related considerations should concentrate on finding conditions that preserve the products physical integrity.

Highly Sensitive Products=products having a limited range of storage and transport conditions. Excursion outside these ranges is an actual cause of product deterioration (*e.g.*, vaccines that deteriorate when frozen).

• These products need extensive studies to assess the exact parameters in which the products keep their unique properties and those in which they are lost. In addition to tests relating to transport conditions, the testing program should embrace temperature, humidity (if not aqueous solutions), light, oxygen, shock, pressure and vibrations such as those experienced during transport and X-rays if transported by air (*cf.* airport security systems). They usually cannot be transported outside their long-term storage conditions.

Sensitive Products=products with a certain sensitivity to environmental conditions and that have to be protected during transport (*e.g.*, most rDNA biotechnology products)

• These products need the same studies as the Sensitive Products to assess the exact conditions in which they maintain their unique properties and those in which they are degraded.

The manufacturer can choose to transport the product within its storage conditions and should study the effects of transport and possible temperature excursions on the quality of the product until its delivery and use by patients.

The manufacturer can also define transport conditions that are less sensitive to failure of transport operations (*e.g.*, room temperature). If so documented, the product can be handled safely outside its long-term storage conditions, provided the manufacturer has satisfactory data supporting the handling/distribution conditions.

PARAMETERS TO BE TESTED DURING TRANSPORT TESTING

Drugs can be sensitive to environmental conditions such as temperature, humidity, light, oxygen, shock, pressure, vibrations, and X-rays. Drug degradation depends on the value of the environmental conditions and the period of time

during which the product is kept at this value. For small deviations from the storage conditions and short periods of time, the consequences are usually not significant. Risk analysis will show which tests should be planned (see Table I).

Temperature is the main focus for testing because almost all pharmaceutical and biotechnological products are sensitive to temperature. In addition, transport in controlled conditions is not always reliable. There are a number of problems that can arise:

- weather might follow unpredictable changes;
- customs procedures might take longer than anticipated;
- accidents might cause disruption;
- route used for transport might not be that anticipated;
- transport might stop at unsuitable places;
- temperature control systems might malfunction;
- communications between the various transport companies might have blocked the product (this could happen when the transport is contracted out to a chain of transport specialist such as shipper, forwarders, ground handlers/transportation service providers, consignee, air carrier);
- temperature sensors might be defective;
- information on the actual transport conditions might be inexact or lacking;
- other factors.

For these reasons, the manufacturer should make the best possible efforts to obtain formulation that is "stable" under a broad range of conditions.

If this is not possible, the next objective should be to assess extensively the limits in which the product can be handled safely.

There are natural temperature ranges that could be defined. It will be very unusual to have temperatures below −100°C or over 100°C in a natural environment. In Antarctica, temperature minima have been measured at −89°C. Temperature maxima have been measured at +58°C in Libya and in Death Valley. But even if a product is stored in a closed environment under the sun, it will not be heated over 100°C.

Humidity during transport is generally not critical due to the very short period of time when the product is stored at high/low humidity. But humidity can change the characteristics of solids or non-aqueous solutions which are packed in non-tight containers. Preservation of a drug product at high or low humidity is a testing condition of the ICH/WHO studies, and it is usually not necessary to repeat/add this parameter to the transport/distribution stability program.

Light is usually not a testing parameter, since products are shipped in light-resistant internal or external packaging.

Oxygen is usually not a testing parameter, since products are stored and transported in air tight containers.

A drop/rise in *pressure* can damage products if packaging has not been tested for deformation or leakage under high/low pressure. Blisters and sprays are examples of sensitive packaging.

Some very interesting information is given in the IATA document (15):

> "Normal, or standard, atmospheric pressure at sea level is usually defined at … 1013 millibars; however this number varies greatly due to the weather.
>
> Generally speaking, cargo compartments on cargo and passenger aircraft are pressurized to the same levels. The pressure in the each aircraft varies during flight, depending on altitude and pressurization settings. Normally, the pressure varies from sea level pressure of 1013 millibars to a value no less than 800 millibars, ….
>
> It should be noted that 'feeder aircraft' are not subject to the same pressure situations. These trips are potentially non–pressurized and used to transport express air packages to remote areas. In this case, cargo experiences the same ambient pressure as the pilot."

ISTA (15) or ASTM (16) propose standard tests for the vibration, shock, and atmospheric conditioning.

Vibrations might damage solid dosage forms during transport if they are friable. Vibrations have also been shown to increase the appearance of particles in protein-containing solutions and to influence their therapeutic properties. For sensitive pharmaceutical or biotechnological products, this is certainly a parameter that has to be evaluated.

Shocks can damage products if packaging has not been tested for shock resistance. Shock might damage solid dosage forms during transport if they are friable.

Radiation can be an issue for biologic products and those that have been shown to be sensitive to X-rays during tests using this method of sterilization.

The International Air Transport Association (IATA) document has the following information (17):

> 17.13.2 Radio Frequency (RF)
> Most pharmaceutical products are exposed to RF energy throughout the supply chain. RF is used as a tool for inventory purposes as well as supply chain visibility. This low energy is considered to be benign. However the FDA

Table I. Example of Conditions to be Tested for Product Transport

	Temperature	Humidity	Light	Pressure	Vibrations	Shocks	X-ray
Solid in bottles	+	0	−	−	0	0	−
Solid in blisters	+	0	−	+	0	0	−
Liquid in ampoules	+	−	−	−	0	+	0
Liquid in bottles	+	−	−	−	0	+	0
Liquid in sprays	+	0	−	+	0	−	0
Gel in plastic tubes	+	−	−	0	0	−	0
Cream in plastic tubes	+	−	−	0	0	−	0

(−) conditions not requiring tests, *0* conditions possibly requiring tests, (+) conditions definitely requiring tests

has requested that pharmaceutical companies perform RF energy input studies for their Biologics (this is not necessary for non–biologics) to see if there is any modification to the biologic that is not typical of heat degradation.

17.13.3 X-ray (radiation exposure in airplanes and at airports) Pharmaceutical products can be exposed to X-rays (man induced and or naturally occurring) throughout the supply chain. Generally speaking, the amount of X-rays that a product can be exposed to at an airport during screening is significantly less than what the exposure would be in the cargo hull at 35000 ft. If a product is known to be sensitive to X-ray energies, the manufacturer should work with the broker and customs to not have product X-rayed at the exit and entree ports and work with the airline to take appropriate precautions during air travel. Extra shielding might be an appropriate means of protection against this radiation ….

STABILITY STRATEGY

The stability manager has to define what the scope of the transport and distribution studies should be and when to carry them out. This information will be used to develop a stability plan.

When to Run a Stability Test to Assess the Distribution Conditions?

The stability studies covering the company's transport and distribution requirements have to be planned at the right moment as part of the overall development plan. If they are planned too early, they might be invalid if the formulation, the container or the distribution plans are revised, and will then have to be repeated.

In the early phase of the development plan, the manufacturer wants to guarantee that the product is compliant with the requirements for all preclinical and clinical studies. If there is insufficient data, the manufacturer will be forced to use transport and distribution conditions known to be protective for the product; typically, these include liquid nitrogen, dry ice, −20°C or any other conditions where product stability has been demonstrated during the necessary time period.

Stability studies for a product's transport and distribution are reasonably run with the stability of a product prepared for pivotal phase-3 clinical trials. At this product development stage, the manufacturer has already accumulated preliminary stability data, providing an indication of appropriate storage and distribution conditions. These have to be challenged, since the process/formulation/packaging/*etc*. might have been changed before starting phase-3 clinical trials.

Scope

The next point to examine is the scope of the study. The proposed tests should be related to production environment and distribution channels. This can be challenging, since typically at the beginning of the phase-3 clinical trials, the manufacturer often has only a very vague idea of what the marketing and related production and distribution activities will actually be after registration, and later during its commercialization.

Knowing the product's sensitivity to the parameters of concern is the first objective of the study. The correspondence between this sensitivity and the required minimum needs for distribution and subsequent use by customers/patients will determine the product distribution conditions.

The basic scope of the stability study is to define the transport conditions as proposed in Table II.

Having limited understanding of the product's properties at this point in the development lifecycle means that it might require considerable effort to focus on the right testing conditions that are not too drastic (where the product deteriorates too much) or too mild (where the product does not deteriorate and therefore could stand additional stress). Using a mathematical model could help to assess the temperature excursion effect on the product's potency (18). The basic scope can be translated in an alternative scope as described in the Table III.

When the scope is clearly defined and approved, it is time to program the studies.

Program the Study

The proposed analytical strategy for programming the studies on transport stability is described in Table IV.

Limits of the Study

The stability manager should start by evaluating the range of investigations appropriate for the product under consideration. Is the drug substance already present in another drug product? Is the product a well-known type of product in the company? What are the relevant experiences available for the present product? What are the parameters that impact the quality characteristics? What are the limits of these parameters? Are they limited on both sides by maximum/minimum values? Are there intermediate values that could be relevant? Is it a multidimensional study? Are there potential dependent parameters? What are the limits for the investigations?

Stress Studies. At the beginning of a drug substance's development, manufacturers conduct stress tests to determine its sensitivity to different environmental conditions. They usually choose temperature, humidity, light, and

Table II. Example of Basic Scope

Set the conditions that are best suited to the filling/packaging/distribution operations	The company will determine the conditions that are best to handle the product. How can we fill and pack products that are stored at −70°C? or −20°C?
Assist the QP in evaluating the release of batches that were subjected to excursions	The company will determine the action plan in case of a temperature deviation. Are there potential deviations that could place the patient at risk and/or damage the product?

Table III. Translation of Basic Scope in Alternative Scope

Determine the temperature that the product can support during 1 h (*e.g.*, temperature of extreme sensitivity) 8 h (*e.g.*, temperature of one shift work; 4-h shift plus 2 h in and out storage) 24 h (*e.g.*, temperature of daily work) 72 h (*e.g.*, temperature of standard local transport time) 1 week 2 weeks 1 month	This scheme will tell the company what the sensitivity of the product is to the tested parameters and help determine the conditions and methods for filling/packaging/distributions preparations/distributions/receipts/final use.

oxygen as stress factors and push the studies conditions up to when degradation paths are activated and detected. These tests will show two main correlated factors:

- the value of analytical methods for detecting product degradation;
- the nature of the degradation paths.

In Fig. 2, the drug substance has been placed at 50°C for 3 and 7 days. It can be seen on the HPLC traces after 3 days that two degradation peaks are built before and after the main peak and that these peaks increase after 7 days.

It is of utmost importance to determine the toxicity of degradation byproducts. Are they much more toxic than the drug substance, or is their toxicity close to or less than the substance? The answers to these questions are needed to determine the specifications of the drug substance and later of the drug product.

The results of these studies give direct indications for transporting drug substances, showing whether special precautions should be defined or if ambient conditions are satisfactory.

For drug products, the results of stress studies are usually not directly interpretable, with the exception of the products that are similar to the drug substance, since the presence of excipients should modify the intrinsic properties of a drug substance in a positive way. The main focus should be an understanding of the degradation pathways and of the corresponding detection methods. This knowledge can be used to build formulations that are able to protect the product from degradation. Additionally, it will help the manufacturer to define the testing program for the transport conditions.

Supportive Accelerated/Long-term Studies. Supportive accelerated/long-term stability studies show the consequences of temperature on a drug product. It would be a great help to have the ICH/WHO stability studies results from early development

Table IV. Stability Study Roadmap

Step	Key elements
Establish the limits of the study, using present knowledge (similar project, preliminary tests, …)	Check the data available for the same type of product. Same active as other products already developed? Same dosage form? Same packaging? What are the parameters for non-acceptance? Which parameters are important/what are the extremes/are intermediates values critical? What is the min/max reasonable temperature What are the min/max reasonable humidity, light, oxygen, shock, pressure, vibrations and X-rays?
Define the standard distribution plan for this product	Which are the standard distribution schemes? How many, how long, how large exposures to temperature outside storage temperature can be projected?
Assess the related risk	What is standard practice of use by patients? What are the main risks? How can we mitigate the risks?
Establish the safety margin that apply to the product	What are the parameters for non-acceptance? What is the error on the analytical results? What safety margin applies if the distribution plan goes wrong, until the product is no good anymore?
Write a stability plan to cover the full range of the project	Long term, accelerated, cycling, excursions, special points Combination studies (cycling+long term/accelerated, …) Additional studies (vibration, radiation, …) Is DOE useful?
Run the plan and draw conclusions	

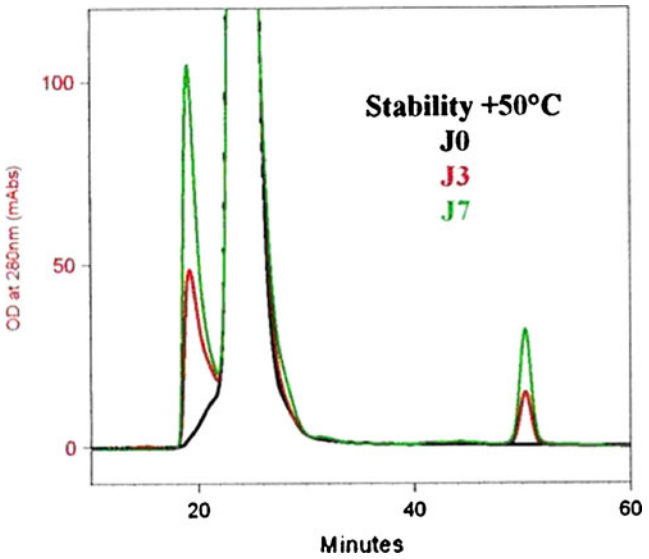

Fig. 2. Degradation study: example of HPLC traces after 3 and 7 days at +50°C, compared with the initial data

batches, or other supportive data, since this could make it possible to model product stability. For liquid products, using the long-term and accelerated data can help determine the Arrhenius pre-exponential *A* and Activation Enthalpy *dHa* parameters. Based on these, a mathematical simulation of the product degradation can be run showing the product stability performances (18).

Distribution Channels

With these initial data, based on the available experience the stability manager and the distribution manager can study the best routes/transport conditions for distributing the product, from initial product storage down to patient administration. They will study the answers to questions such as: "Which is the best option for the packaging? Is a thermostatized pack better that a thermostatic container filled with standard boxes? Which road to follow? If the product has to be stored in a freezer, how can it be handled for filling and labeling?"

Different situations for the handling of medicinal products when packed in their final container need to be considered, as illustrated in Table V for a product to be stored under refrigeration.

In the previous example, the conditions for formulation, filling and intermediate storage should be studied independently, since the packaging of bulk product is not the same as drug product.

Safety Margin

The next question pertains to the risk attaching to the distribution channel. What to do in the worst case? How long could the transport last? At what temperature? How long could the user store the product? At what temperature? Knowing all this makes it possible to define the safety margin.

The safety margin will depend on the type of product (a solid might be less sensitive to unexpected degradation than a liquid, due to the speed of reactions in solid phase *versus* liquid phase).

The safety margin should also take into account the uncertainty regarding the tests results, (assessing the error on the temperature/testing method/time) and the company's risk policy.

The safety margin could be in different forms:

- Percentage of time (set the official limit at x% of real experimental time when degradation is observed);
- Percentage of product (set the official limit at y% of the real experimental quantity where toxicity is observed).

The safety margin might also be dependent on the number of experiments available; the first batch placed in stability will not provide as much confidence as the tenth. The margin might be modified over time as experience grows.

Table V. Example of a Product to be Stored Under Refrigeration

Step	Temperature	Study
Formulation of the drug product	Room temperature	Bulk stability study
Storage of drug bulk product	2–8°C	Bulk stability study
Preparation of the product for filling	Room temperature	Bulk stability study
Filling of the product	Room temperature	Bulk stability study
Storage of filled drug product	2–8°C	Long term
Preparation of the product for the packaging	Room temperature	Accelerated and cycling
Packaging of the product	Room temperature	Accelerated and cycling
Storage of packed drug product for step 1	2–8°C	Long term
Preparation of the product for the transport	Room temperature	Accelerated and cycling
Transport of drug product 1 to 2	2–8°C	Long term
Storage of drug product for step 2	2–8°C	Long term
Preparation of the product for the transport	Room temperature	Transport study
Transport of drug product 2 to3	Room temperature	Transport study
Storage of drug product for step n	2–8°C	Long term
Preparation of the product for the transport	Room temperature	Transport study
Transport of drug product n-1 to n	Room temperature	Transport study
Use of the product by the consumer	Room temperature	Stability in-use, cycling and accelerated
	Extraordinary situations	
Temperature excursions		Temperature excursions/Cycling studies/additional studies

Table VI. Summary Table

Temperature range, °C	Time
<8	36 months
8–13	36 months
13–23	3 months
23–27	1 month
27–32	2 weeks
32–−38	1 week
38–42	3 days
42–50	2 days
50–62	1 day
62–79	8 h
>79	Do not use

STABILITY PLAN

Once these preparatory steps are finished, the stability plan can be written. Note that the ICH/WHO long-term and accelerated stability conditions start with a 1-month testing timeframe. This period is not adapted to handling operations.

Knowing the projected properties of the product and the anticipated distribution channels, the stability manager will be able to write a plan demonstrating that the studies correctly supports the distribution channels and also adequately supports deviations that could occur during the product's transport.

Different types of studies are suitable for defining product's sensitivity to distribution.

- *Temperature excursion studies* and *cycling studies* (*e.g.*, PDA technical report 39 (19)).
- *Freeze-thaw studies* are another type of study that can be valuable for biologics or biotechnological products since their structure might be changed by freezing/thawing conditions. Presence of particles has also been observed after such temperature variations.
- *Real time studies* such as those performed with a temperature program simulating the real transport conditions *e.g.*, during summer and winter times are best suited when the manufacturer knows quite accurately what are the distribution channels.

Additional Tests for Transport

Testing required to assess transport effects on the product should be distinguished from tests aiming to evaluate the effect of temperature excursions outside the stated temperature ranges.

The manufacturer defines transport conditions based on the available data from his experience. Having performed a risk analysis, he defines the transport conditions guaranteeing that product quality meets the requirements when the product is used by the patient as prescribed. This is usually referenced in a table such as the one presented in Table VI.

Tests such as those described by the PDA (9) document under temperature cycling or in the article of Bishara (14) are examples that can be indicative for the manufacturer looking for a set of conditions to be followed.

If the chosen transport temperature differs from the long-term storage temperature, the conditions must be fully tested and shown to be suitable for the desired purpose. To reach this goal, it might be necessary to conduct tests to assess the suitability of transporting the product at a controlled temperature. The simplest situation is when products are transported between two sites such as manufacturing and distribution sites; in this case, manufacturers can simulate transport conditions knowing time and transport roads and using meteorological extremes between the starting and recipient locations. Classical studies use two profiles, one simulating winter conditions and one simulating summer conditions. Product is placed in the chosen transport container during a period of time corresponding to the longest anticipated transport duration. Temperature is cycled at values simulating daily and night external temperatures as they have been measured during previous transports or recovered from meteorological historical data.

A special situation occurs when the starting location is in the Northern hemisphere and the receipt location in the Southern hemisphere or the reverse. In this case, mixed testing conditions should be used, simulating the actual seasonal conditions at the starting and recipient locations. These types of profiles are called summer-winter or winter-summer profiles (see Fig. 3).

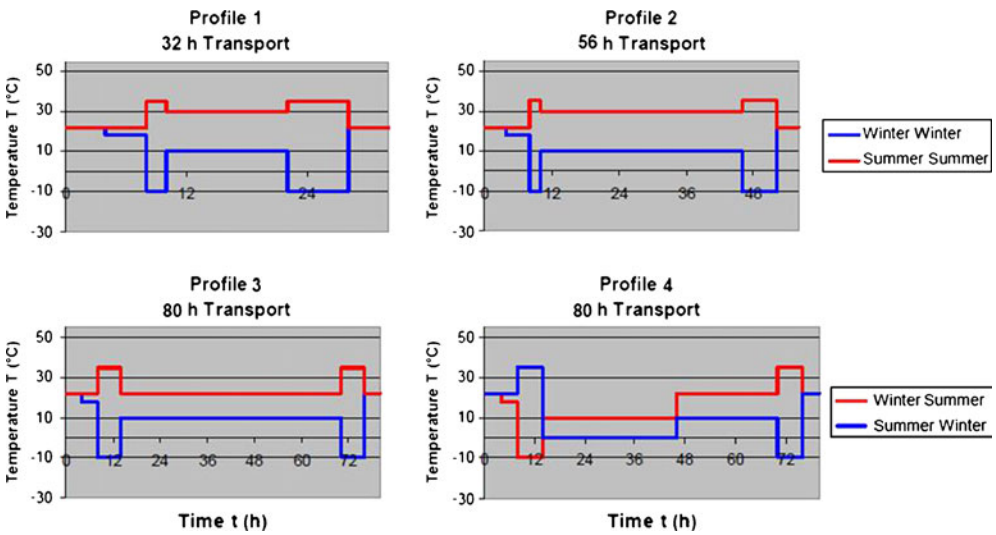

Fig. 3. Transport temperature profiles

When the profiles are defined, the product packed in its transport box is tested for a defined period in these conditions. The product temperature should remain within the specified limits at all times.

The other situation is represented by transport of products from a distribution center to many uncontrolled recipient locations. In this case, there is no real model and it is the responsibility of the manufacturer to ensure that the instructions given to the distribution channel are clear enough to ensure the quality of the product. Stability tests as described above and other tests are to be used as described below.

Additional tests should be considered when risks related to the vibrations or radiations are identified. ISTA (15) or ASTM (16) propose standard tests for vibrations, shocks and atmospheric conditioning.

These tests should simulate as closely as possible the projected transport scheme. But it is important to have a long-term vision to extend the transport schemes to new distribution channels, as marketing will boost sales.

Additional Tests for Temperature Excursions

Tests to assess the consequences of temperature excursions are different in that they are carried out to check the effects of additional stress on the product, such as those resulting from a dramatic situation outside the standard conditions.

Preparing them is difficult, since no one knows what will happen in the next deviation situation. Some suggestions are to consider the MKT approach and to evaluate the range where the product can keep its properties when stressed by temperature excursions. The MKT is an indirect approach as it gives an evaluation of the temperature supported by the product, which is not a representation of the stress supported by the product; it gives no information allowing the person in charge to evaluate the consequences of the deviation.

Another approach is to use a mathematical evaluation of the product degradation during the temperature excursion as recently described (18). This paper presents a mathematical approach to dealing with temperature excursions. It is based on existing tools, such as the Arrhenius equation and the first-order kinetic equation. The aim is to help the Qualified Person (QP) decide whether to release a product that has experienced a temperature excursion. The available stability data are worked out and completed with additional short tests. This evaluation makes it possible to determine the potential degradation that has occurred during the temperature excursion.

If this approach is not practicable, the standard development methods, Design of Experiment (DoE) or "Trial and Error" approach based on the available experience can be used. Some guess studies such as "Temperature Excursions" can help the manufacturer to identify possible limits and respond to temperature deviations.

Combination Studies. A related question is the need for combination studies. Each stress condition imposed on the product will increase the degradation mechanisms that affect its quality. Some of these will have a negligible effect, but others will have significant consequences. For example, if the product is subject to transport outside its storage conditions, it is important to ensure that the expiry date as determined during long-term studies remains valid. Studies with this aim are best run as combination studies, where the product is subjected to transport conditions *e.g.*, at the beginning, middle and/or end of long-term stability studies.

Similarly, temperature excursions studies should be performed at different time points of the long-term study, to simulate the real-life conditions.

Scheduling the Studies for Storage, Transport and Temperature Excursions

Having a comprehensive view of the activities to be carried out will help the stability manager to be more efficient. Studies can be scheduled logically, considering the number of samples to be placed in different conditions and the time when the analysis will be performed. There are excellent reviews on this activity elsewhere (19)

The best plan is to run the studies in two phases:

- The first phase consists of assessing short-time sensitivity (up to one month) and establishes if the initial estimate was within the target range.
- The second phase is to run the full set of tests, taking into account the findings of the first phase.

BUILDING STABILITY KNOWLEDGE OR HAVING A CLEAR VISION OF THE STABILITY PROPERTIES

For Product Distribution

How to interpret the available stability data?

The goal is to assure patients and health authorities that the manufacturer can control product quality until use. To achieve this goal, the manufacturer should build knowledge and understand how to control product degradation or conversely to understand the reasons underlying the presence of an unacceptable amount of degradation products.

He should first determine what is the acceptable amount of degradation products and in what conditions they will be formed. As described above, temperature is the most important parameter for most of the sensitive products.

The main information is the temperature/time relationship and the manufacturer will find out that certain periods of time are more relevant than others (see Table III). Fixing the standard operational times will decrease the number of observations to the minimal amount. For example, it is difficult to handle a medicinal product in less than 1 h. Handling a batch of thousands of units (*e.g.*, taking it out of the storage room, preparing dispatch, loading a truck) lasts at least this period of time. Labeling this same batch on an automatic machine will last one shift or more. Transporting a batch from one manufacturing site to a distribution site abroad might last a couple of days.

It is now time to determine the temperature limit at which the product can be placed until it is degraded at the acceptable value. This can be done by using the mathematical model described in Ref. (18).

At the beginning of product development, knowledge is scarce and the picture is all dark gray (see Fig. 4a). Defining the theoretical upper limit of product stability, using the mathematical model presented elsewhere will be of great value and will allow the manufacturer to better understand

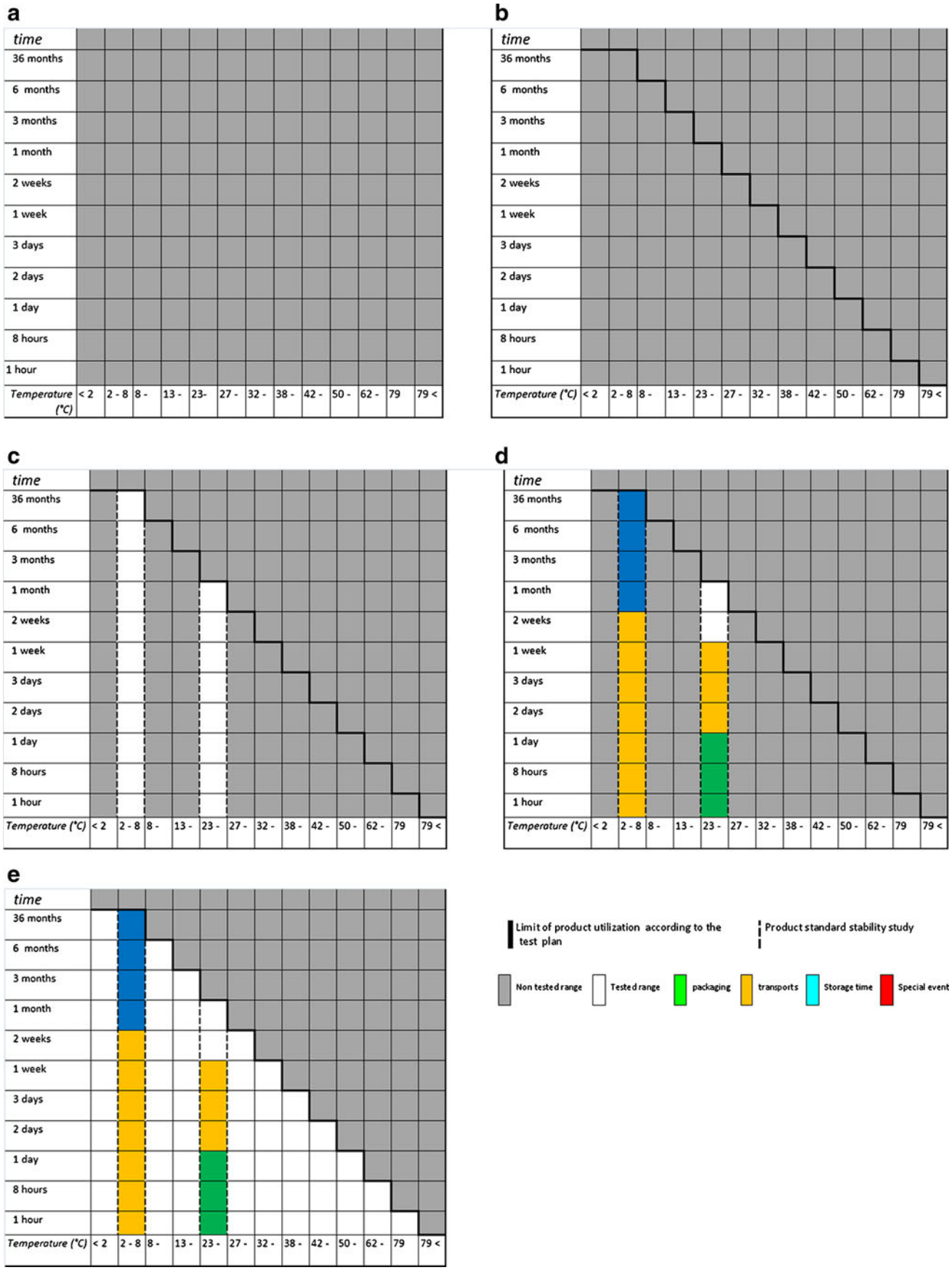

Fig. 4. Example showing how to build stability knowledge. **a** At the beginning. **b** With the preliminary mathematical model and safety margin. **c** With the ICH/WHO stability program. **d** With the preparation/distribution plan. **e** With a full set of tests

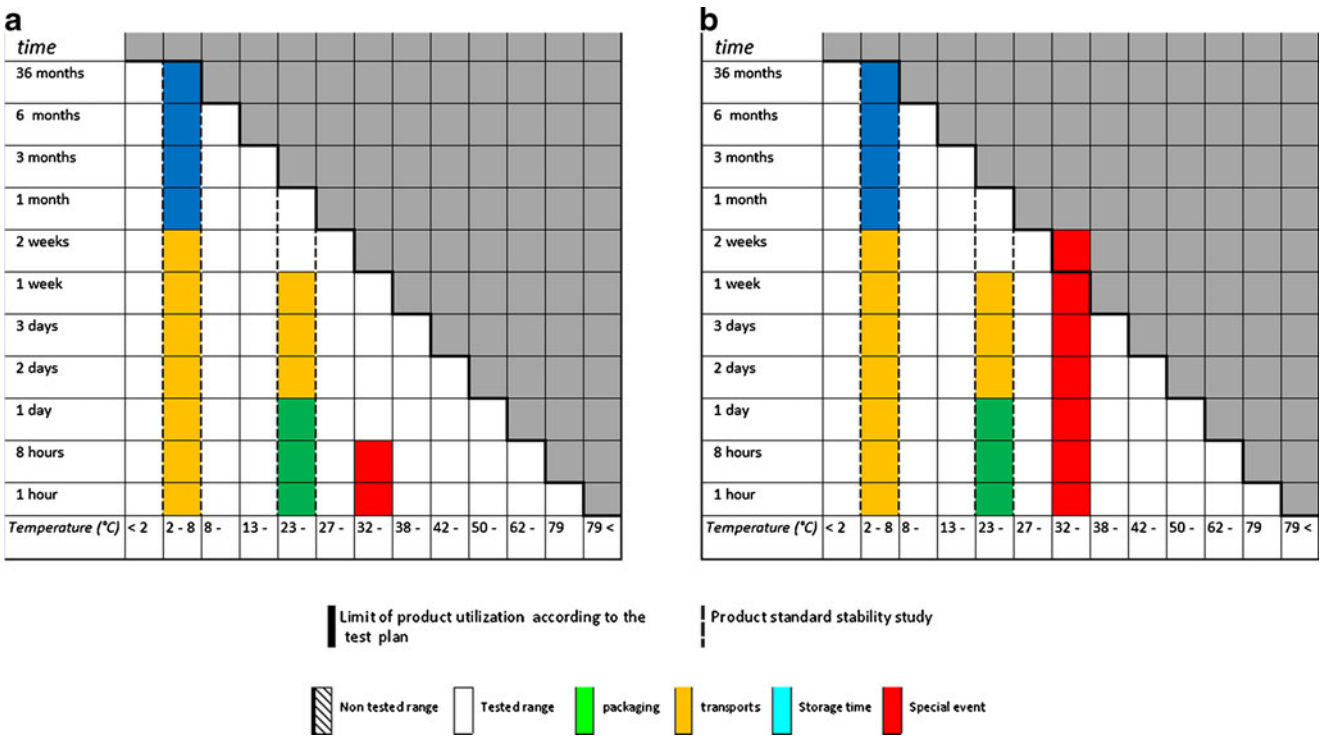

Fig. 5. Example showing how to use the stability knowledge in case of temperature excursions. **a** With temperature excursion for less than 8 h at 34°C. **b** With temperature excursion for 10 days at 34°C

the product. The data from early stability tests will be valuable to plan the initial evaluations. If in addition, the manufacturer defines the safety margins that apply to the product, the range in which the product can be handled safely can be clearly defined (see Fig. 4b).

The ICH/WHO stability data guidelines define appropriate temperature ranges for the different study ranges −20°C±5°C, +5°C±3°C, 25°C±2°C, 30°C±2°C, 40°C±2°C (see Fig. 4c). The manufacturer will have a better view within the tested ranges and find how to organize the manufacturing and transport operations (see Fig. 4d). But there will still be a lack of information outside these ranges.

Additional studies should focus on clarifying the ranges in which the manufacturer needs information to deal with transport and temperature excursions (see Fig. 4e). Using standard periods of time (see Table III) the manufacturer will determine the parameters of the tests to be conducted. The product will be placed at the upper temperature of each range and tested for degradation during the time that has been determined. If the degradation's value is at or below the limit, the manufacturer can reasonably fix the limits for accepting a temperature deviation. Obviously, all stability-determining parameters must be evaluated.

This is how manufacturer can build his stability knowledge.

When this set of analysis is complete, the final version has to be settled and will be useful for temperature excursion investigations.

For Temperature Excursion

This same representation can be useful for decisions relating to temperature excursions. The information is reported directly on the product temperature profile. The decisions that have to be taken are supported by real data.

In the example below, one batch of product has been stored at 34°C for 8 h (see Fig. 5a). The person in charge can report this value in the table and show that the quality of the product is still within the accepted values of the parameter tested. In the second example, one batch has been stored for 10 days at 34°C (see Fig. 5b). Here it is clear that the quality of the product is endangered by this temperature excursion. The other tests parameters which are relevant for stability studies still have to be evaluated before releasing or rejecting the batch.

Fig. 6. Label of IATA: the exact transport information has to be printed in the white section

FINAL CONSIDERATIONS

After all the tests have been performed and evaluated, the company will obtain a table similar to Table VI.

These are the specifications that are supported by the data and include the safety margin. They show the authorities that the manufacturer has adequate control of the product stability profile that will be included in the application for marketing approval.

These values must be restrictively provided to persons who have a limited view of the full batch history and are unaware of the product properties. This will prevent the uncontrolled risk that a stakeholder or patient takes a wrong decision based on his partial and incomplete knowledge.

The labeling should be clear, and a proposal has been provided by the IATA (15) in its regulation *e.g.*, see Fig. 6.

By keeping track of the handling conditions and by summing the time at each temperature, the manufacturer can assess whether the batch is acceptable for use by the patient.

Temperature excursions are examined in the light of the available data set. If a mathematical model has been developed, it can assist evaluation of the consequences on the criticality of the excursion.

CONCLUSION

The manufacturer must ensure that products delivered to patients comply with the marketing authorization. For products sensitive to transport conditions, this means that the manufacturer has to control the product stability profile and choose the correct storage conditions and appropriate transport systems. When the transport conditions deviate from the specified values, there is a sound basis to decide whether to release or to reject the batches.

The storage conditions are best determined in accordance with the ICH/WHO stability testing programs.

Transport conditions have to be determined considering the risks of product degradation. If the product is very sensitive to one or more parameters, the manufacturer has little margin to set the transport conditions. Tight limits, identical or close to those of the storage conditions, will be required. On the other hand, if the product is somewhat resistant to extended parameters for a short period of time, it is in the interest of the manufacturer and the users to have extended transport conditions. In the example of a refrigerated product, the chosen transport conditions could be “room temperature” or “controlled room temperature”, allowing the product to be transported in conditions that are not too difficult to guarantee for the many transport operations that are necessary to reach the patients. The risks of deviations are diminished, without increasing the risk to the patients.

The preliminary information needed to optimize transport conditions is knowledge about product sensitivity to the relevant transport parameters. Tests in addition to those proposed by the ICH/WHO guidelines should be planned to complete the picture.

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