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Perspective

Industry Perspective on Temperature Cycling Studies to Meet Regulatory Temperature Excursion Support Requirements: Survey Outcome and Recommendations

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ABSTRACT

Temperature cycling stability studies can be appropriately designed and utilized to ensure that drug product quality, efficacy, and safety are not compromised when materials are subjected to short term temperature excursions from intended storage that may occur during e.g., shipping, transport, or patient use. Some countries, such as Australia and Brazil, impose specific regulations that specify the need to conduct stability studies that are supportive of "real world" excursions as part of licensing approval requirements. These temperature cycling stability studies extend beyond what is described in ICH Guidelines Q1A(R2) and Q5C, and companies may be challenged in designing studies that not only satisfy country specific regulations, but also satisfy all global regulatory health authority expectations. This article focuses on responses to a cross-industry survey conducted within the International Consortium for Innovation and Quality (iqconsortium.org) member companies, regarding practices related to temperature cycling stability studies, in order to determine how these requirements are being interpreted and met. The results indicate that while there is no one-size-fits-all approach to performing temperature cycling stability studies, there are common and best practices that can be followed to satisfy global health authority regulatory guidelines and requirements.

Purpose: The purpose of this paper is to describe the outcome of an industry survey and common/best practices on temperature cycling stability studies performed on drug product (DP) to satisfy the requirements established for marketing authorizations in Australia and Brazil or any other countries that may have similar requirements. The framework is proposed within the context of late phase and commercial development of common biological and/or large molecule modalities, such as monoclonal antibodies (mAbs, including bispecific antibodies), fusion proteins, complex proteins, oligonucleotides, and antibody-drug conjugates (ADCs), but many of the general principles involved may be applied to other therapeutics, such as Virus Like Particles (VLP), gene or cell therapies (GTx or CTx), or vaccines.

For the purposes of this paper, temperature cycling stability studies refer to studies that are designed, in part, to support short term temperature excursions that drug product may be subjected to during shipping and storage activities and is outside of the labeled storage condition of the product.

Introduction

ICH Guidelines Q1A(R2) and Q5C address information to be submitted in a core stability data package in registration applications for new investigational drug substances and products, to provide evidence of how the quality of the drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and establish a retest period or shelf-life, and recommended storage conditions.[1,2] While there is general mention that data from accelerated or intermediate storage conditions can be used to evaluate the effect of short-term

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Table 1
Temperature cycling stability study requirement comparison.

Requirement	ICH Q1A (R2) stability testing of new drug substances and products 6 February 2003 ICH Q5C stability testing of biotechnological/biological products 30 November 1995	ANVISA RDC No. 412 20 Aug 2020	TGA stability testing for prescription medicines 6 Mar 2017
Temperature cycling study	Does not explicitly require or describe	Yes, to support deviations to storage conditions	Yes, to support deviations to storage conditions
Number of Batches	N/A	At least one	Preferably three
Manufacturing Scale	N/A	Representative of commercial scale	Commercial scale
Cycle description	N/A	Representative of the temperature deviation. Further cycle design examples or description not given.	Representative of temperature deviation (magnitude of time and temperature), examples given. At least one cycle, multiple may be included.
Storage at long-term storage condition through shelf life	N/A	Yes	Yes
Justification required if study not conducted or completed	N/A	Yes	Yes

excursions outside the label storage conditions, such as during shipping or handling, there is no further guidance with respect to additional studies that may support real world excursions that could be encountered. Additionally, the ICH guidelines do not address specific national or regional expectations. Some countries have incorporated more specific requirements for temperature cycling stability studies for drug product into their regulations or guidance documents. Table 1 details a comparison of temperature cycling stability study requirements from ICH, ANVISA (Brazil's regulatory authority) and TGA (Australia's regulatory authority).[1–4]

In response to industry questions, the Temperature Excursion Stability IQ Working Group was formed in 2018 to develop a corresponding guidance. The IQ Working Group authored a survey for industry with the intent to gather information from IQ member companies on how these requirements are being interpreted and to recommend common practices on temperature cycling stability for fulfillment of global regulatory requirements, if appropriate.

Method

To evaluate both general temperature cycling stability study practices and those used to address Brazil's and Australia's requirements, a survey was circulated to IQ consortium member companies. The survey comprised 45 questions (*please see supplementary online material).*

Results

Out of 21 biopharmaceutical/biotech companies contacted 13 responded. Fig. 1 provides an overview of the product types included in the responses.

The majority of the survey participants indicated that they strive to use a common world strategy approach when designing temperature cycling stability studies, however, alternative strategies have also been utilized, as demonstrated in Fig. 2. Where a common world strategy is not being carried out, companies may instead be using separate strategies to address each specific country requirement or a common regional strategy, where the requirements of Australia and Brazil are coupled together and used in conjunction with other studies that support other world markets.

In general, temperature cycling stability studies are performed throughout product development and those early studies augment data generated in either the registration phase for global markets or in a post-approval/ lifecycle stage of the product to enable a successful submission in Australia and Brazil.

The following sections present all available data received from the responses for the key topics from the survey.

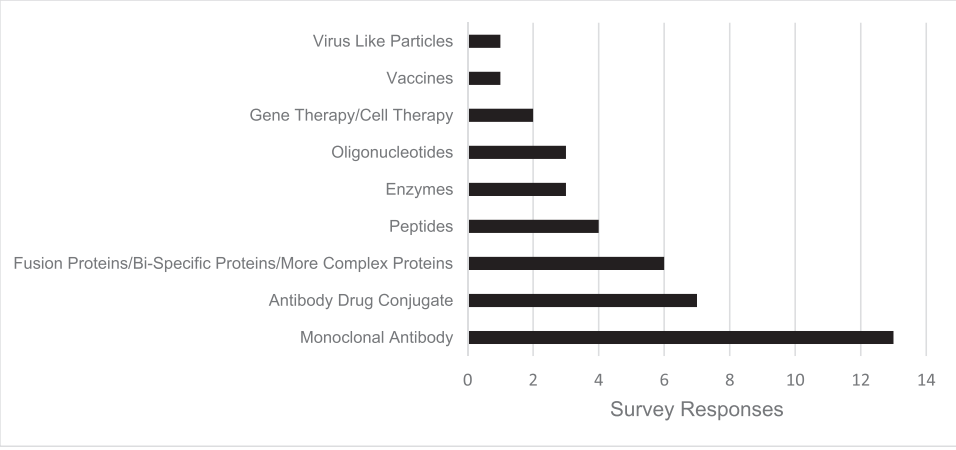

Figure 1. Overview of product types included in company response.

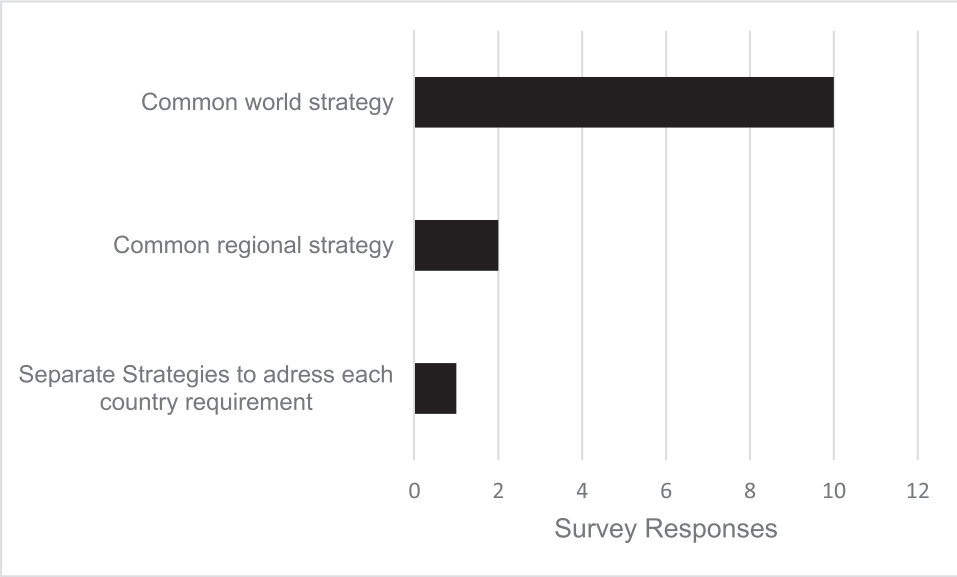

Figure 2. Summary of how responding companies currently address requirements.

Material and Batches

About 50 % of the responding companies use materials from three batches to meet the preference set out by the Australian and Brazil agencies in a combined approach, whereas the other 50 % submitted data for one batch only (Fig. 3). If materials from multiple batches are used, a bracketing/ matrixing strategy to support multiple product strengths or presentations is often employed (e.g., fill volume/headspace; container/closure systems).

The majority of responding companies utilize drug product materials available throughout the development life cycle, such as batches supporting toxicological studies, development batches, or GMP batches, as long as the batches meet representativeness criteria, in the design of temperature cycling stability studies. However, all companies reported eventually also utilizing commercial scale materials in temperature cycling stability studies (either ICH/primary/registration materials or process validation (PPQ) batches) (Fig. 4).

Temperature Cycling Stability Study Design

Two study designs were described by the survey participants:

- In the first study design type, one or two temperatures (one above the storage condition and if desired one below) are included within a single cycle (or block) followed by placing the materials at the long-term temperature conditions.
- The second design type utilizes a multi-step temperature profile (more than 2 temperatures) in multiple cycles with subsequent placement of the material at the long-term temperature conditions.

Tables 2 and 3 show a summary of the cycling conditions used by the companies on the same sample; the actual study design, (e.g., the order in which the cycles were applied before placing the material on long-term stability to the end of shelf-life) may not be reflected as it

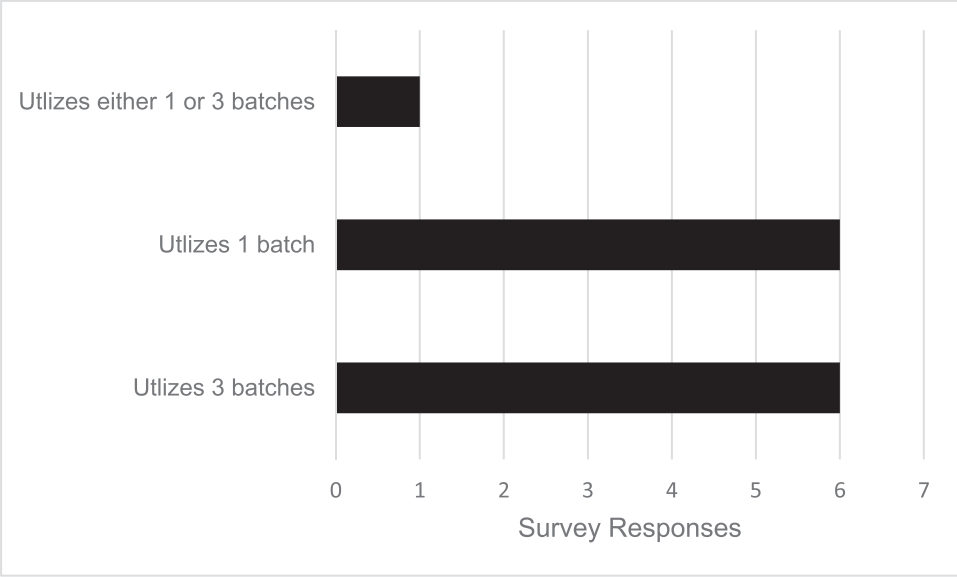

Figure 3. Summary of number of batches being utilized in design of temperature cycling studies.

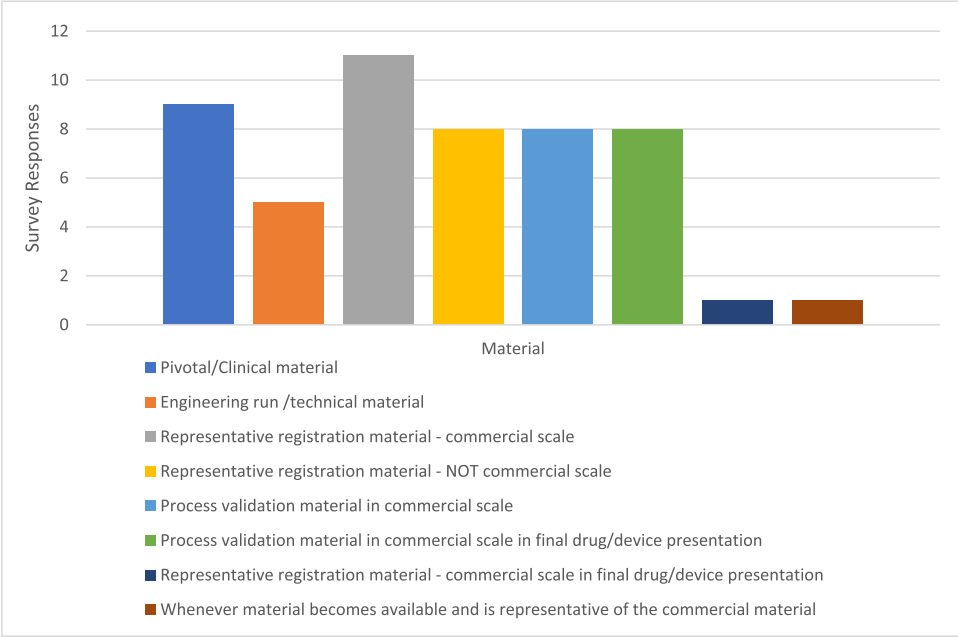

Figure 4. Summary of material being utilized in design of temperature cycling studies.

Table 2
Minimum and maximum conditions in a single cycle (or block).

	Temperature [°C]	Days	Modality
Company 1	−50	180	Gene / Cell Therapy Products
	5	2	
Company 2	−20	7	Monoclonal Antibody
	25	32	
	30	32	
Company 5	−20	30	Virus Like Particles (VLPs) | Antibody Drug Conjugate | Vaccine
	25	30	
Company 11	25	14	Monoclonal Antibody | Antibody Drug Conjugate | Fusion Proteins/Bi-specific Proteins/More Complex Proteins
Company 13	25	30	Monoclonal Antibody | Antibody Drug Conjugate | Fusion Proteins/Bi-specific Proteins/More Complex Proteins

depends on the specific product characteristics. Of companies using a single cycle or block design (Table 2), two companies only test for high temperature in a single cycle followed by the end of shelf-life study.

In order to mimic or exceed the maximum likely duration of "real-life" temperature excursions and be prepared for both low and high excursions, most companies investigate the effects of temperature excursions by performing multiple alternating low and high temperature excursions versus exposing the product to a single excursion at one or both extreme temperatures.

The cycling in all the above study designs is then followed through the end-of-shelf-life at the recommended storage condition.

More than 50 % of the companies do not have a requirement in which timeframe after manufacture the temperature cycling study should start. For those companies that recommend a start date for the temperature cycling study, most of the companies will schedule the study within the first six months after manufacture (Fig. 5).

While drug product may be subjected to stress factors other than temperature excursions during shipping (such as light exposure, vibrations, etc.), these factors are typically outside of the scope of the temperature cycling stability studies discussed here. Temperature, light and other stress conditions are evaluated in forced degradation studies as part of product development and characterization. Shipping validation studies may also incorporate multiple forms of stress.

Testing Strategy

As indicated in Fig. 6, the overwhelming majority of companies include all shelf-life specification tests into the testing program. Very few also conduct additional characterization on the product. One company only performs these studies with a minimal subset of stability indicating tests.

If changes to critical quality attributes (CQAs) are observed on the stressed material, most companies perform investigations as part of their quality system obligations (out-of-trend/ out-of-specification). However, if the change does not impact meeting the specification acceptance criteria no action is taken. If the specification acceptance criteria are not met, then companies either restrict the allowance for excursions or look for alternatives to control their shipping process (e.g., shipping containers). One company exposes additional subsets of batches to shorter or longer excursion periods as a contingency.

Data Package Used for Submission

How much data is provided to the agencies may depend on the submission strategy a company pursues. On the extremes, one company is generating full shelf-life data prior to submission, while four companies have the excursion study started, but do not provide any stability data when submitting. The remaining companies submit with the data available at the time of filing, ranging from 3 to 12 months. The companies that submit with no or less than full shelf-life data from the cycling study typically provide additional available data upon request of the health authorities. Only one company commits to provide the data to the agencies prior to launch.

Additional Considerations for Temperature Cycling Stability Studies

To explore acceptability of utilizing data generated for accelerated studies as part of the developmental stability program in lieu of the

Table 3
Minimum and maximum conditions in multiple cycles.

	Cycling Temperature [°C]	Days per Cycle	No of Cycles	Modality
Company 1	−30	3	3	Monoclonal Antibody | Fusion Proteins/Bi-specific Proteins/ More Complex Proteins
	30	3	3	
Company 2	−20	2	3	Monoclonal Antibody
Company 3	−20	7	3	Monoclonal Antibody | Antibody Drug Conjugate | Gene / Cell Therapy Products | Peptides | Enzymes | Fusion Proteins/Bi-specific Proteins/More Complex Proteins
	30	14	1	
	40	1	1	
Company 6	−70	3	4	Monoclonal Antibody | Antibody Drug Conjugate | Vaccine | Gene / Cell Therapy Products | Peptides | Enzymes | Oligonucleotides | Virus Like Particles (VLPs) | Fusion Proteins/Bi-specific Proteins/More Complex Proteins | Nanoparticles
	−20	4	3	
	−5	4	3	
	5	3	3	
	25	3	3	
	30	3	3	
Company 7	0.5	7	2	Monoclonal Antibody | Peptides | Fusion Proteins/Bi-specific Proteins/More Complex Proteins
	15	24	1	
	25	2.5	1	
	25	1	4	
	35	1	1	
Company 8	25	2	3	Monoclonal Antibody
	30	2	3	
Company 9	−20	3	3	Peptides | Enzymes | Monoclonal Antibody | Antibody Drug Conjugate | Oligonucleotides
	0	30	1	
	5	3	6	
	10	30	1	
	25	3	3	
Company 10	−5	3	1	Monoclonal Antibody | Oligonucleotides
	15	4	5	
	30	0.2	11	
	30	4	3	
	40	0.6	1	
Company 11	−20	1	4	Monoclonal Antibody | Antibody Drug Conjugate | Fusion Proteins/Bi-specific Proteins/More Complex Proteins
	5	1	4	
Company 12	25	2	3	Monoclonal Antibody | Antibody Drug Conjugate | Fusion Proteins/Bi-specific Proteins/More Complex Proteins

temperature cycling stability studies to support excursion, additional questions were included into the survey.

Device Stability

If the commercial product includes a device, all companies consider the impact of excursions on the functionality of the device delivery system (Fig. 7). However, not all companies include device functionality as part of their testing strategy in the temperature cycling stability studies. Those companies that do not include device functionality testing (25 % of the responding companies) support this approach by utilizing excursion studies performed separately in the device design verification study. If device testing is included, functional tests like break-out and gliding forces measurement, delivered volume, and functional hands-on-tests like trigger button actuation are the most used tests (Fig. 8).

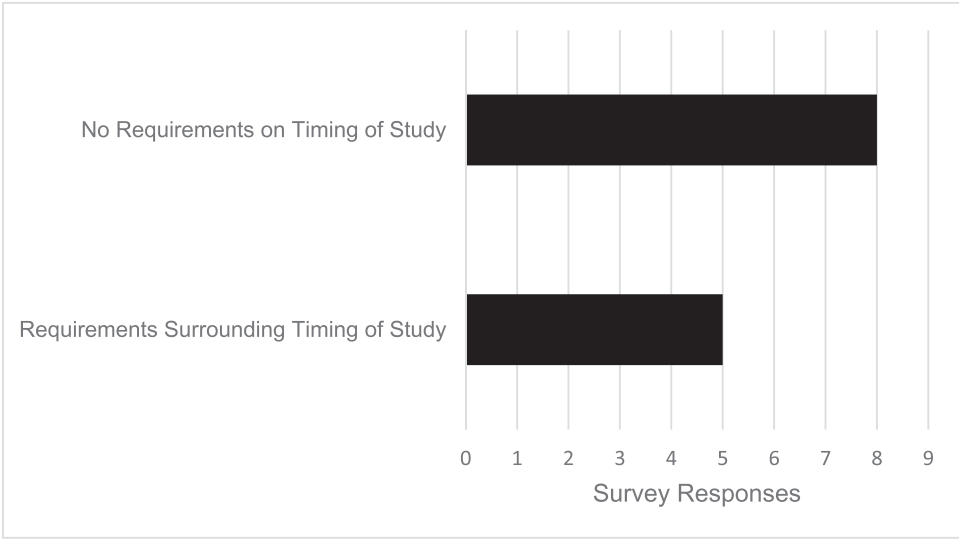

Figure 5. Requirements surrounding timing of temperature cycling study start.

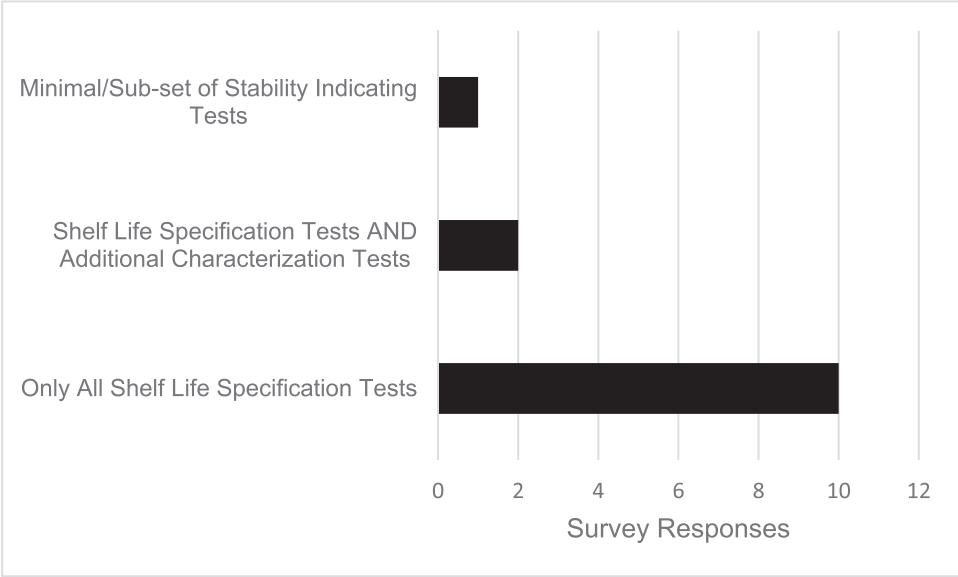

Figure 6. Type of testing being performed on temperature cycling study.

Modeling

While all companies were supportive of robust and scientifically sound strategies, such as modeling, to reduce the resources needed to conduct stability testing, currently, the majority of companies do not incorporate reduced testing strategies into temperature cycling stability study design (Fig. 9). Only two out of 13 companies used Arrhenius modeling to reduce the number of stability studies.

Discussion and Conclusion

Companies are responsible for designing stability studies to support temperature excursions that may occur during handling and/or transport of the product. A variety of general articles exist regarding such studies, with differing degrees of specificity to biologics and fewer with reference to specific regional requirements.[5–10]

The survey responses highlight the following commonalities:

- that a universally applicable recommendation for a successful temperature cycling stability study design cannot be identified since varied strategies have been successful.
- that all companies have common challenges when designing temperature cycling stability studies.
- that all companies were supportive of robust and scientifically sound strategies, such as modeling, to reduce the resources needed to conduct stability testing.

With regards to the second and third bullet above, current approaches to meeting the guidelines issued by Australia and Brazil place a high burden on the organizations with respect to the competing needs to supply material for temperature cycling stability studies to support temperature excursions while building launch supply to meet patient needs. Incorporation of science and risk-based approaches, in choice of material, study design, or use of stability models, may improve time to market while ensuring safe and efficacious drugs as intended by current guidelines.

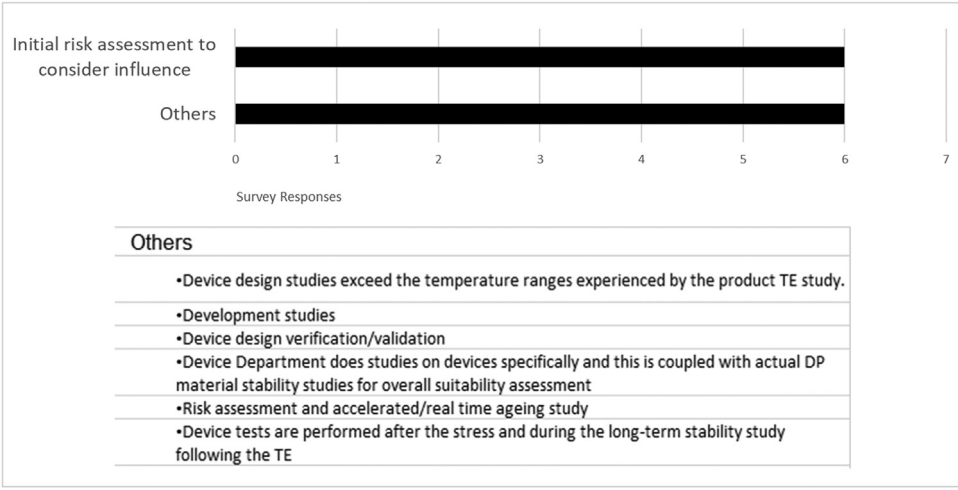

Figure 7. Addressing the temperature influence on the device.

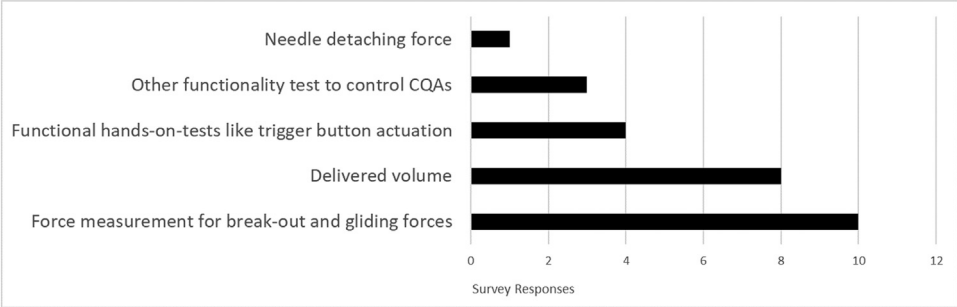

Figure 8. Functionality test applied.

Table 4 details common challenges that companies are currently facing with discussion on possible solutions to overcome these challenges.

The approach to the design of temperature cycling stability studies depends on the prior knowledge about the molecule (e.g., susceptibility to degradation), the type of product presentation (liquid/ lyophilized/ vial/ prefilled syringe), recommended storage condition (frozen versus refrigerated), as well as the intended transportation routes (e.g., by land, water, air) and the shipping containers. All these factors influence the design of the excursion program to be executed to meet the Australia and Brazil submission requirements. However, some common practices were identified and are detailed in Table 5.

Using these common practices, it may be possible to create a few general temperature cycling designs based on common product categories, with justification of specific design based on product knowledge. Table 6 summarizes a few temperature cycling stability study designs for traditional biologic products, such as mAbs, ADCs or peptides. The recommended example temperature cycling conditions in the table are based on general scientific knowledge as well as the survey outcome. With the suggested cycling conditions below, temperature can be controlled using commonly available stability chambers.

The proposed cycling designs can be seen as a starting point. The decision about acceptable cycling conditions normally starts after commercially representative material is available. Specific conditions for each product should be driven by product stability knowledge acquired through the development. If the product is part of a combination product or device, there will be additional considerations. For example, the impact of freezing temperatures on container closure integrity for a prefilled syringe product, as well as any knowledge gained from the characterization of siliconization during development should be considered in study designs for these types of products. Additionally, cycling temperature impact on device functionality should also be considered, e.g., a battery powered device may not tolerate frozen storage.

The varied responses in the survey also highlight the need for continued discussion with regulatory health authorities and potential alignment of guidance and regulations. Table 7 summarizes the considerations for potential discussion with agencies for the temperature cycling stability study design based on the responses obtained in the survey.

In summary, while a universally applicable recommendation for a successful temperature cycling study design cannot be identified, a reflection of science and risk-based approaches in material selection, study design, and use of stability models in the guidelines may provide distinct advantages to the ability to meet the guidelines for Australia and Brazil, and other global markets, more efficiently while providing evidence and understanding of the impact of temperature excursions on the drug product. The following case study is presented which demonstrates that consideration of the above can result in a successful overall global strategy that was accepted by Brazil and Australia.

Case Study Molecule - Global Strategy Including Brazil and Australia

In the following example, one member company established a general approach incorporating many of the responses from successful studies as described in this publication. The conditions covered by the temperature cycling stability study were designed to confirm the proposed allowances outside of the recommended storage

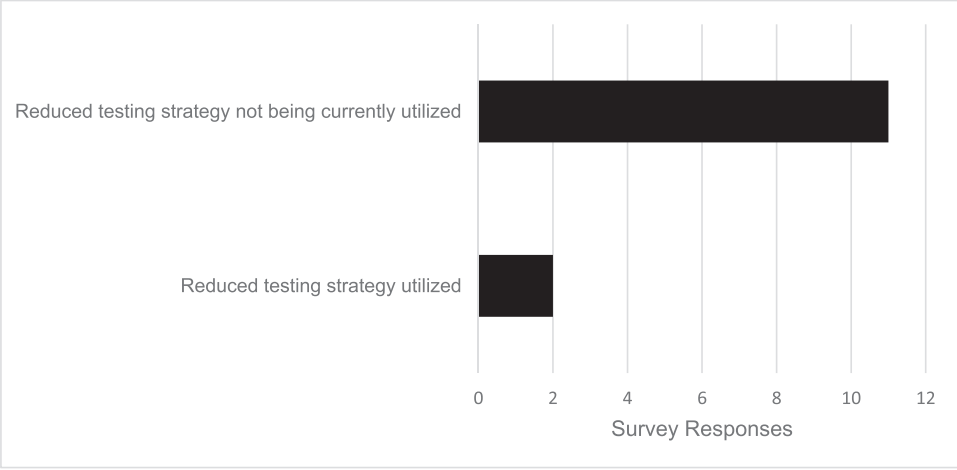

Figure 9. Summary of companies that incorporate reduced stability testing strategies.

Table 4
Common challenges.

Challenge	Proposed Solution and Justification
Temperature cycling stability study material needs limit supply to patients	Incorporation of science and risk-based approaches, in choice of material, study design, or use of stability models, may improve time to market while ensuring safe and efficacious drugs as intended by current guidelines. Consideration should be given to matrixing and bracketing approaches if different presentations (strength, presentations) are intended for commercialization.
Limited success/experiences using stability modeling approaches	As stability modeling approaches are used in study design and stability data evaluation elsewhere in the registration of drug products (in support of the stability data package, or in establishment of shelf-life) their role in the design of temperature cycling stability studies for excursion assessments should be considered as well. While acknowledging that biological medicines can be subject to multiphasic and non-linear degradation, there exist stability models[11–15] that have proven useful to define stability over relevant ranges. These stability models in addition to other stability knowledge might be used to assess excursions.
Limited success using prior knowledge	If changes throughout development are viewed as a continuum supported by comparability studies, utilization of earlier development studies are justifiable in lieu of conducting a dedicated temperature cycling stability study using commercial batch material. Good scientific justifications exist to leverage previously generated data in addressing the temperature excursion requirements, especially when these data are combined with mathematical models (e.g., Arrhenius or other models[11])
Interpretation of current guidelines across regions for different type of products	The design of the study should be based on, and supported by, the product knowledge gained through the development process. An understanding of the stability and degradation behavior is built through stability studies conducted at long-term, accelerated or stress conditions. Fundamental principles for the molecule, such as melting temperature (Tm), eutectic temperature of frozen mass (Te), glass transition temperature of frozen mass (Tg') or dry mass (Tg), may be considered and helpful to identify regions of greater or lesser concern and justify the choice of temperatures used for cycle design. The quality target product profile, including the presentation (e.g., liquid or lyophilized drug product), recommended storage condition (frozen, refrigerated, or controlled room temperature), and drug product administration (including clinical or home use environment) may also drive the need for a particular cycling design.
Application of current guidelines to new modalities	The current guidance/regulations were established at a time when biological drug products primarily consisted of mAbs and vaccines, which have traditionally had intended storage conditions of refrigeration (or possibly room temperature). In the past decade, new modalities have emerged with frozen/ultracold intended storage and these materials are in a frozen solid state during shipping. Exposure to Zone I-IV temperatures would often mean that a phase change from a frozen solid to a liquid has occurred as part of the excursion. As these exposure types would often have a higher probability of adverse impact on the drug product, as it is a more stressed excursion, temperature cycling stability studies outlined by current guidance may not be needed to support shipping and storage excursions. Instead, studies where the impact to the quality attributes of the material is examined as a result of subjecting the material to phase changes may be more appropriate than a study that cycles above and below the intended storage condition. It is recommended that these additional factors be considered and alternative supportive stability data and/or alternate studies to those outlined in this paper may be utilized to support shipping and storage excursions of the products. The existing standard may require updates for these new modalities.

temperature of 5 °C, in order to support time needed for manufacture, packaging, shipping operations, and distribution. Additionally, the conditions also support if a designated allowance for the end-user-convenience time is necessary and to encompass allowances for potential unexpected temperature excursions. The study started with a single drug product batch representative of the final commercial manufacture process (e.g., Process Performance Qualification batch) that was cycled to multiple temperatures below the recommended storage condition, followed by elevated temperatures for pre-determined durations, and then cycled back to the recommended condition of 5 °C to be monitored through the end-of-shelf-life.

The approach is used as the single global strategy and has been approved in global submissions, including by TGA and ANVISA. Although a specific amount of data to support temperature

Table 5
Common practices.

Category	Common practice
Minimum number of batches used in temperature cycling stability studies	1
Temperature cycling stability study	Place material at long term condition after temperature cycling exposure for duration of shelf life in order to demonstrate continued compliance to specifications within the established shelf life. The use of temperature cycling approaches provides data to support varying temperatures encountered during transportation. The data supports continued use of the product and mitigates rejection of material subject to a temperature excursion such as during shipping. When end-user convenience time is a part of the label claim, it should be included in the temperature cycling stability study design. The end-user convenience time is the storage of the product for a period of time at a second temperature (usually ambient temperature) prior to administration. Such a 'patient use period' or 'in-use allowance' adds convenience for end-users and improves patient experience.
Testing Strategy and Data Assessment	Utilize shelf-life specification test methods and utilize them according to typical ICH testing intervals. Additional characterization testing may be considered in order to gain a deeper product stability knowledge. Changes to CQAs should be scientifically understood with appropriate controls in place to monitor. If specifications are not met, temperature excursions during shipping could be entirely restricted if required.

Table 6
Example cycling designs[3] for biologic products stored in vials.

Product presentation	Nominal storage temperature	Recommended temperature cycling condition
Liquid	Refrigerated (2–8 °C)	−20 °C[1] for 3 days, 25 °C or 30 °C for 3 days, 3 cycles
Liquid	Frozen (below 0 °C)	N/A[2]
Lyophilized	Refrigerated (2–8 °C)	−20 °C for 3 days, 25 °C or 30 °C for 3 days, 3 cycles
Lyophilized	Controlled room temperature	−20 °C for 3 days, 40 °C for 3 days, 3 cycles

[1] −20 °C as an example frozen condition, generally above from Tg' or Te. Note: low temperature cycle may be above the freezing point if the product or container-closure are not stable for freeze/thaw cycling.
[2] N/*A* = not applicable. Many frozen mass phase transition temperatures should be considered to determine cycling conditions for frozen stored DP. Each product should be assessed individually.
[3] long term stability to be evaluated after the temperature cycling, including end-user-convenience time, if required.

excursions is defined for the initial market application (IMA) for approval, the data provided at the IMA submission typically has included the completion of temperature cycling prior to the initiation of the stability study at the long-term storage condition. While ANVISA is more open to the information provided, a shortened shelf-life may be granted, or temperature excursions may not be allowed by TGA due to the limited data set at the initial submission. The intended shelf-life claim is approved by TGA once a full set of temperature cycling data including the end of shelf-life has been provided.

Table 7
Considerations for agency discussion based on survey responses.

	Study design based on survey responses	Considerations for discussions with the agencies
Study Setup	• Expose material to cycling conditions (low and high temperature compared to long-term storage/shipping temperature) considering the knowledge about potential shipping excursions. • The excursion study is followed by storage at the long-term storage condition • Patient convenience period needs to be included at the long-term storage condition, if applicable.	A cycling approach (versus a block excursion) reduces the risk if multiple temperature excursions are experienced during the same shipment.
Study Setup	• Best to use material within six months of manufacture	N/A Utilizing material in early stages of the shelf life reflects the real-world scenario of product being shipped. It also allows for assessing the impact of an early excursion on the full shelf life.
Material from Number of Batches Exposed to Temperature Excursion	• Material from one commercial scale batch per presentation • Consider matrixing and bracketing for different strengths, presentations, manufacturing sites, etc.	Brazil requires data from one batch, Australia prefers data from three batches, both agencies agree on commercial scale in the to be marketed presentation (i.e., incl. device if applicable). Consideration should be given to matrixing and bracketing approaches if different presentations (strength, presentations) are intended for commercialization. Consideration should be given to the possibility of providing the stability of multiple product presentations by supporting the choice of a worst case for excursion followed by long-term stability (e.g., highest concentration as a worst case for aggregation growth).
Parameters Tested	• shelf-life specification tests for drug product only	Additional drug product testing as demanded by product might be executed. Consideration could be given to not including device testing if data for device performance are available that cover excursion temperatures (e.g., from device development).
Timepoints Tested	• Prior to excursion, directly after excursion, followed by the regular timepoints at the long-term storage condition (ICH interval)	Consideration should be given to possibility for reduced timepoint design for the long-term storage condition.
Data Evaluation	• Data will be evaluated against (anticipated) shelf-life specifications	Data need to be (re-) evaluated against commercial specifications granted by the authorities.
Data Package Submitted to Agencies	• Full shelf-life data set is not needed at time of initial submission	Full dataset needs to be generated for subsequent submission or response to questions to avoid the risk of reduced shelf-life for product that experienced an excursion. Consideration should be given on whether data for non-cycled batches that are bridged by comparability studies could be utilized to support the full shelf life while additional data are generated for the batches that had experienced the cycling conditions.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xphs.2023.09.014.

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