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Review Article

Theme: Quality by Design: Case Studies and Scientific Foundations
Guest Editors: Robin Bogner, James Drennen, Mansoor Khan, Cynthia Oksanen, and Gintaras Reklaitis

The Application of the Accelerated Stability Assessment Program (ASAP) to Quality by Design (QbD) for Drug Product Stability

Kenneth Craig Waterman[1,2]

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Abstract. An isoconversion paradigm, where times in different temperature and humidity-controlled stability chambers are set to provide a fixed degradant level, is shown to compensate for the complex, non-single order kinetics of solid drug products. A humidity-corrected Arrhenius equation provides reliable estimates for temperature and relative humidity effects on degradation rates. A statistical protocol is employed to determine best fits for chemical stability data, which in turn allows for accurate estimations of shelf life (with appropriate confidence intervals) at any storage condition including inside packaging (based on the moisture vapor transmission rate of the packaging and moisture sorption isotherms of the internal components). These methodologies provide both faster results and far better predictions of chemical stability limited shelf life (expiry) than previously possible. Precise shelf-life estimations are generally determined using a 2-week, product-specific protocol. Once the model for a product is developed, it can play a critical role in providing the product understanding necessary for a quality by design (QbD) filing for product approval and enable rational control strategies to assure product stability. Moreover, this Accelerated Stability Assessment Program (ASAP) enables the coupling of product attributes (*e.g.*, moisture content, packaging options) to allow for flexibility in how control strategies are implemented to provide a balance of cost, speed, and other factors while maintaining adequate stability.

KEY WORDS: accelerated aging; QbD; shelf life; stability.

INTRODUCTION

Among the challenges involved in developing acceptable commercial dosage forms for active pharmaceutical ingredients (APIs) is demonstrating adequate chemical stability (1,2). Expiration dating is generally determined based on the time a drug product remains within specification limits of potency or of individual or total degradation products at a recommended storage condition. This review introduces a procedure for stability assessments of solid drug products and solid APIs that provides credible predictions for product expiration dating, improves product understanding, reduces uncertainty, and has the potential to change the way the pharmaceutical industry meets its stability commitments for clinical investigations, drug product registration, and post-approval changes. This process also significantly reduces the time needed to make stability assessments without adding any risks to patients. Moreover, it increases product understanding which allows for more complete formulation and process understanding. The concept of quality by design (QbD) for pharmaceutical products, as stated in the International Conference on Harmonization Pharmaceutical Development Q8(R2) guidelines (2009), involves first identifying critical quality attributes (CQAs), linking the raw materials and processes to the CQAs, determining a design space, and developing a control strategy. The process described in this review is well-suited to both identifying CQAs and determining the design space related to API and drug product chemical stability. Moreover, as will be shown, the basic understanding this approach engenders enables a scientifically based control strategy for drug product stability.

We have called this approach the Accelerated Stability Assessment Program, or ASAP. It consists of five elements: (1) the concept of isoconversion to compensate for the complexity of solid-state kinetics; (2) a moisture-corrected Arrhenius equation that explicitly takes into account the effect of relative humidity (RH) on reaction rates in the solid state; (3) a statistical design and analysis to both provide reasonable estimation of parameters and explicitly determine error bars for extrapolated shelf lives; (4) combining the effect of RH on stability with the protection afforded by packaging to assess the shelf life at different storage conditions and packaging configurations; and (5) the ability to determine the CQAs that impact drug stability. With this, at a minimum, one

[1] Pfizer Inc., Eastern Point Rd., Groton, Connecticut 06340, USA.
[2] To whom correspondence should be addressed. (e-mail: ken.waterman@pfizer.com)

can produce a commercial drug product with confidence that the shelf life will remain acceptable batch to batch. In addition, the effect of any changes to the production process or incoming materials can be anticipated. Based on such a scientific understanding, it can be possible to submit a QbD filing.

ISOCONVERSION

In solution, molecules can react to give product with a kinetic rate that is characterized by the order of the reaction; *i.e.*, reaction rates will depend on the molecule's concentration to a power dependent on the mechanism. In the solid state, this is complicated by the fact that molecules can exist in multiple, non-equilibrating states due to low mobility. These states include crystalline bulk, crystalline surface, amorphous material, and material dissolved in other materials (solid solution). Each of these states can potentially react to form product with its own kinetics. The overall kinetics for this heterogeneous situation can become extremely complex. Even in the simple case of two states, one more reactive and the other relatively stable, it can be difficult to deconvolute the individual contributions from a product profile. Moreover, one would need to collect multiple time points and carry out a stability experiment to significant drug degradation levels to do so. The concept of isoconversion (3,4) provides an alternate approach. For this concept, one considers only the time required for reaction to give the specification limits for loss of potency or formation of degradant(s). While strictly speaking, this does not provide a chemical reaction rate constant, it still provides a usable rate constant (*i.e.*, specification limit divided by time).

If one assumes that differences in reaction rates among the different physical states of the API are mostly due to mobility rather than factors likely to influence activation energies, the curve shape of the degradant (or loss of API) *versus* time plot would remain more or less constant. Thus, employing the isoconversion concept provides a new way of conducting accelerated stability studies which can increase accuracy. To understand this, consider the historical approach for accelerated aging and stability studies in general: protocols used are generic with fixed time points at different storage conditions. The amount of degradant formed (or potency lost) is determined at these time conditions which is then used to estimate the behavior at an extrapolated condition with respect to time and temperature. With ASAP, instead of keeping time points fixed and determining the amount of degradant/potency change, isoconversion keeps the amount of degradant/potency change constant at the specification limit and varies the time. Since, with most drug products (about 65% in our experience), formation of degradant (loss of potency) is not linear with time, the rate measured for the historical approach will vary with the extent of conversion: typically, rates decrease as more reactive API states are consumed (Fig. 1). The result is that the effective rate constant at any storage condition and time will not be reflective of the rate to a different conversion level since varying amounts of each API state is involved. In contrast, with the ASAP isoconversion approach, the rate constant at every storage condition will have the same contributions from different states (Fig. 2). While the historical approach permits generic protocols to be employed across a company's product portfolio, in many cases, it provides inaccurate predictions especially under high-temperature conditions. In fact, many cases where drug product systems appear to have anomalous behavior at high temperatures will adhere to an Arrhenius relationship if the isoconversion approach is used.

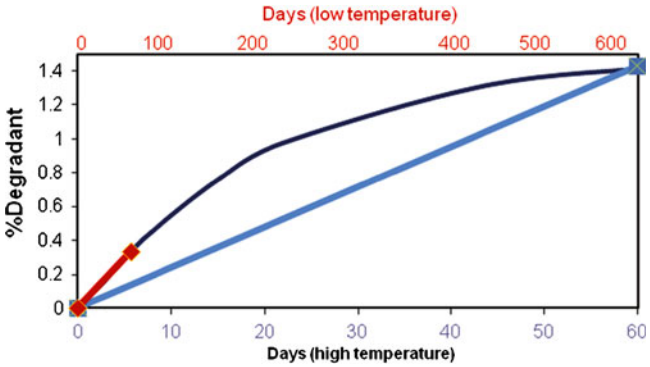

Fig. 1. Degradation of a solid drug in a drug product is shown progressing in a non-homogeneous manner at either high (*blue*) or low (*red*) temperatures. In the historical approach to stability studies, a fixed time (here 60 days) is used at each temperature and the amount of degradation measured. Since the rate is not linear, a rate constant will depend on the amount of degradation

RELATIVE HUMIDITY EFFECTS ON REACTION RATES

Solid API and drug product chemical stability is affected by the RH that the sample experiences. The moisture-modified Arrhenius equation (Eq. 1) quantifies drug product stability as a function of temperature and RH (1,2)

$$\ln k = \ln A - \frac{E_a}{RT} + B(\mathrm{RH}) \tag{1}$$

where k is the degradation rate (typically percent degradant generated per day), A is the Arrhenius collision frequency, E_a

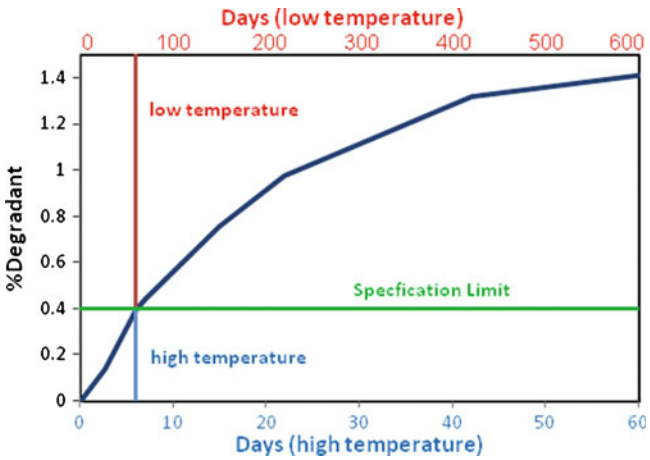

Fig. 2. In the Accelerated Stability Assessment Program (ASAP) isoconversion approach, samples are removed from stability chambers at the same, specified degradation level (here shown to be 0.4%) corresponding to different times at different conditions: the time at a condition is chosen to match the specification limit. This approach allows for accurate temperature extrapolations using the Arrhenius equation

is the energy of activation for the chemical reaction, R is the gas constant (1.986 cal/(mol K)), T is the temperature in Kelvin, and B is a humidity sensitivity constant which has been found experimentally to vary from about 0 to 0.10 (5). The form of Eq. 1 indicates that chemical stability decreases (shorter shelf life) exponentially with an increase in RH. RH can have a very significant effect on chemical stability, depending on the B term. For example, with B equal to 0.09, a shelf life at 60% RH of 5.0 years would drop to only 1.2 years at 75% RH (without packaging protection). Because of the significance of the RH, accelerated stability studies that do not explicitly control RH will not be predictive. In fact, if packaged product is used for accelerated stability studies, the RH the sample is actually exposed to must be accounted for to provide accurate predictions even if the external RH is controlled. Since many historical accelerated stability studies do not compensate or control properly for RH, data are often erratic and non-predictive.

STATISTICAL DESIGN AND ANALYSIS

Equation 1 provides the framework for an explicit determination of the isoconversion rate constant at any condition of temperature and RH. In order to take advantage of this capability, three terms must be determined from a data set: A, E_a, and B. Fitting these parameters requires a minimum of three experiments where temperature and RH are varied. In practice, it is generally advisable to use designs for varying temperature and RH that involve at least five experiments (two degrees of freedom). In the ideal, these experiments will involve storage of samples (API or drug product) at times that provide for degradation corresponding to isoconversion. In addition, it is important that the samples be stored at the RH under open conditions so that the RH of the samples is at a known equilibrium value. An example of a screening protocol that provides reasonable data for most solid dosage forms is shown in Table I. APIs tend to be more stable, so this protocol may be too mild to hit specification limits for many APIs. Since this protocol assumes that one knows the degradant level before actually having measured values, determining the appropriate conditions for a given sample can require multiple iterations. Fortunately, in the drug development process, early assessments of stability can have a wider range of uncertainty. As product development proceeds through different phases, protocols become more refined, and greater precision (and accuracy) is provided.

Table I. Typical Protocol for Accelerated Screening of Solid Dosage Forms

T (°C)	% RH	Time (days)
50	75	14
60	40	14
70	5	14
70	75	1
80	40	2

Two-week screening accelerated stability protocol for solid drugs in dosage forms (all samples should be open to the indicated environment) (3). The actual protocol used for a drug product should be specific to that product based on the times needed to reach the specification limits and desired precision while allowing for decoupling of relative humidity (RH) and temperature (T)

Once data are generated, statistical analysis is important to propagate errors from measurements through to projected conditions. We have found that use of a Monte-Carlo simulation process provides a method for the estimation of shelf-life (use period). A number of consequences fall out of the statistics: First, the precision of the assay will affect the precision of the final shelf life. This can be improved by repeats; but in many cases this is not necessary; *i.e.*, the precision may be sufficient to assign a shelf-life without repeats. Second, a greater extrapolation distance on the temperature or RH axis results in greater error bars in the predictions. This means that highly accelerated stability studies (*e.g.*, high temperature, high RH) may provide quite accurate predictions of ambient stability in very short times, but the range within a given confidence interval (typically 90%; *i.e.*, 95% confidence that the true shelf life is greater than the lower limit) will be large. For some drug products and APIs, even a large range can still provide an acceptable determination. For others, when estimations fall between 1 and 4 years, greater precision may be needed. This precision can often be achieved by some combination of adjustments to extrapolation distance (*e.g.*, lower temperatures with longer storage times) or more repeats.

PACKAGING

For drug products, packaging can provide protection from the external RH. With ASAP, one can determine the effect of RH on the time for drug degradation to reach the specification limit. Below, a method for calculating the RH as a function of time in packaging is shown. In many cases, the rate of degradant formation up to the specification limit is relatively linear (although it may curve at higher degradant levels), it is often possible to combine the ASAP-determined degradation rate as a function of RH with the determination of the RH as a function of time inside packaging. When the degradation as a function of time is linear, it becomes possible to explicitly determine the amount of degradant formed as a function of time for a given packaging at a given storage condition (6–9). Even when the linear approximation is not accurate, the prediction of shelf life to the specification limit will generally be reasonable since the functional dependence of the time to reach the specification limit on the RH will be accurately reflected in the B term derived using isoconversion.

Determining the effect of packaging on the RH inside the package over time involves two key elements: moisture transfer into or out of the package and equilibration of moisture within the package. Equilibration of moisture inside a package is so much faster than moisture transfer into or out of a package that one can assume that the internal moisture of the pharmaceutical materials and the headspace inside a package are always at equilibrium.

Moisture transfer into or out of a package can be described in terms of a moisture vapor transmission rate, MVTR. The MVTR of a package (bottle, blister) is the mass (in units of milligrams of H_2O per day) of water permeating into the headspace volume for a given temperature plus the difference between internal and external RH. When an empty container (*i.e.*, one with no components or moisture) is placed

in a stability chamber, moisture from the chamber environment will permeate through the walls into the headspace at a rate related to the MVTR and the difference in RH. With no water-adsorbing components, any moisture transferred must directly accumulate into the bottle headspace. The mass of water entering the headspace will change the RH based on the ratio of the new water concentration in the headspace as a proportion of the saturated water concentration at that temperature. As an example, with a 60-cc high-density polyethylene (HDPE)-sealed pharmaceutical bottle, the internal RH goes from 20% to 75% RH in only about 10 days when stored at 40°C/75% RH.

Moisture inside a package will equilibrate among the components (*i.e.*, tablets, powders, capsules, and desiccants) based on how much moisture each component holds at a given RH. Materials will adsorb moisture to different degrees as described by their moisture sorption isotherms, comprising a plot of water percent in the material as a function of the RH. The moisture sorption behavior of most materials can be described according to the Guggenheim–Anderson–de Boer (GAB) equation (10–12). Because the moisture sorption isotherm of a combination of multiple components can be modeled using the weighted sum of the GAB parameters for those components, one can calculate the moisture sorption isotherm for a drug product based on its formulation using its component GAB parameters. Similarly, desiccants, materials that adsorb moisture with a relatively high capacity, are effective at keeping the RH inside a package lower than it would otherwise be, although it will still increase with time.

The RH as a function of time inside a package can be calculated quite accurately by combining information about the initial RH of the internal components, their corresponding moisture sorption isotherms and the MVTR of the package, as demonstrated in the example in Fig. 3. This RH dependence can be coupled with the explicit knowledge of the RH dependence of the API reactivity according to Eq. 1 to give a point-by-point determination of degradation as a function of time. The result is that the degradation level for solid APIs and drug products in packaging can be determined accurately even using accelerated stability studies. An example of the RH and degradant level calculations and experimental validation is shown in Fig. 4.

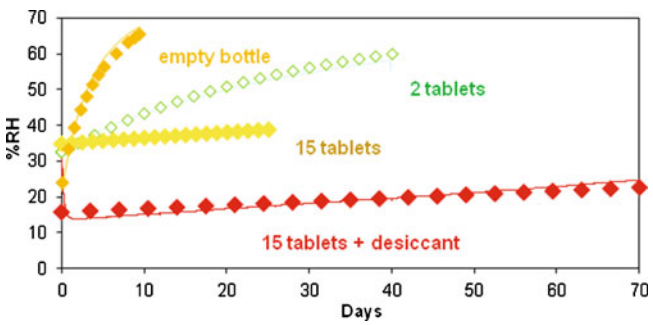

Fig. 3. Relative humidity (RH) as a function of time in 60-mL high density polyethylene (HDPE) bottles stored at 40°C/75% RH with varying numbers of tablets of CP-481,715 (6). The *symbols* (measured) and *lines* (predicted) show good agreement for a range of storage conditions validating that the model can accurately predict the RH inside a package over time

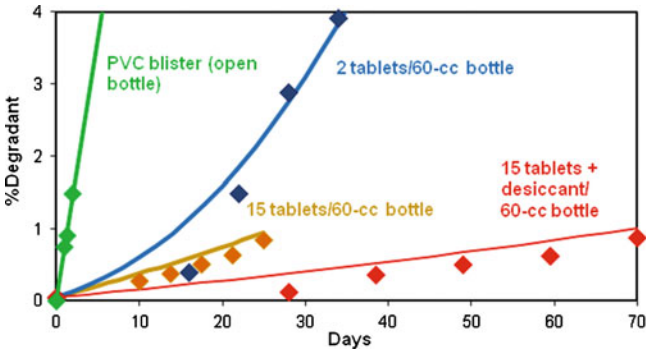

Fig. 4. Drug degradation as a function of time for tablets of CP-481,715 stored in 60-mL high-density polyethylene (HDPE) bottles stored at 40°C/75% RH (6). The *symbols* (measured) and *lines* (predicted) show good agreement for a range of storage conditions validating that the ASAP model can accurately predict the drug degradation inside a package over time as a function of the predicted internal relative humidity

USING ASAP FOR DESIGN SPACE UNDERSTANDING AND CONTROL STRATEGIES

In the transition from pharmaceutical development, production, and release in a quality by testing to a QbD paradigm, one of the necessary elements is a linkage between the product attribute (in this case, drug product stability) and the factors that influence it (13). The most straightforward application of ASAP to this QbD paradigm is using the ability of ASAP to rapidly evaluate stability for a given batch of drug product to effectively test manufacturing processes, excipients, and API variations in a timely and efficient manner. One important aspect of this is the ability of ASAP to readily assess if a change has a statistically meaningful impact. In a stability study using historical methods, degradation at, for example, 3 and 6 months at 25°C, 30°C, and 40°C might show degradant formation that is on the order of the standard deviation of the measurements for two lots. As a hypothetical example, if lot 1 and lot 2 of a drug product show 0.04±0.03% and 0.08±0.03% of a degradant in a study at a single condition, it would be difficult to determine if indeed they are the same with respect to the ultimate shelf life. Worse still, in many stability protocols, these values would either be considered below a limit of quantification, or reported as "passing" on a stability screen. With the ASAP model, times and conditions are chosen such that degradant levels are near the specification limits (based on the isoconversion paradigm), and the overall fitting provides two slope parameters and a projected shelf life, which makes comparisons between lots more meaningful. This can be seen in Table II with a comparison of a hypothetical solid drug product prepared by varying an excipient. The real-time approach shows little difference at ambient conditions, but lot 2 appears more stable at 40°C/75% RH (in packaging). Examination of the ASAP analysis, however, shows that lot 2 is less stable at ambient conditions. The faster degradation of lot 1 at 40°C/75% RH is accompanying by higher activation energy such that the ambient degradation rate is less (greater slope). While the standard (6-month) stability analysis would conclude both products are equivalent or rank lot 2 as the

Table II. Comparison of a Traditional Stability Evaluation *Versus* an Accelerated Stability Assessment (ASAP) Evaluation for Two Lots of a Hypothetical Drug Product Prepared with the Same Excipient from Two Vendors

	Parameter	Lot 1	Lot 2
Traditional	25°C/60% RH, 6 months	0.04±0.03%	0.08±0.03%
	30°C/65% RH,6 months	0.08±0.03%	0.10±0.03%
	40°C/75% RH, 6 months	0.35±0.04%	0.22±0.04%
ASAP	E_a (kcal/mol)	29±2	21±2
	B	0.031±0.005	0.029±0.005
	Shelf life at 30°C/65% RH, (years to 0.4%)	2.6±0.4	1.6±0.3

more stable based on the 40°C/75% RH data, the 2-week ASAP analysis would confidently determine that the two lots are different and rank Lot 1 as the more stable. From these types of analyses with varying material and process parameters, a decision can be made to tighten specifications or to take other remedial actions (*e.g.*, package with desiccant) in a control strategy.

One of the ASAP parameters generated from fitting the data is the activation energy, E_a. Lower activation energy, as seen for example in lot 2 *vs*. lot 1 of Table II, could be indicative of catalysis. Such catalysis can be assumed to be related to a different excipient surface pH (for hydrolyses), or metal ion contamination for oxidations. Excipient effective pH can be influenced by both the materials and the process for making the dosage form (14). By understanding how variations in materials and processes impact the activation energy, the quality of the final product can be assured by incorporating appropriate controls, such as metal ion specifications or specific selection of excipients.

One of the important benefits of ASAP when applied to QbD formulation and process design for drug stability is the ability to couple attributes rather than treat each attribute according to individual specifications. This is most obvious with respect to the impact of moisture on drug product stability. As discussed above, once an ASAP model is developed for a drug product, the impact of moisture (RH) on that product's shelf life can be explicitly accounted for. With a given drug product, the moisture a sample will experience during its shelf life is influenced by the dosage form's initial water content (water activity), the packaging, the amount of the dosage form in the package, and the presence of desiccants. As an example of the ASAP advantage for coupling product attributes, suppose one has a tablet as a drug product. In this case, suppose the product has a water content specification of 3% (*w*/*w*), which if the tablet is 2:1 microcrystalline cellulose/spray-dried lactose corresponds to a water activity of 0.33 (33% RH). As can be seen in Fig. 5, this product would have only a 2-year shelf-life at 30°C/75% RH in Aclar® blister packaging, and would require the more expensive, cold-formed foil–foil packaging to get the desired 3-year shelf-life. If on the other hand, the product could be prepared with a 2% water content corresponding to a water activity of 0.16 (by, for example, additional drying after film coating), Aclar® blister packaging would provide the desired 3-year shelf-life. As this example shows, understanding the moisture sensitivity as part of the ASAP model allows the rational trade-off of processes and costs, while maintaining the overall QbD approach to a stable product.

CONCLUSION

An isoconversion paradigm, where times in different temperature and humidity-controlled stability chambers are set to provide a fixed degradant level at the specification limit, was shown to compensate for the heterogeneity of solid drugs and drug products (3). Reliable estimates for temperature and RH effects are handled using a humidity-corrected Arrhenius equation. A statistical protocol is employed to determine best fits for the stability data, which in turn allows for precise estimations of shelf-life at any storage condition. Once the RH dependence of a drug or drug product's stability is determined, the shelf life inside packaging can be calculated knowing the MVTR and moisture sorption isotherms of the internal components. These methodologies provide far better predictions of shelf life (expiry) than previously possible in significantly less time. Precise shelf-life estimations can generally be determined using a 2-week, product-specific protocol, which allows for formulation development, package selection, expiry setting, and determining the effects of post-approval changes in process or materials

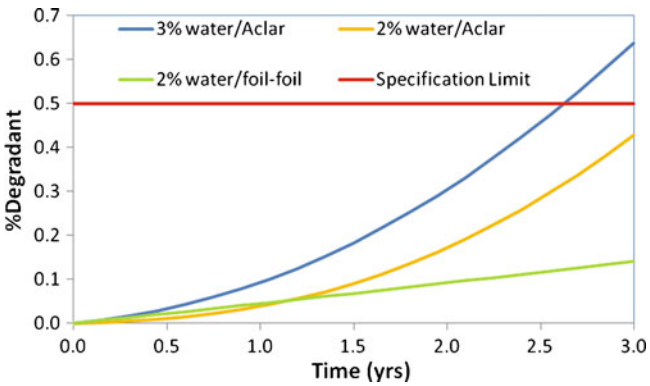

Fig. 5. A solid drug product (tablets consisting of 200 mg of microcrystalline cellulose and 100 mg of spray-dried lactose) with an ASAP model (E_a=30 kcal/mol; ln A=38.5; B=0.07) will have different shelf lives when stored at 30°C/75% RH (to a specification limit of 0.5%) depending on the coupled terms of water content (water activity) and packaging. The result is that either packaging option gives a 3-year shelf life when the tablet water activity is 2% *w*/*w* or less, but with a water activity of 3%, only the more expensive foil–foil blister packaging is viable

(15). Once the model for a product is developed, it can play a critical role in providing the product understanding necessary for a QbD filing for a product approval and enable rational control strategies to assure product stability. Moreover, ASAP enables the coupling of product attributes (*e.g.*, moisture content, packaging options) to allow for flexibility in how control strategies are implemented to provide a balance of cost, speed, and other factors while maintaining adequate stability. In addition, ASAP provides the basis for adapting different control strategies for different regional storage requirements.

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