Understanding Internal Release Limits

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Internal release limits help ensure that a batch of drug product remains within specifications throughout its shelf life. This article explores what internal release limits are and why they are important.

The manufacture of pharmaceutical and biopharmaceutical drug products is a complex process that takes place in a highly regulated environment (1). Success requires a combination of scientific, engineering, and regulatory knowledge. One critical part of drug development is formulating the compound into a final drug product, ensuring that desirable physical and chemical properties remain stable for an acceptable period of time and meet regulatory and commercial requirements for specifications for the product (2).

One key requirement is that the drug retain its physical and chemical properties such as potency, purity, and bioavailability for a set period of time, referred to as its shelf life (3). Once a shelf life has been defined for the drug, control strategies must be instituted to provide a high level of assurance that batches of drug product released into the market remain within specifications throughout the drug's shelf life.

One critical control strategy is the use of internal release limits. This article discusses how these limits are calculated and applied to ensure drug product quality.

Internal release limits (IRLs) are one- or two-sided bounds that ensure that a batch of drug product is sufficiently likely to remain within specifications throughout its shelf life. These limits are internally derived and represent good business practice, by accommodating producer risk (i.e., the likelihood of rejecting a "good" lot that fails to meet acceptance criteria) and consumer risk (i.e., the likelihood of releasing a lot that meets specifications during manufacture but fails to meet them through product expiry date).

Internal release limits account for uncertainties that are caused by product instability and measurement variation, and are applied to a given batch's measured critical quality attributes (CQA) at time of manufacture. The decision of what constitutes "acceptably high" assurance and the details of the calculations in relation to a statistical model are considered to be an internal business practice and are not prescribed by regulatory requirements.

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Figure 1: Illustration of the difference in calculation between internal release limits (IRLs) and control charts.

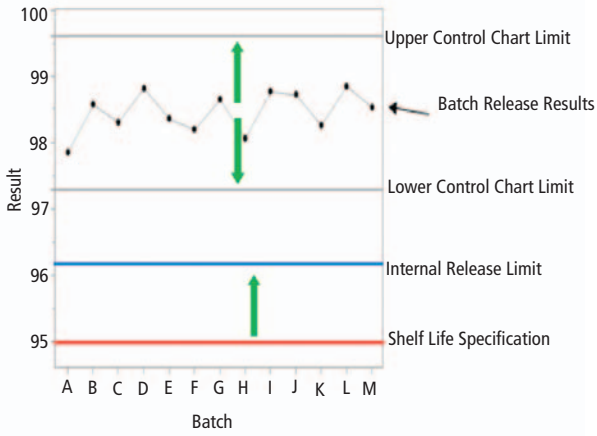
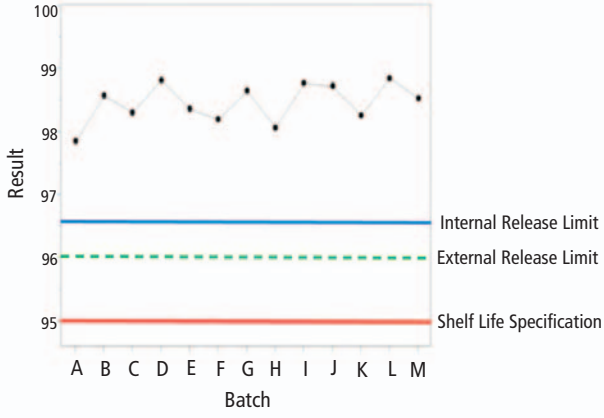


Figure 2: Illustration of an internal release limit that is more restrictive than the external release limit.



Relationships among limits

During batch manufacture, release results are compared to various criteria, the most common of which include:

- IRLs
- Shelf-life specifications
- External release limits (also referred to as release specifications)
- Control chart or process-control limits.

Each of these limits has a different purpose and may be applied at different times. For example, a shelf-life specification is a registered limit that a CQA must meet from the time of release until expiry. An external release limit is a registered limit that is required in some, but not all, markets. CQAs must meet external release limits at the time of batch release only (i.e., not throughout expiry). IRLs, as described previously, are internal (not registered) limits that are met at the time of product release. Control chart limits are designed to monitor and control process performance.

IRLs are calculated as a buffer to protect the shelf life specification and, as such, are set by moving in from the shelf life specification. In contrast, control chart limits (another internal limit that could be applied at release) are calculated as a range of typical release results and are set by moving out from the center of the release data. **Figure 1** demonstrates the ideal relationship between the two, using the lower specification as an example.

Internal and external release limits share a similar purpose: to provide assurance that a batch will meet the shelf life specification at expiry. Each limit is determined in part by the stability change that occurs to the CQA during expiry and the level of risk deemed acceptable.

It is possible for internal and external release limits to be different, as shown in **Figure 2**. This may be due to different levels of acceptable risk, internally and externally; additional data generated since the registration of the limits; or other factors. When the calculated IRLs are less restrictive than external release limits, then the IRLs should be set to the tightest external release limit across markets.

Determining the need for IRLs

IRLs should be established for CQAs and stability indicating tests representative of pharmaceutical products. In addition, an IRL may be recommended for stable CQAs, because the method variability on retest could cause an out-of-specification (OOS) result later on, if the initial time point is close to the specification.

Typically, CQAs would include such characteristics as:

- Product potency and/or purity
- Impurities
- Moisture or water content
- Protein concentration.

A risk assessment may be used to determine whether an IRL is necessary or IRLs can be put in place for all CQAs.

Risk assessment

Any risk assessment should consider the degradation rate and measurement variability. Generally, closer attention must be taken in proposing release limits based on methods that show high variability. A risk assessment strategy assists in identifying whether an attribute that falls outside of specifications might adversely impact patients or lead to other negative consequences such as product complaints and other negative customer interactions.

These assessments examine potential product failure modes, estimate their frequencies of occurrence, and identify the potential impact of exposure on a patient. Frequency of occurrence and severity of patient impact can be categorized based on review of available quantitative data or on qualitative ratings provided by medical or scientific experts.

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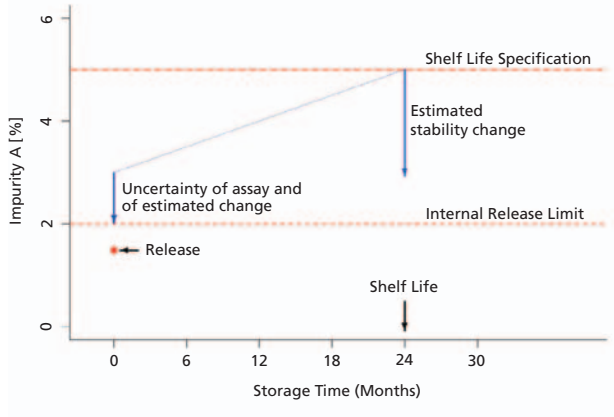
Figure 3: Illustration of the method for calculating an upper internal release limit from an upper shelf life limit (4). The illustration is based on an impurity that increases during stability.



It may be necessary to reevaluate the frequency of occurrence as more data become available.

When in the lifecycle should IRLs be calculated?

Typically, preliminary IRLs are calculated at the time of Stage 2 validation and are used during validation. All batches from development that are similar to the full-scale process should be included in the calculation.

Because the number of batches may be limited and formulation or analytical methods may have changed during development, the amount of data available at Stage 2 may be limited. Once IRLs have been established, their appropriateness should be reviewed periodically. The components of an IRL calculation (specification, change on stability, variability of that change, and analytical variability) may need to be updated.

For products that are at an early developmental stage in their lifecycle, IRLs may have been based on limited data. Additional stability data will become available that may improve the estimates of change and variability. Therefore, it may be necessary to reevaluate the IRLs as more stability data become available.

For more mature products, additional stability data are unlikely to alter the calculation unless a process change has occurred that affects the change on stability or the analytical variability increases or decreases. Therefore, for mature products, longer intervals (i.e., every two to three years) between IRL evaluation will suffice. If the shelf-life specification changes, the IRL must also change. Alternately, IRLs can be evaluated regularly (e.g., annually) and compared to the current limits. If a newly calculated IRL differs significantly from the current value, this can signal a change in the process or the level of analytical variability.

Calculating the IRL

The commonly used method (4) for calculating IRLs relies on the principle that a batch is released if there is sufficient statistical confidence, typically 95%, that the batch will comply with registered shelf-life limits throughout its shelf life.

The IRL is calculated from the shelf-life specification, by subtracting the estimated change during stability, uncertainty of the latter, and the assay uncertainty (**Figure 3**). A distinct feature of this method is that the decision is based only on:

- The average of the release results at the time of manufacture
- Historical stability data and analytical method precision data.

The rationale behind this approach is that the release results at time of manufacture is a reasonable approximation to the true batch mean value, and the disposition of the batch can therefore be based on this estimate. This contrasts with methods that also imply an assumption about the manufacturing process being in a state of statistical control producing a population of batches (5).

The batch is released if the release result is within the IRLs. The principle is illustrated in the example below, both for constant parameters and for parameters that follow a linear stability change over time.

CQAs that remain stable during shelf life

Consider a CQA (e.g., content, with a lower shelf-life limit [LSL]), and suppose the product is stable and also that it is reasonable to set the change during long-term stability to zero. In this case, the lower internal release limit (LRL) should only account for the expected variability and is given by **Equation 1**.

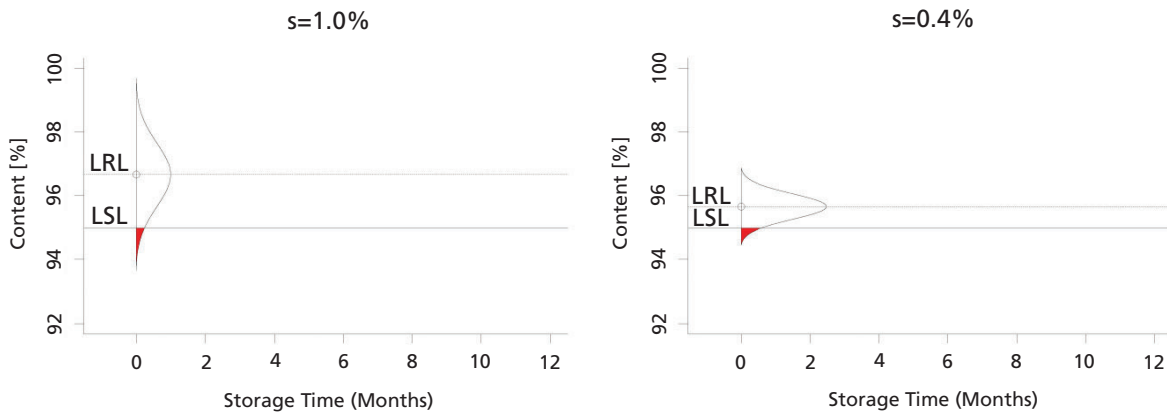
$$LRL = LSL + t_{0.95f}\sqrt{S^2 / n} \qquad \text{[Eq.1]}$$

Where s^2 is the uncertainty of assay method (estimated intermediate precision),
f is the degrees of freedom of the variance estimate,
n is the number of determinations of this QA at release, and $t_{0.95,f}$ is the upper 95% quantile of a t-distribution with f degrees of freedom. The t-quantile is typically in the order of 1.7 to 2.0 depending on the degrees of freedom. Tables are readily available in any standard statistical methods reference book.

Suppose the LSL for content is 95.0% of target and that a batch is released based on a single content result with an intermediate precision standard deviation of 1.0% (absolute % of target) with 10 degrees of freedom. The t-quantile is $t_{0.95,10}$=1.81 and the LRL is given by the following:

$$LRL = 95.0 + 1.81\ (1.0) = 96.81$$

Figure 4: Illustration of the lower internal release limit (LRL) for a quality attribute that does not change on stability with large analytical variation (left) and smaller analytical variation (right). The risk, that a batch with release result exactly at the LRL does not comply with the shelf life limit, is 5% in both situations as illustrated by the red region. LSL is lower shelf-life limit.



The principle is illustrated in **Figure 4.** Notice that the gap between the IRL and the shelf-life specification will become narrower when the analytical uncertainty is lower. This is a natural consequence of the method, because the decision to release a batch is based only on the release result; the more precise the result is, the closer to the shelf-life limit the release limit can be, while still providing the required confidence that the batch remains within specification at end of shelf life. An upper release limit could be constructed in a similar way, by subtracting the error term from the upper shelf-life limit.

CQAs that change during shelf life

Consider next a quality attribute that changes linearly during long-term stability, for instance high molecular weight proteins (HMWP), for which an upper specification limit (USL) is registered. In this case, the upper internal release limit (URL) is given by **Equation 2**.

$$URL = USL - \hat{b}T_{0.95,f}\sqrt{S_b^2T^2 + \frac{S^2}{n}} \qquad \text{[Eq. 2]}$$

where:

$\hat{b}$ is the estimated stability slope (change per month),
T is the shelf life in months, and
S_b is standard error of the estimated stability slope.

The principle is illustrated in **Figure 3**. Notice that there is an extra term under the square root sign, $s_b^2T^2$ compared to the formula given in **Equation 1**. This accounts for the uncertainty in the estimated stability slope, which depends on the precision of the stability data available.

The degrees of freedom *f* are either associated with the error term (if the variance estimates are from the same stability study) or calculated using Satterthwaite's formula if the variance estimates are from independent studies (6).

Suppose the USL for an impurity is 5.0% and the estimated degradation rate is 0.10%/month (absolute) with a standard error of s_b=0.0028%/month with 17 degrees of freedom. The intermediate precision standard deviation is 0.10% (absolute) with 10 degrees of freedom, and a single result is obtained at release. The shelf life is T=24 months.

The total degradation during shelf life is estimated to be 0.10 x 24 = 2.40%. The total uncertainty under the square root sign is given by:

$$\sqrt{S_b^2T^2 + S^2} = \sqrt{0.0028^2 24^2 + 0.10^2} = \sqrt{0.67^2 + 0.10^2} = 0.12$$

The degrees of freedom can be calculated to 18.5 and t-quantile to $t_{0.95,f}$= 1.73. The upper release limit is therefore

$$URL = 5.0 - 2.40 - 1.73 \times 0.12 = 2.39\%$$

To ensure that the (unrounded) release result is less than 2.39%, an effective release limit of <= 2.3% is needed, when rounding the limit to one decimal.

CQAs with batch differences in slope

In the previous examples, a common slope *b* is assumed for all batches, which is generally a reasonable assumption, in particular for solid dosage forms and small-molecule products, where the degradation is due to simple kinetic reactions.

For some products, however, the stability slope may differ between batches (i.e., the slopes are significantly different

according to the International Council for Harmonization [ICH] Q1E and there is a scientific basis for the difference). This can be the case for liquid formulations of biological products, where, for instance, the formation rate of high molecular weight proteins may depend on formulation constituents or on a property such as pH, which is inevitably subject to some level of random variation. Batch differences in the slope can be included in the IRL, to the extent that they can be explained and justified as small random perturbation in the stability behavior.

Inclusion of batch differences complicates calculations

Inclusion of batch differences complicates the calculations and the interpretation of the limits, and should only be used when properly justified by data and product understanding. A single outlying batch or an outlying result in a stability study may be an outlier due to some special cause effect, and this should not be confused with random batch differences. The random effect due to differences between batches is best estimated through mixed effects modeling.

When a random batch-slope difference is justified, this can be included in the release limits by the following extension of the formula used in the method previously discussed (4), as shown in **Equation 3**.

$$\text{URL} = \text{USL} - \hat{b}T - t_{0.95,f}\sqrt{S_{\beta}^2 T^2 + S_{\beta}^2 T^2 + \frac{S^2}{n}} \qquad \text{[Eq. 3]}$$

where s_b^2 is the variance of the random slope in the batch population.

Suppose that, in addition to the figures provided in example two, that a slight variation around the common slope exists with s_b = 0.0060% /month (with 5 degrees of freedom). The total uncertainty under the square root sign is now,

$$\sqrt{S_{\beta}^2 T^2 + S_{\beta}^2 T^2 + S^2} = \sqrt{0.0060^2 24^2 + 0.0028^2 24^2 + 0.10^2}\sqrt{0.144^2 + 0.067^2 + 0.10^2} = 0.19\%$$

The degrees of freedom can be calculated to 12.8, which gives a t-quantile of 1.77, and the upper release limit (URL) is, therefore, 5.0 – 2.40 –1.77 x 0.19 = 2.27%. A tightening of the release limits from example 2 of 0.1% to <= 2.2% is needed in this case, to account for the random batch-slope variation.

When results are outside of IRL

A result outside an IRL may lead to a batch not being released to market so company quality systems may treat it like an OOS result and have standard operating procedures for mitigation. Note that, by definition, a result outside of an IRL is not an OOS result unless the IRL is set to the same value as the corresponding registrational release or shelf-life specification. The result should be confirmed through lab investigation as a typical first step. Review of the batch record and recent history would generally be next if no lab-related cause were found. A retest protocol may be employed to confirm or overcome the original result when no probable cause is found only if documented in operating procedures.

The risk implications of the final result should be estimated so that company quality authorities have the information relevant to the batch disposition decision. Probability estimates of failing before expiry both for the batch average and individuals are important inputs to that decision. The risk thresholds, however, may be different for different companies; it should be noted that failing an IRL is already breaching an established risk alert level. Releasing the batch with a reduced expiry could be considered.

Understanding risk for release limit calculations

Regulatory guidance documents (i.e., ICH Q8, Q9, Q10, and the 2011 FDA process validation guidance [7–10]) suggest a need for quantitative risk assessments including IRLs. The risk assessment exercise is intended to characterize product and process uncertainties to improve product development and manufacturing.

Out of internal release limit (ORL) cases may trigger technical and operational improvements. The negative impact of ORLs include higher investigation costs, increased doubts about product robustness and quality, and potential rejection of a batch that may stress inventory and supply and add to operational costs.

Quantitative risk assessments are critical in making decisions related to IRLs and address at minimum prediction of process capability (against IRLs), probability of OOS, sources and control of variabilities, and impacts to filing and supply.

In pharmaceutical applications, the risk of a harm is commonly defined as a combined effect of its:

- Probability of occurrence
- Severity
- Detectability.

Quantitative approaches

Quantitative approaches will generate more robust data for all three elements, especially the probability of occurrence. Statistical expertise can be valuable in optimizing these data, in conjunction with scientific, engineering, and business principles.

As reflected in the formulas in this article, an IRL risk assessment should be an integrated evaluation of IRL, shelf-life, registered specifications, and product performance including at least stability, process, and analytical components. To achieve the desired benefits, IRLs must be set at appropriate levels in order to control both producer's risk and consumer's risk.

Bayesian modeling provides a comprehensive framework for assessing a producer's and a consumer's risk. It also per-

mits inclusion of prior knowledge in making predictions and accounts for parameter uncertainties.

The details of the Bayesian approach are outside the scope of this article, but essentially the approach involves a mixed-effects model with parameters for process mean, batch-to-batch variability, and changes over time.

Deeper product knowledge

In summary, a more systematic quantitative risk assessment carried out throughout the product lifecycle will lead to deeper product knowledge. This approach will collectively strengthen the two enablers of pharmaceutical quality systems: knowledge transfer and quality risk management.

Note that the concept and associated benefits are applicable to scenarios besides IRLs. Therefore, this is an area that is worthy of more effort and investment by the pharmaceutical industry.

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