Extending a commercial specification beyond the clinically qualified limits, how to overcome the challenges

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Inspired by **patients.**
Driven by **science.**

Agenda

1. Context
2. Initial proposal and challenges
3. Revised approach
4. Conclusions

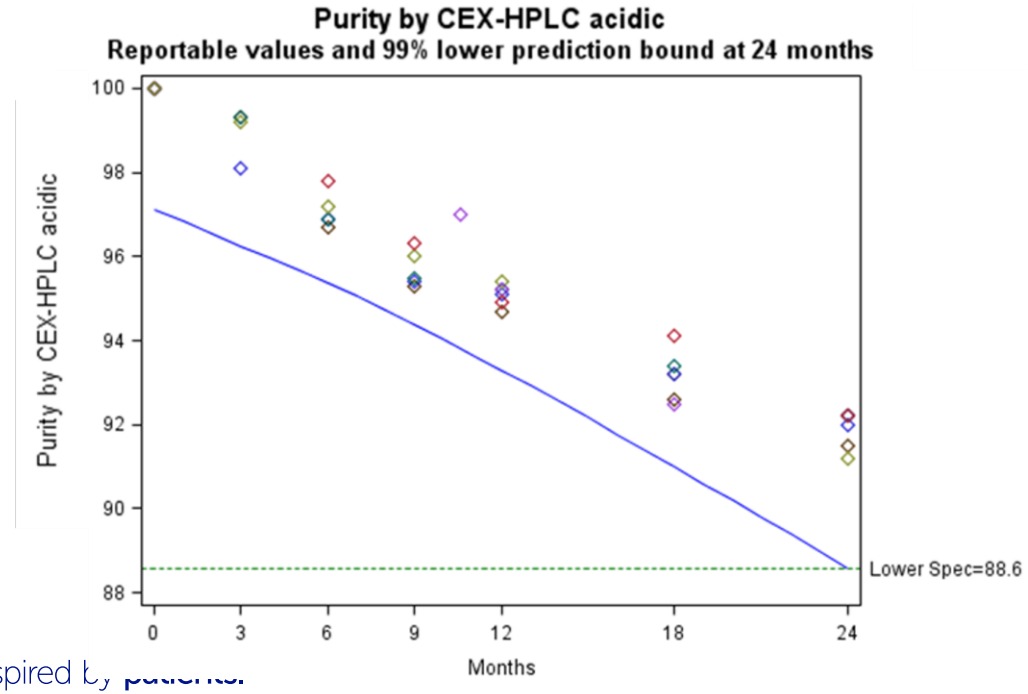
Context

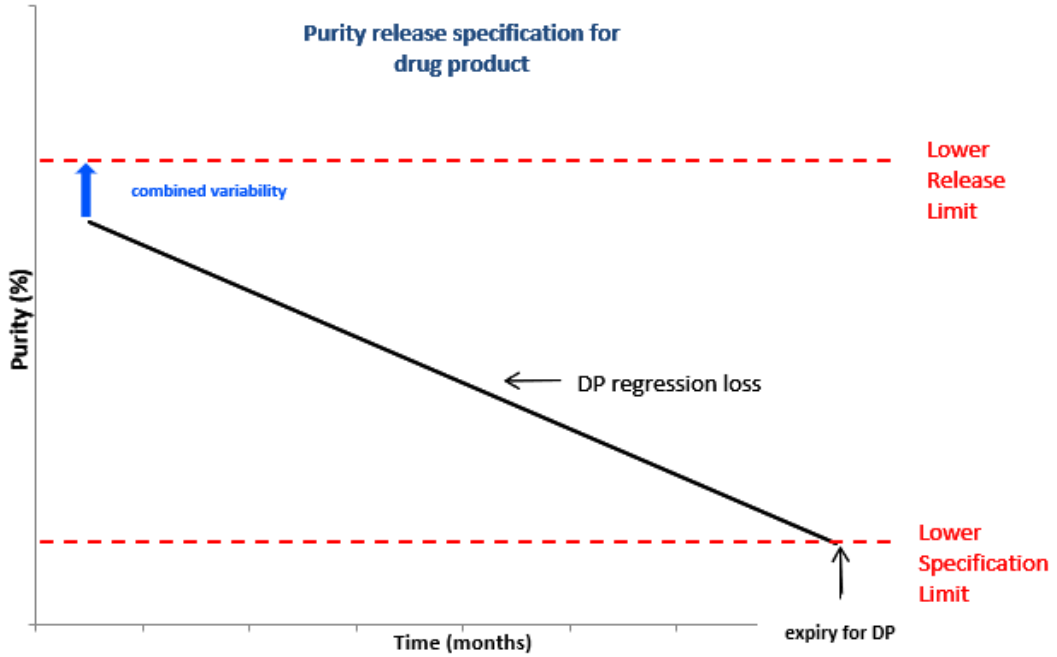
- Legacy product approved with either 24 months SL (shelf life) in some countries or only 18 months SL in other countries due to limited specifications on some parameters
- Increase SL to 24 months would improve drug access (18 months SL does not allow supply on time in some countries)
- Increasing the SL would impact the SL specifications

Initial proposal to the Health Authorities

Initial proposal to the Health Authorities

- Specification setting for stability evolving parameters were set using a degradation slope approach for purity and impurities
- Example for (acidic) purity by CEX-HPLC - using 6 historical batches with 24m data (verified with 10 additional recent batches)





Initial proposal to the Health Authorities

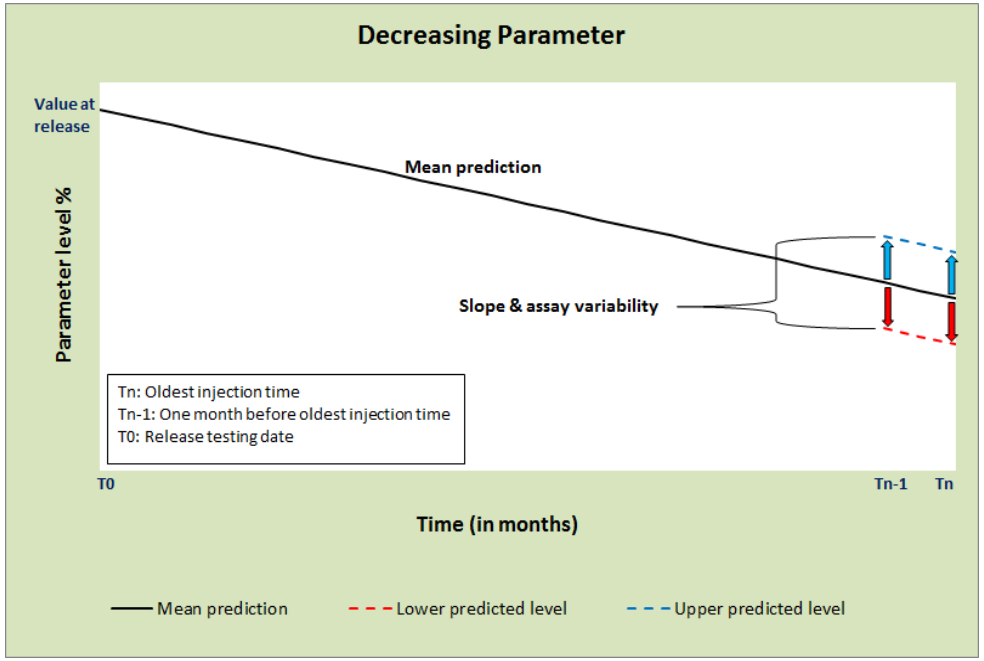
Clinical exposure :

- 10 worst case DP clinical batches* ie with lowest purity and highest impurity levels at release
  - 554 to 832 patients received at least 1 dose
  - 31 to 210 patients received more than 3 doses
- Determine the exposure levels at the oldest injection date → extrapolation from release results.
- A fixed effects analysis of variance (ANOVA) linear model with the average degradation rate from 16 batches
- Verification based on stability data at 24m (when available) compared to predicted range based on 99% confidence level

→ Proposal: lower/upper 99% predicted levels were set as the clinically qualified levels for purities/impurities

* From clinical studies were safety and efficacy were demonstrated and for approved indication

Initial proposal to the Health Authorities



- Example for (acidic) purity by CEX-HPLC :
  - Batch age at its last injection : 23.98months
  - Mean predicted level: 89.6%
  - Lower 99% predicted level: 87.7%

→ Predicted worst case level administered to patients is 87.7%

→ Proposed end of shelf life limit : NLT 87.7%

- Clinically qualified lower predicted levels patients may have been exposed : 87.7%
- 99% PI (prediction interval) based on stability data : 88.6%

Initial proposal to the Health Authorities

Feedback from the Health Authorities :

- HA agrees that to support the extension from 18 to 24months the SL limits should be revised
- Revision of limits should be based on clinically qualified levels
- The definition of clinically qualified levels is not accepted (based on lower/upper 99% predicted levels)
- The mean predicted levels should be used or further justification should be provided.
- Example for (acidic) purity by CEX-HPLC :
  - 99% PI based on stability data: 88.6%
  - Mean clinical predicted level: 89.6%
  - ~~Lower 99% clinical predicted level: 87.7%~~

→ proposed limit should be 89.6% (stricter than routine data)

Revised approach

Revised approach

- The 99% PI limit based on stability data was considered relevant to propose SL as it takes into account the routine data and assay variability (example: 99% PI = 88.6% vs mean predicted level = 89.6%)
- Further justifications to justify the difference is not expected to impact on safety and efficacy:

1. Overview of the quality of DP used in non-clinical studies and safety impact (as indicator for clinical safety)
2. Overview of stability data in accelerated conditions and impact on activity (as indicator for potential impact on clinical efficacy)
3. Understanding of potential impact of product related species that increase during storage
4. Overview of *in-vitro* serum studies that mimic *in vivo* evolution of the product related species injected to patient

Revised approach

1. Non-clinical data

- Studies conducted in cynomolgus monkey demonstrated good tolerability of the drug with sustained exposure, low immunogenicity and no safety findings observed
- Studies with frozen DS (so limited degradation of the product) or with DP stored at 2-8°C up to 19 months
- Material used overall with lower degradation than in clinical studies.
- Extrapolation of purity/impurity levels of batches used as previously from release data and based on average degradation rate.
- Levels at time of administration:

Eg: acidic purity by CEX-HPLC 99.7% at release vs 93.7% at time of administration (proposed limit: 88.6%)

Revised approach

1. Non-clinical data

- But monkeys were exposed to higher doses with higher dosing frequency.

	Cmax (µg/mL)	AUC (µg.day/mL)
Study in monkey	3420	15300
Study in human	58	1178
Ratio Monkey:Human	**59:1**	**13:1**

Where Cmax is the maximum serum concentration after administration
AUC is the area under the curve ie total drug exposure over time

- Based on the pharmacokinetics, the systemic exposure of monkeys was much higher ie over 10-fold.

→Overall toxicokinetic and safety profile of DP with higher impurities is not altered vs other non-clinical studies with frozen DS (low levels of impurities)

→No measurable impact due to exposure of increased levels of impurities

Revised approach

2. Stability data in accelerated conditions and impact on product activity

- Historical data up to 36 months at 2-8°C (intended condition) and 6 months at 25°C/60% RH (accelerated condition)
- Purity/impurity levels are beyond the current and proposed specification limits but no impact detected on product activity (based on activity measured by cell-based assay)
- Example: acidic purity by CEX-HPLC after 6 months at 25°C/60% RH measured ~85-86% but potency still ~100% relative activity (proposed limit of 88.6%).
- No correlation between the evolution of these purity/impurities and the activity measured by cell-based assay

→ Proposed slight widening of the limits is expected to have no impact on clinical efficacy.

Revised approach

3. Understanding of product related species and their potential impact on safety and efficacy

- Further characterisation of purity and impurity species using mass spectrometry and their evolution during storage

Eg acidic species identified deamidation of asparagine /glutamine but outside CDR regions

- Forced degradation studies (eg pH, temperature, oxidation, light etc) and 7 years old sample:

No additional species detected, so appropriate purity/impurities are monitored and quantified in routine

Revised approach

4. *In-vitro* study

- Serum study conducted to mimic the evolution of the charged species once administered to patients (using a release and end of shelf life samples)
- Observations in serum study expected to occur naturally *in vivo* almost immediately after administration
  - ❖ High increase of some acidic species on first 24h with a plateau at >90% after 72h
  - ❖ Level of basic species was not significantly increased or decreased by incubation in serum over 168h
- In conclusion, higher level of acidic species is not expected to significantly impact safety and efficacy profiles as this is expected to occur naturally and rapidly *in vivo*.

Note: 24h is shorter than the half-life of 14 days of the product

Conclusions

Conclusions

- Difference between proposed specification limits and clinically qualified levels

Eg acidic purity by CEX-HPLC: proposed limit based on stability data at 88.6% vs clinical exposure (mean predicted level) 89.6%

- Potential impact on safety and efficacy evaluated:
  - Safety: monkeys exposed to significantly higher levels of impurities but no difference observed on safety or toxicokinetic profiles (indicative of immunogenicity) vs monkeys exposed to less degraded product.
  - Efficacy: accelerated stability data with higher levels of impurities with still 100% potency
  - Efficacy/Safety: based on species understanding (ie deamidation in non CDR regions)
  - Efficacy/Safety: based on serum study, some acidic species increased to >90% very shortly after administration
- In conclusion, the difference (slight widening vs clinical levels) is not expected to have an impact on safety and efficacy

→ Proposed specification limits accepted by the HA to support the increased shelf-life to 24 months.