



Support ICH Q2(R2) implementation for analytical method validation

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ICH Q2(R2): A Paradigm Shift

Regulatory Context

- New edition effective **June 2024** — replaces ICH Q2(R1) after 20+ years.

Transmission to CHMP	8 March 2022
Adoption by CHMP	24 March 2022
Release for public consultation	31 March 2022
Deadline for comments	31 July 2022
Final adoption by CHMP	14 December 2023
Date for coming into effect	14 June 2024

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Regulatory Context

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- Mandatory for all new regulatory submissions.
- Key change: move **from point estimate to confidence interval**-based assessment for accuracy & precision.

VALIDATION OF ANALYTICAL PROCEDURES Q2(R2)

Final Version

Adopted on 1 November 2023

3.3.1.4 Recommended Data

Accuracy should be assessed using an appropriate number of *determinations* and concentration levels covering the reportable range (e.g., 3 concentrations/3 replicates each of the full analytical procedure).

Accuracy should be reported as the mean percent recovery of a known added amount of analyte in the sample or as the difference between the mean and the accepted true value, together with an appropriate $100(1-\alpha)$ % confidence interval (or justified alternative statistical interval). The observed interval should be compatible with the corresponding accuracy acceptance criteria, unless otherwise justified.

3.3.2.4 Recommended Data

The standard deviation, relative standard deviation (coefficient of variation), and an appropriate $100(1-\alpha)$ % confidence interval (or justified alternative statistical interval) should be reported. The observed interval should be compatible with the corresponding precision acceptance criteria, unless otherwise justified.

Adapting to new guidance

Impact on Practice

- Previously established acceptance criteria challenged
- Traditional study designs need revision
- Industry-wide impact

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 - Now mentioned in guideline
 - Not in scope of this presentation

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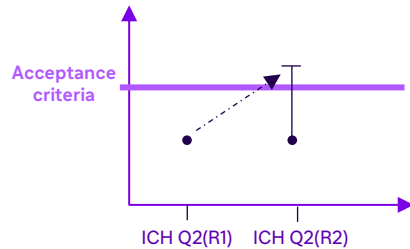
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 - Adaptation of design/acceptance criteria
 - Focus of this presentation
 - Focus on Precision validation

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Q2(R1) : $CV_{ip} < \text{Criteria}$ ➡ Q2(R2) : 95% One-sided upper confidence bound $CV_{ip} < \text{Criteria}$

Simulation-based methodology - Objective



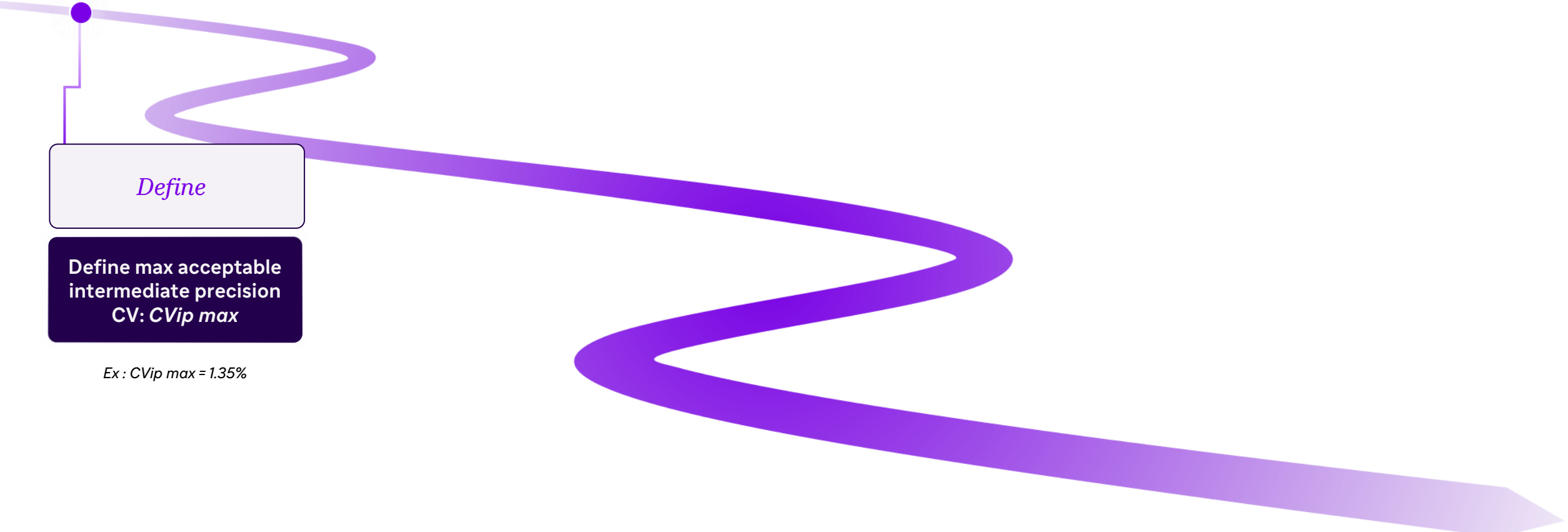
Simulation-Based Methodology: Overview

Precision validation



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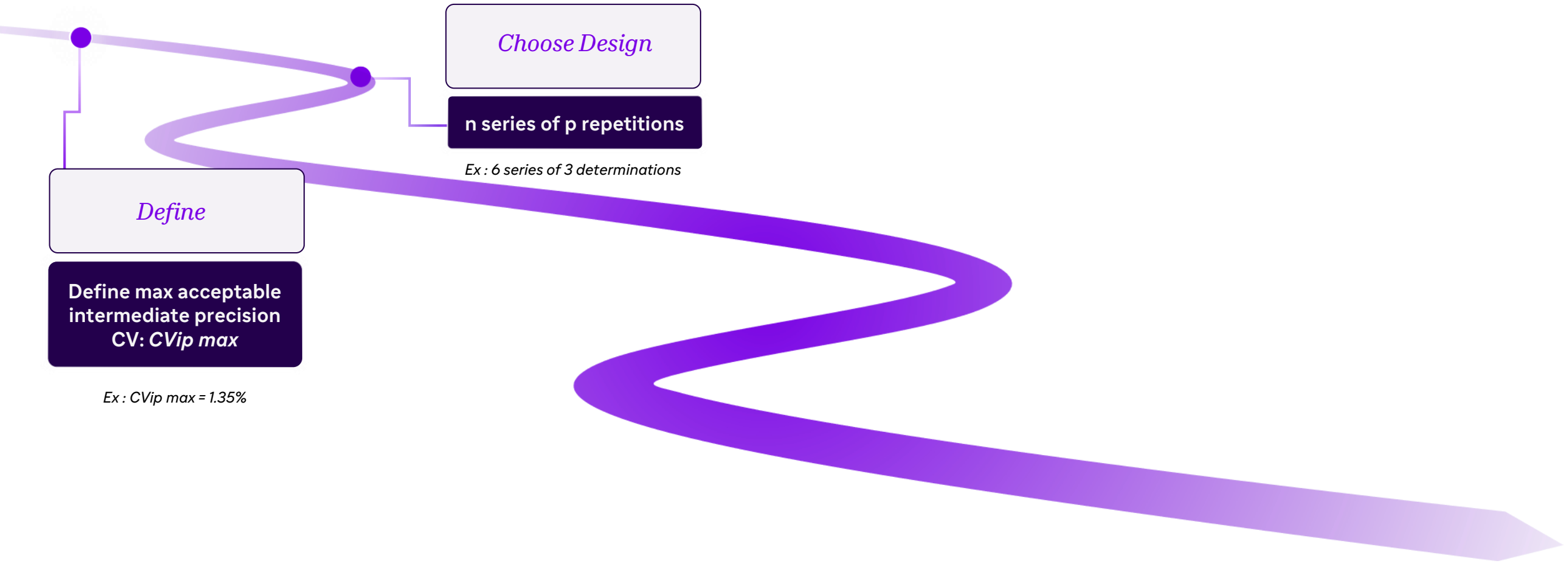
Define

Define max acceptable
intermediate precision
CV: *CVip max*

Ex : CVip max = 1.35%

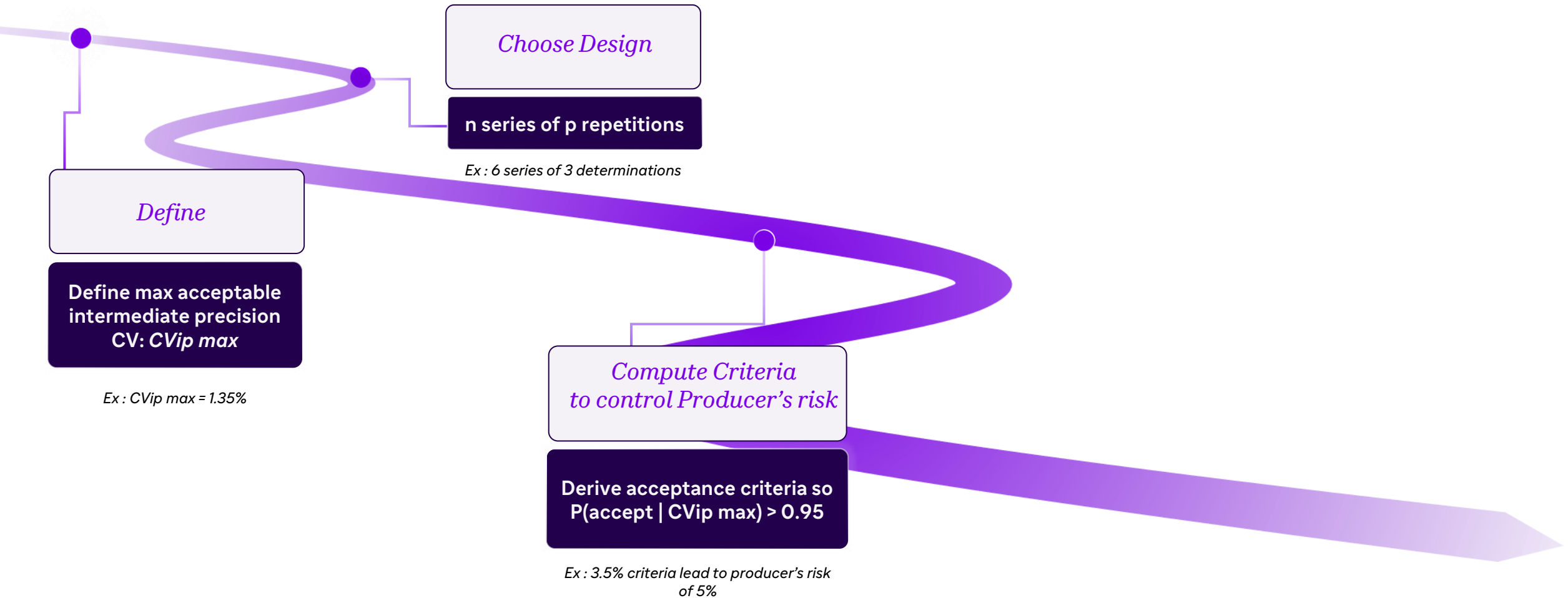
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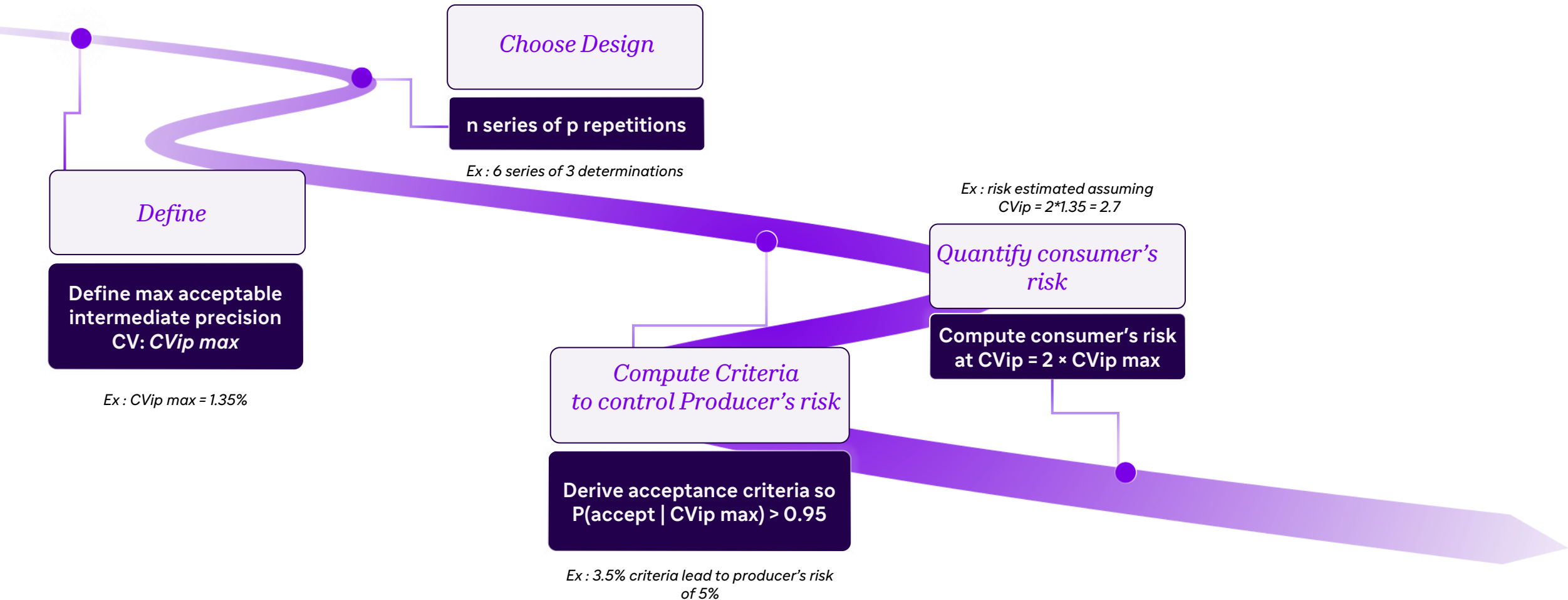
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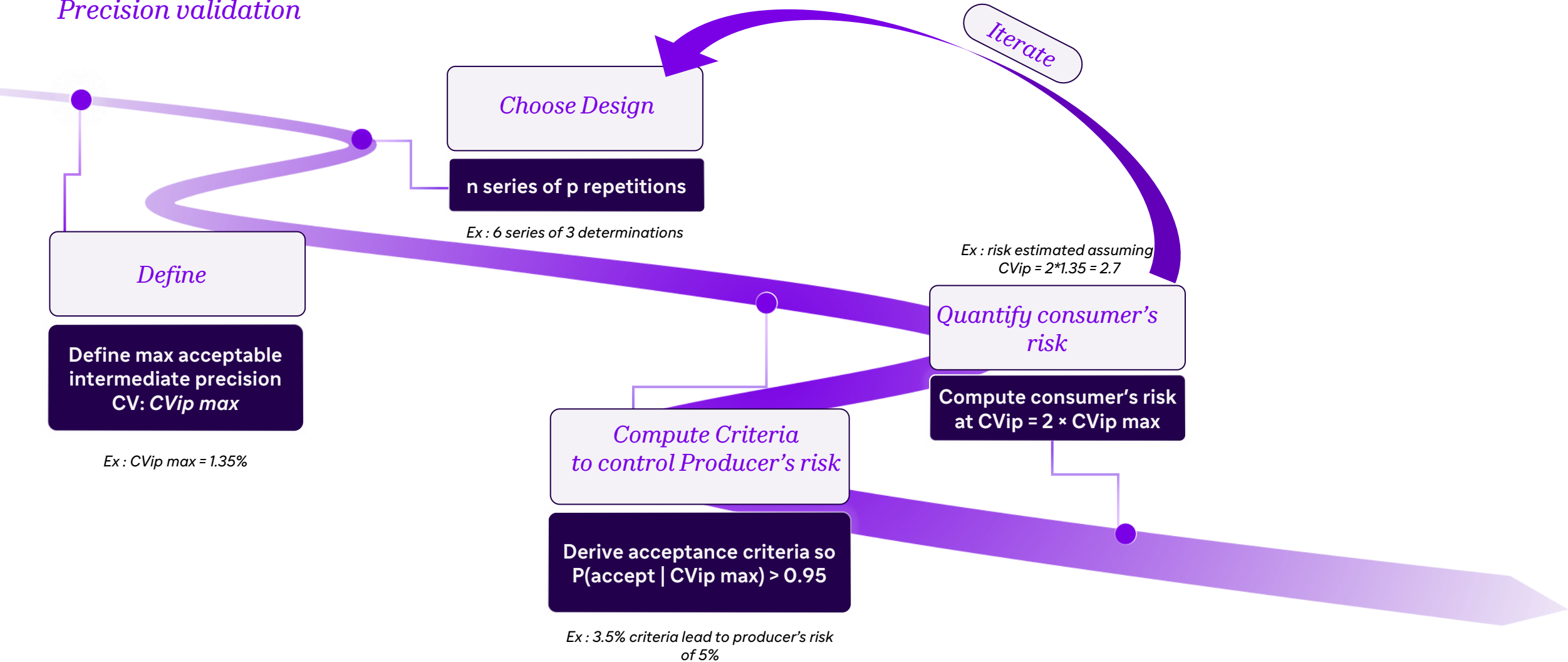
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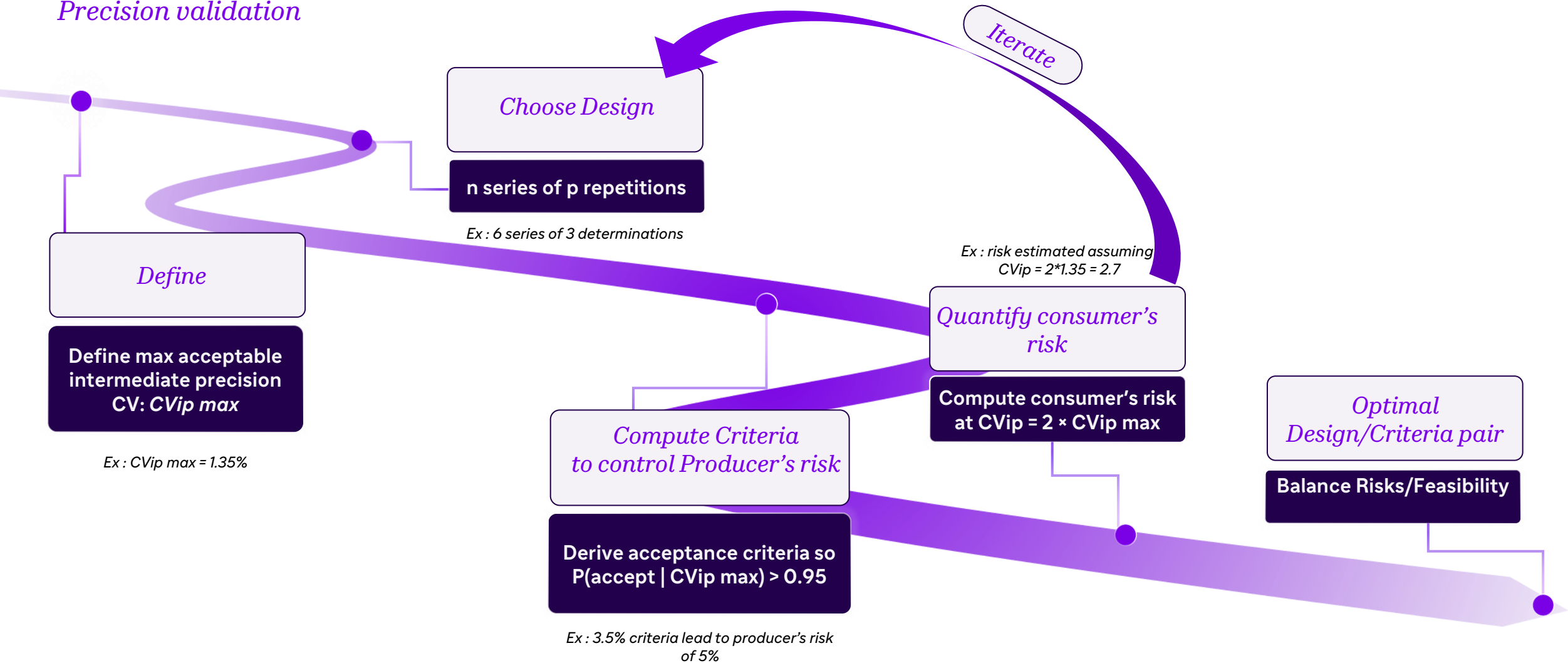
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Based on CVip observed on past validated methods.

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From Previous criteria ?

Back-calculate the CVip max tolerated by prior point-estimate-based criteria and designs

- ✓ Continuity with previous practice
- ✗ May inherit sub-optimal thresholds

Example of application

Validation of an API assay method

Assay of the API in a Synthetics Drug Product

Commonly used criteria for Q2 (R1) : 2% on Point Estimate

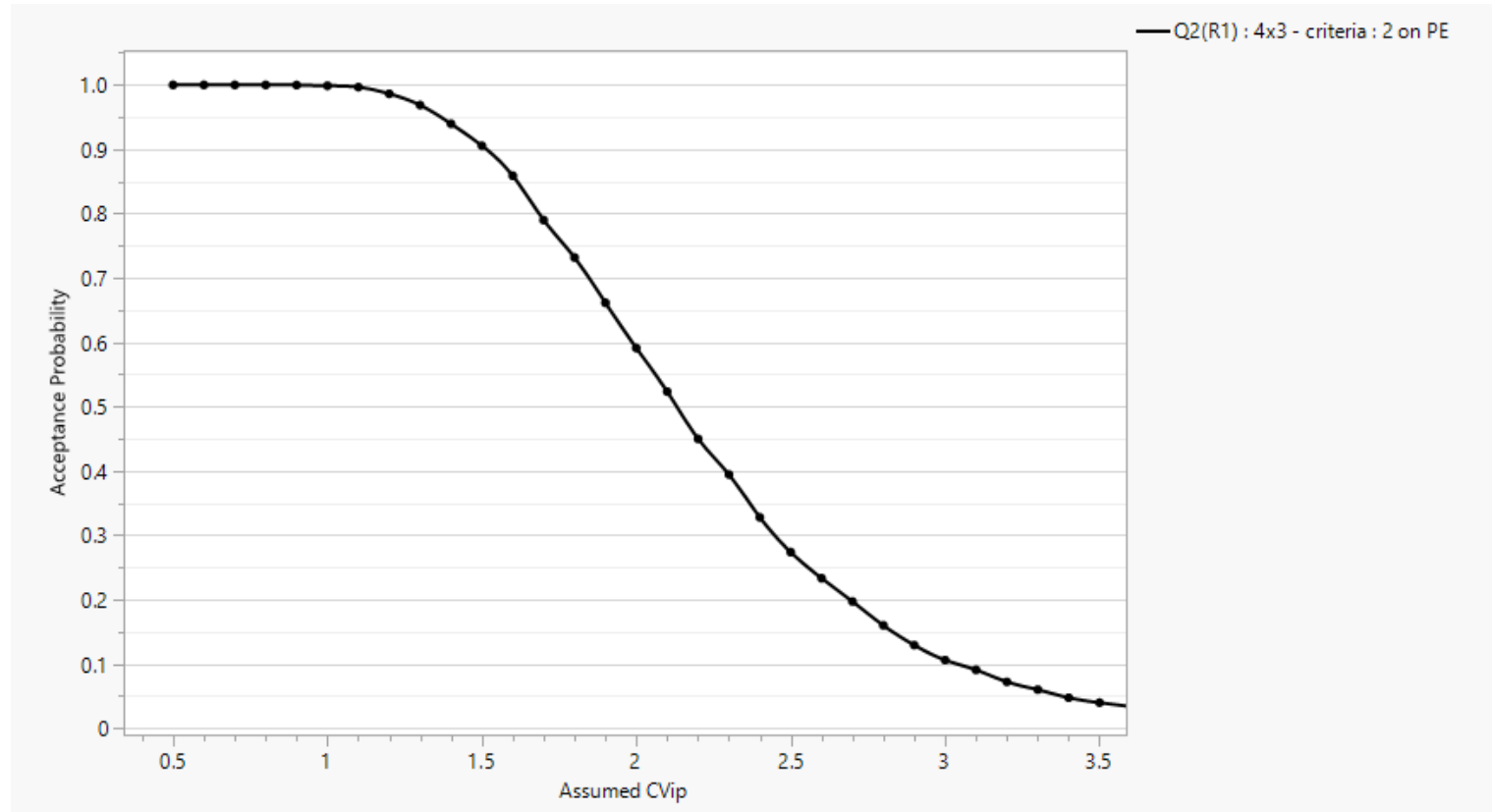
Commonly used design : a 4x3 (4 series of 3 determinations) design

Specifications: [95% - 105%] of Label claimed

Which design and criteria should we use for Q2 (R2) ?

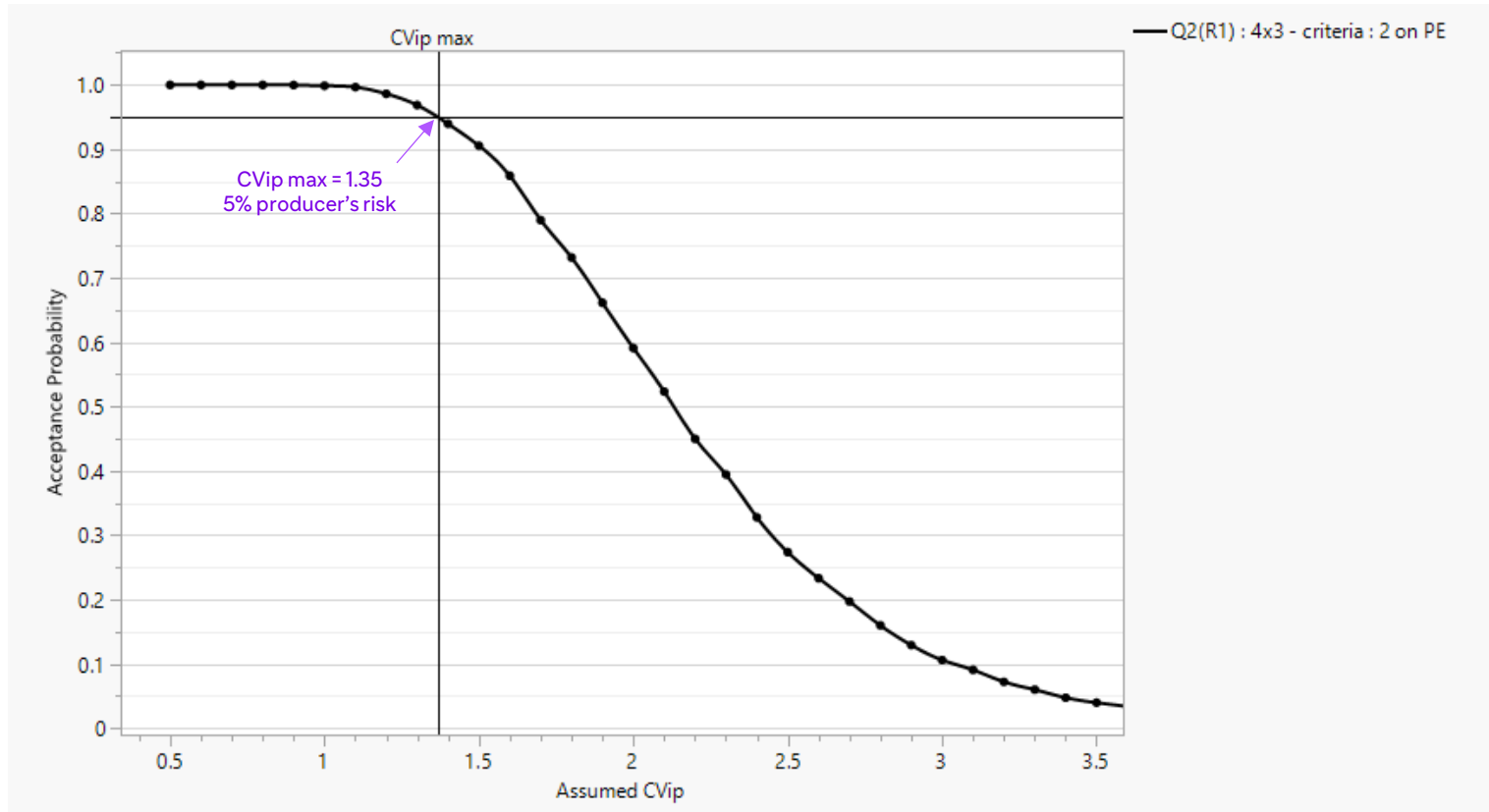
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Example of application

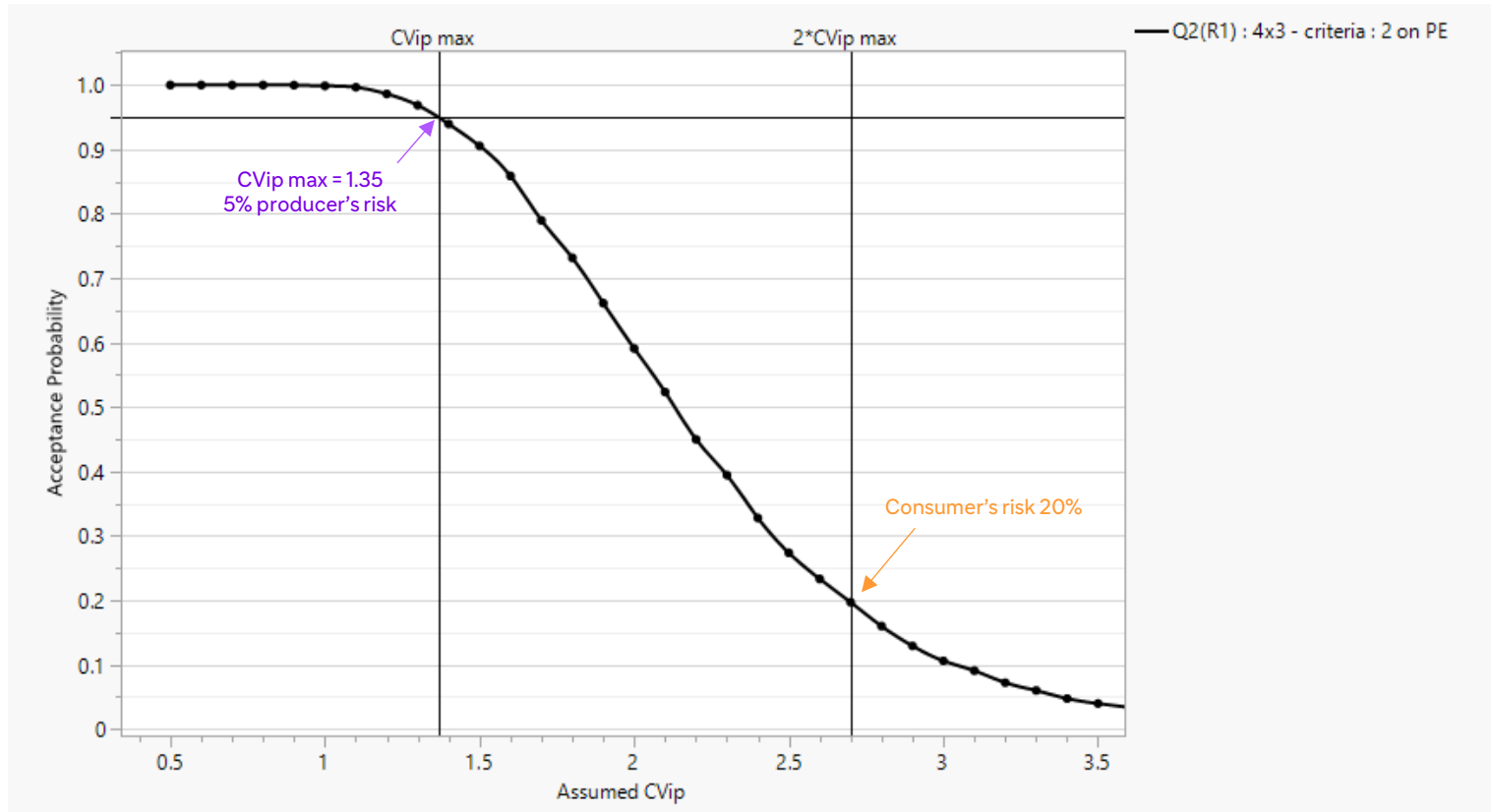
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From Q2(R1) criteria : CVip max = **1.35%**
(consistent with specifications [95% - 105%])

Example of application

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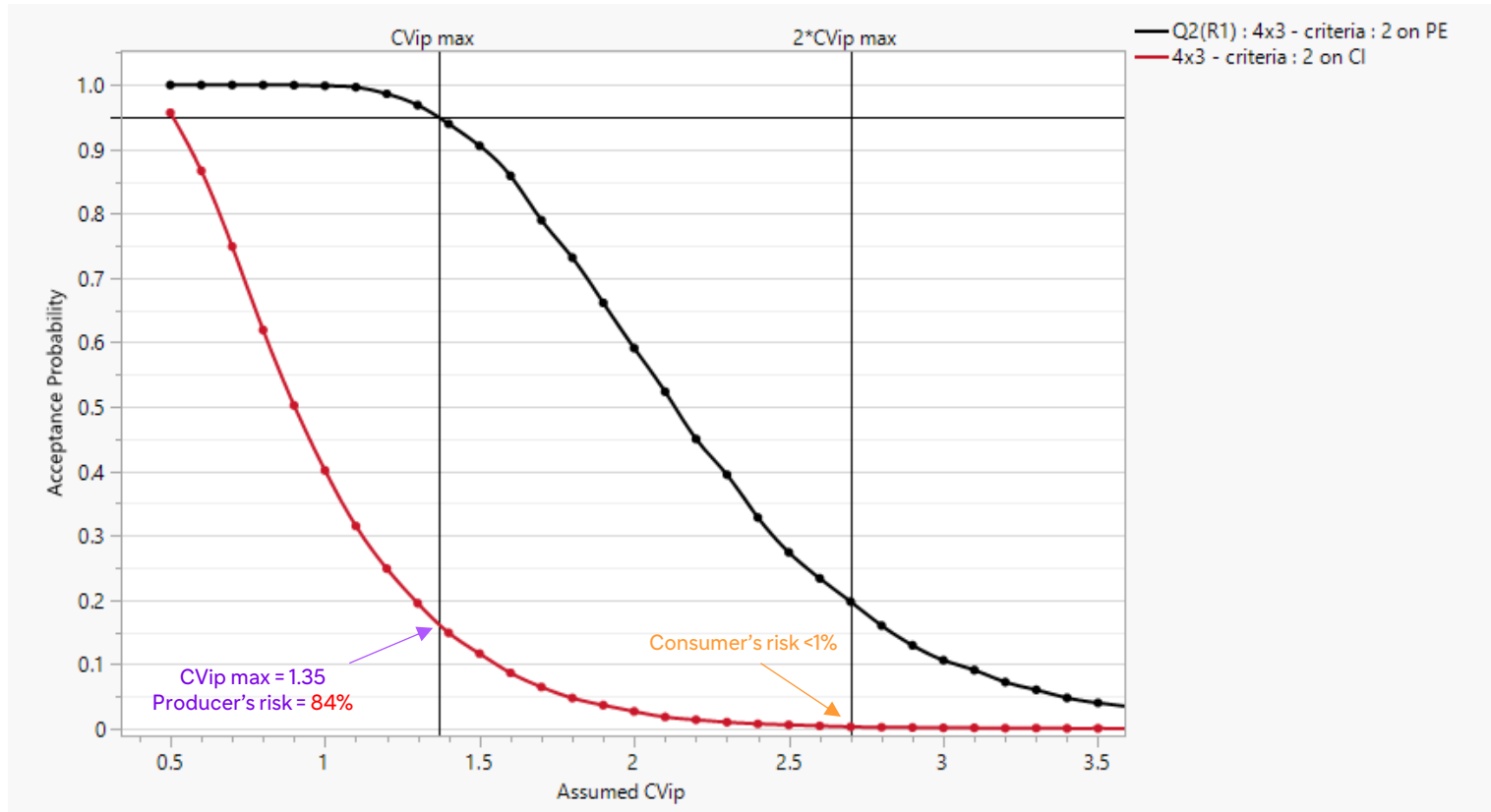


From Q2(R1) criteria : CVip max = **1.35%**
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Design	Criteria (Q2 (R2))	Producer's risk	Consumer's risk
• 4x3	2% (Q2(R1))	5%	20%

Example of application

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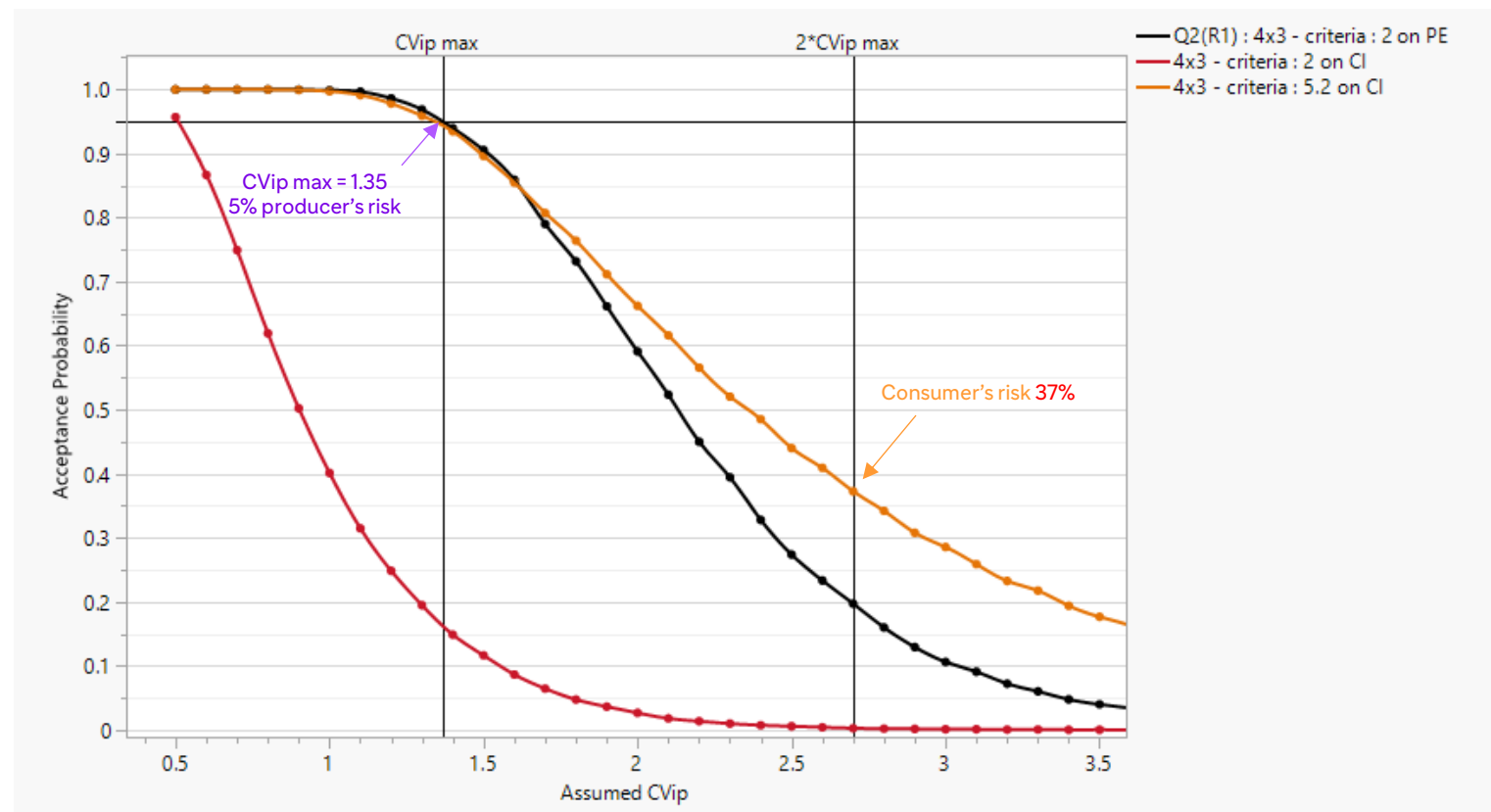


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• 4x3	2%	84%	<1%

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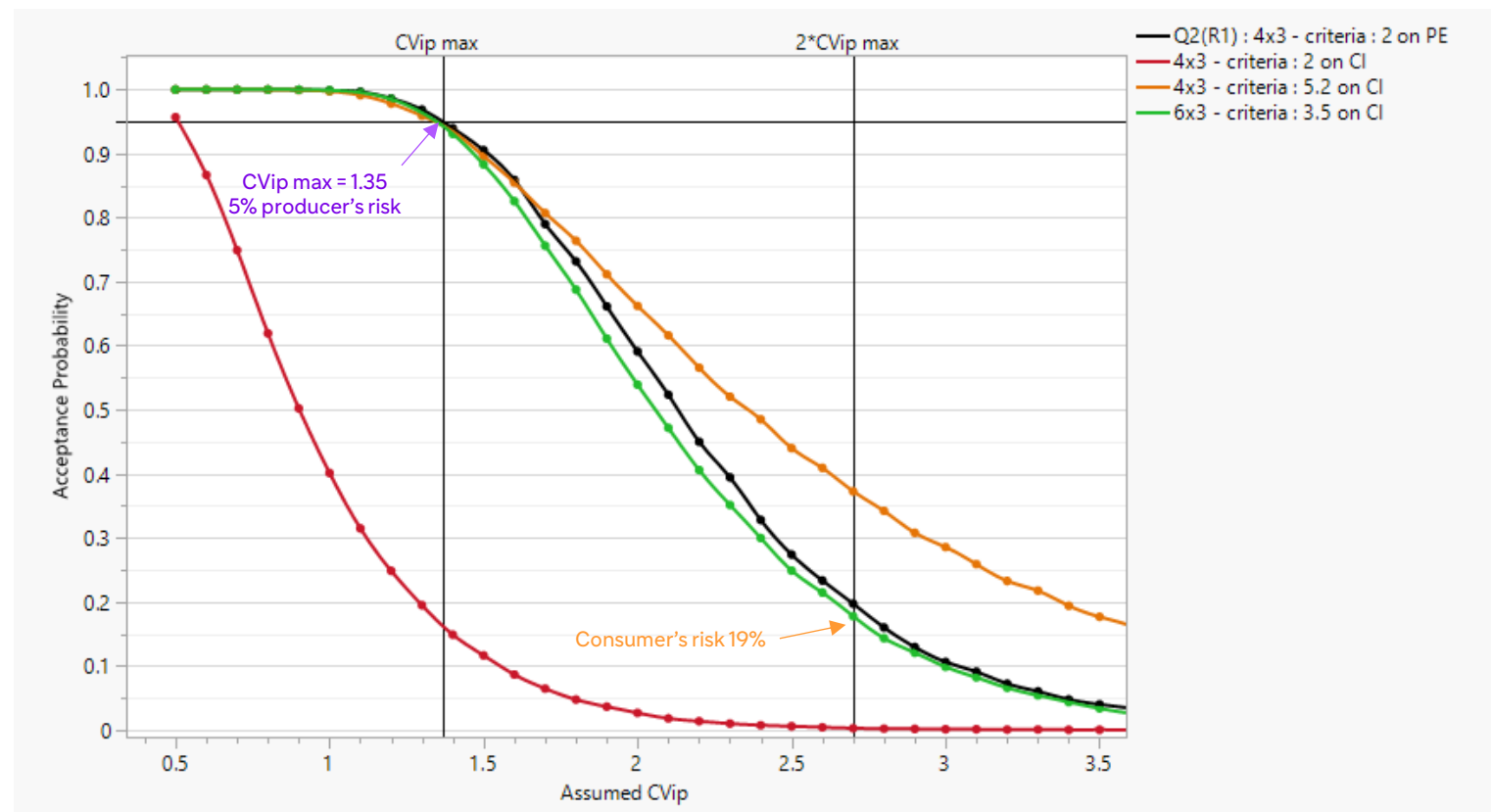


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● 4x3	5.2%	5%	37%

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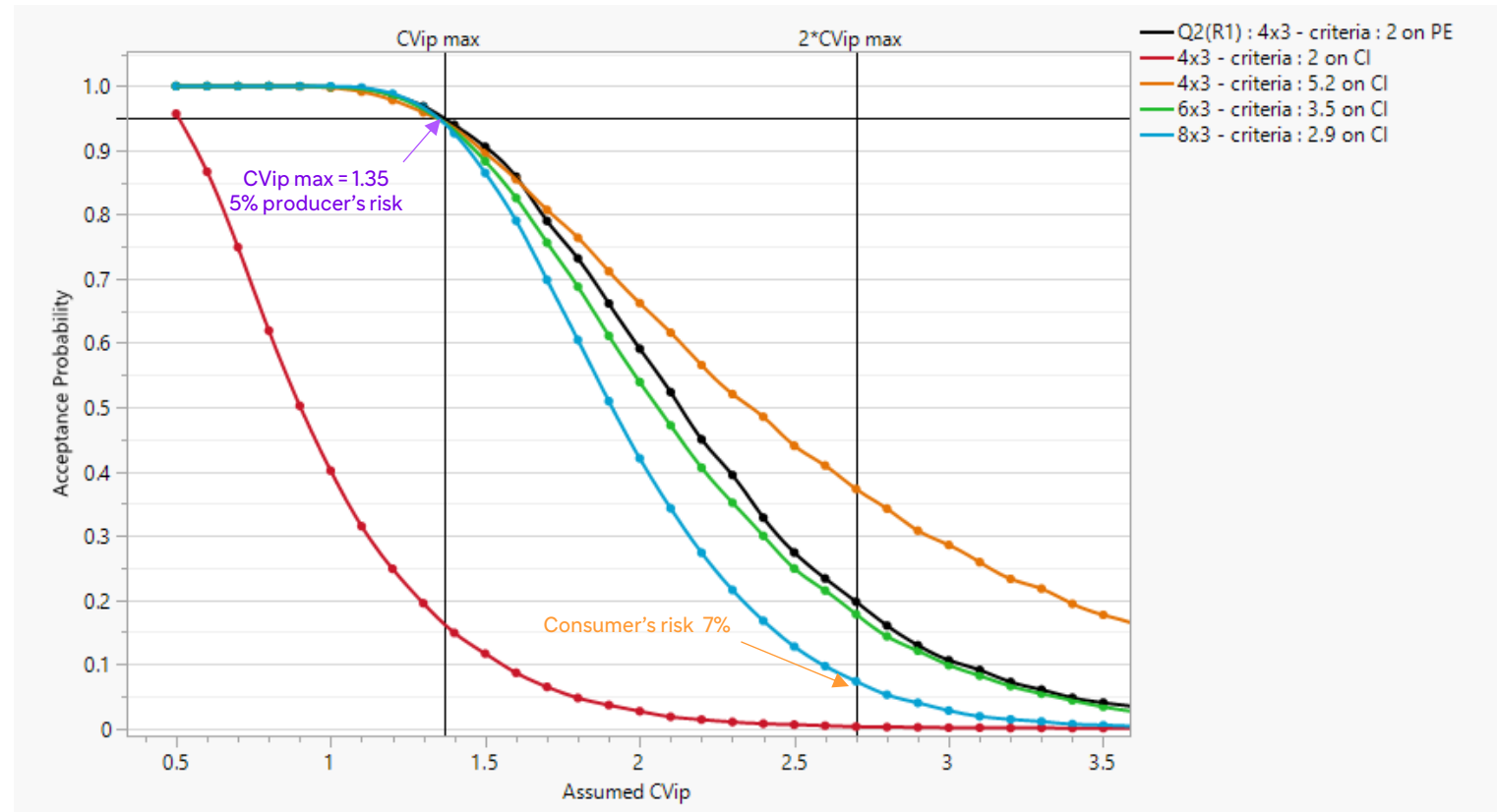


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● 4x3	5.2%	5%	37%
● 6x3	3.5%	5%	19%

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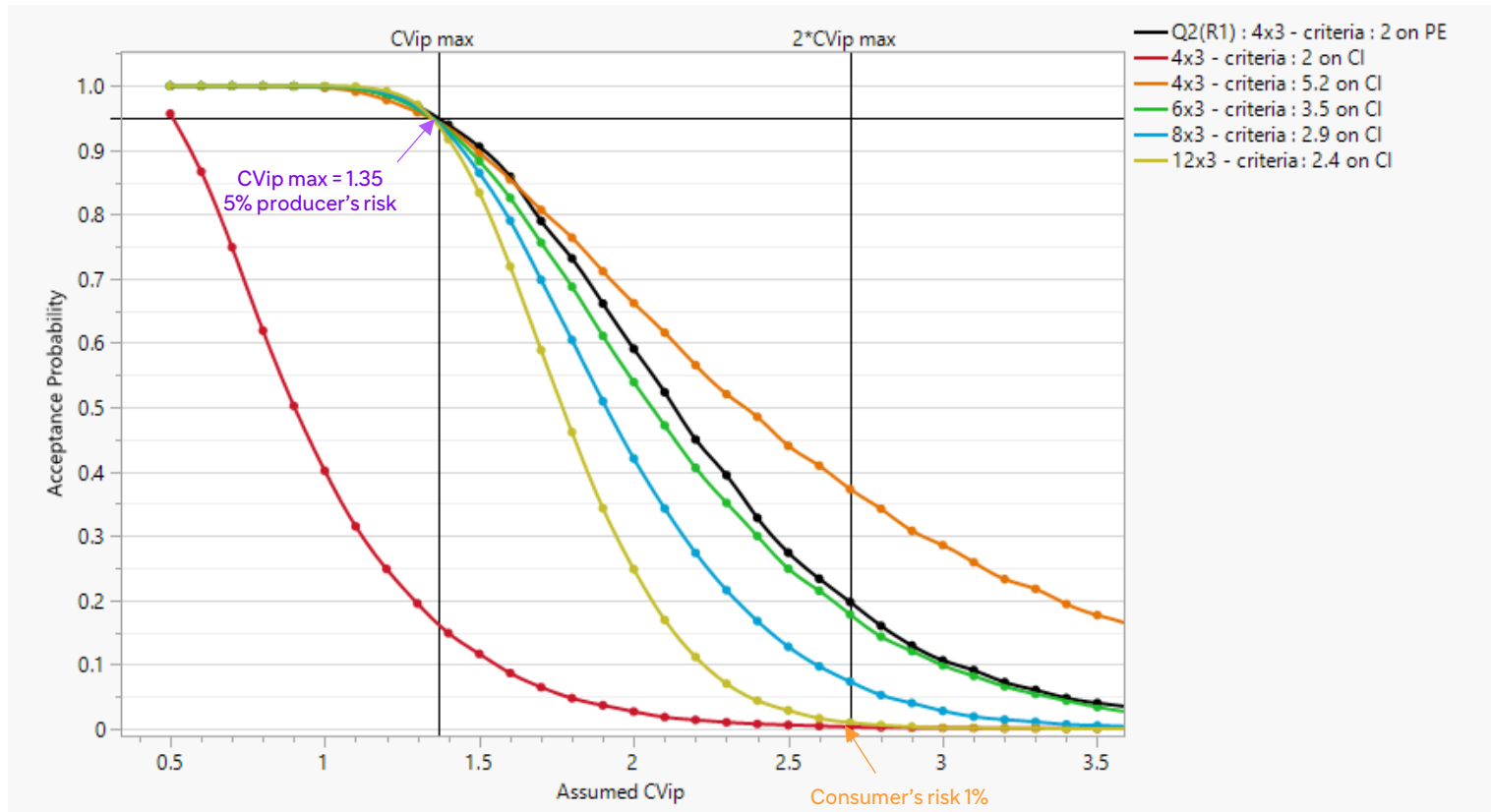


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● 6x3	3.5%	5%	19%
● 8x3	2.9%	5%	7%

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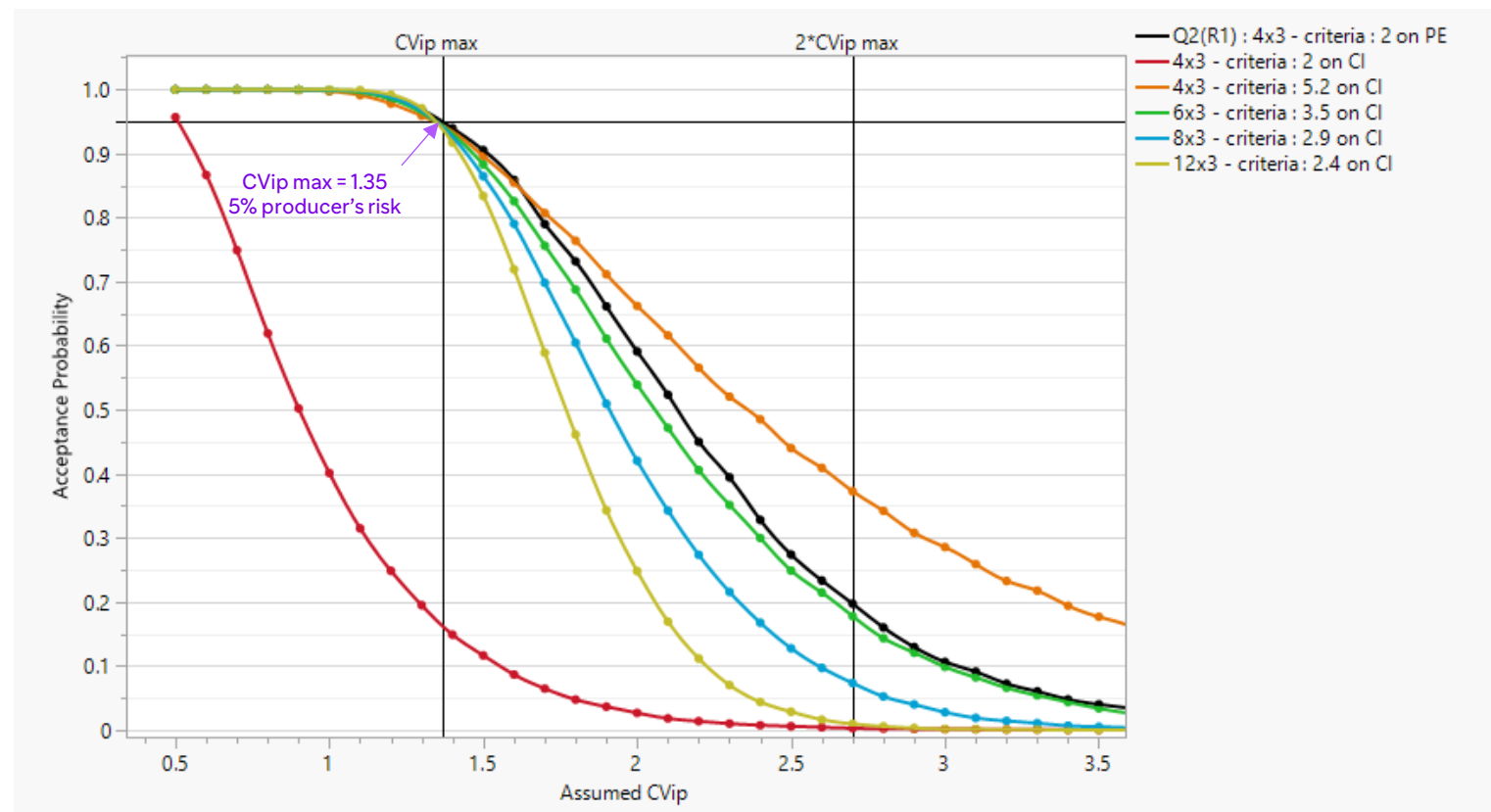


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● 8x3	2.9%	5%	7%
● 12x3	2.4%	5%	1%

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● 8x3	2.9%	5%	7%
● 12x3	2.4%	5%	1%

Proposed Design : 6x3

Proposed Criteria :
95% One-sided upper confidence bound CVip ≤ 3.5%

Conclusion

- A simulation-based framework to justify designs & acceptance criteria under ICH Q2(R2)
- **Flexible & adaptable** — Fine-tune to your context:
 - Fit to your own definition of “good method” and “bad method”,
 - Fit to acceptable consumer’s risk
- **Extendable** — A similar approach can be applied to accuracy validation



Thank
You

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