EMA /US FDA Workshop on

support to quality development in early access approaches

Case studies on control strategy
Impurity Control Strategy for an Oncology drug

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Bio Biotechnology Innovation Organization

ebe european biopharmaceutical enterprises

efpia European Federation of Pharmaceutical Industries and Associations

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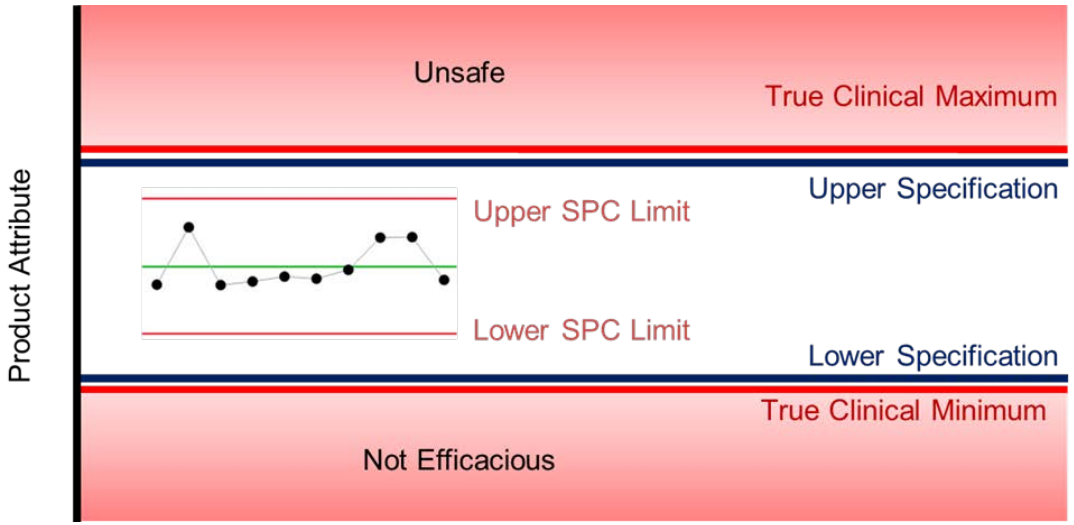
Outline

1. Overview of data challenges
2. **Non-mutagenic Impurities** challenges of setting specifications based on limited data
   - Alignment to safety qualification data
   - Correlation with existing guidelines
3. **Mutagenic Impurities**
   - ICH M7 / ICH S9 key concepts

Non Mutagenic Impurities

- Safety established through non-clinical safety studies (qualification).
- Based on principles within ICH Q3A / Q3B limited batch data makes specification setting difficult.
- Tension between batch data and safety data is more disruptive when there is very limited batch data available.
- Conflict exists when Q6A specifically directs that the acceptance criterion for a drug substance impurity be set based on the mean + upper confidence level seen in 'relevant' batches.
- Interactions between applicant and authorities during development highly valuable.



Illustrative Relationship between patient-centric specification boundaries and batch data experience

Specification limits for Non-Mutagenic Impurities

- *Typically for an impurity a specification based on a 3SD approach is applied however where limited manufacturing experience is available a more negotiated position has been reached.*

- *The table illustrates the difference often seen between mean +3SD and available toxicological cover.*

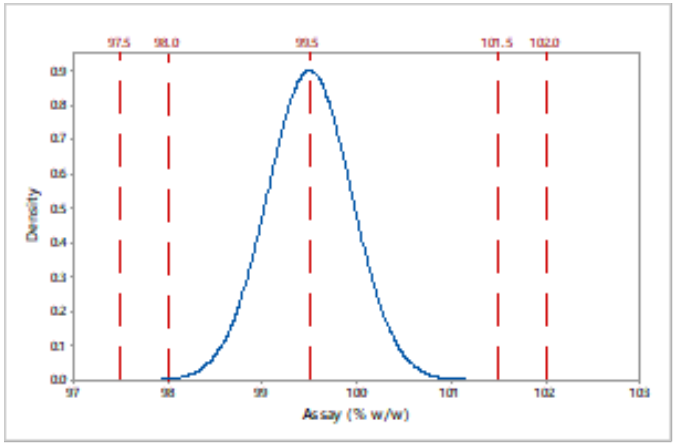
Acceptance criterion (%)	Impurity range	Mean+3SD	Level qualified based on 80 mg dose (%)
0.4	ND -0.23	0.31	10.3

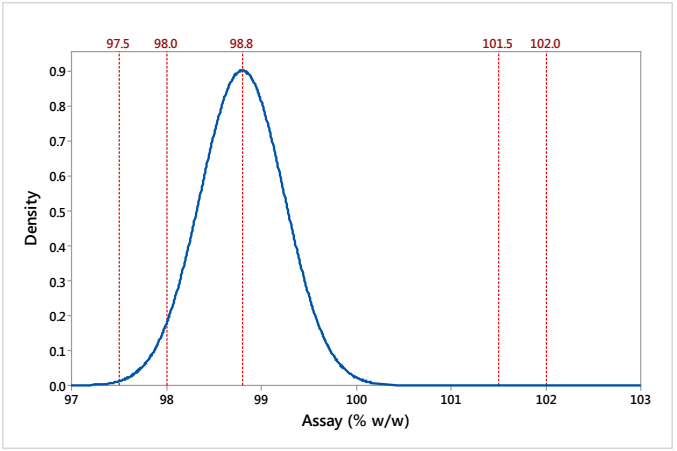
- *Where manufacturing experience is low it should be possible to leverage a patient safety centric approach which will mean that both safety and manufacturability concerns are met.*

In fast moving projects this initial flexibility will ensure there are no unnecessary batch failures leading to potential medicine supply issues.

Specification Limits for Assay

- With limited data consideration should be made to potential drift of the process within industry norms in setting for example Assay specifications on little data.





In this example a the LHS shows distribution based on a limited data set for an accelerated project. The RHS shows the effect of a process shift of 1.5 sigma, which is not unreasonable for statistically controlled process over time.

Such a shift would result in the failure of a significant number of batches should a limit of 98.0% be set based on the limited available data set.

Mutagenic Impurities

ICH M7 provides a very effective framework for development of MI control strategy for Oncology drugs

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Two key concepts

- Limits based on risk / benefit
  - This in turn is aligned to ICH S9
- Limits aligned to duration (modified Haber's Law)

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

ICH M7 -Relationship to other guidelines – ICH S9

- This guideline does not apply to drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH S9.
- *What does ICH S9 state?*
  - For genotoxic impurities, several approaches have been used to set limits based on increase in lifetime risk of cancer. Such limits are not appropriate for pharmaceuticals intended to treat patients with advanced cancer, and justifications described above should be considered to set higher limits.

WHAT IS AN APPROPRIATE HIGHER LIMIT?

Tagrisso:

- Developed for the treatment of Advanced non-Small Cell Lung Cancer patients with EGFR mutation (T790)
  - Patient population previously treated with another EGFR TKI
- Expected lifetime <5 years
- Acceptable intake set at 100 µg/day ✓

ICH M7 – MI control

SECTION 8 -CONTROL

- Greater flexibility in terms of mechanism to prove absence.
- Options other than to simply test for presence in final API.
- Ability to more widely use chemical / process based arguments to assess purging.
  - Expressed in terms of Process Impurities in terms of a series of control options

Option 4

- So reactive – no testing required

Option 3

- Test at intermediate stage with a higher limit + understanding of process capacity.

Option 2

- Test for the impurity in the specification for a raw material, starting material or intermediate at permitted level

Option 1

- Test for the impurity in the drug substance

Purge Factor Calculation – Basic Principles

The following **key factors** were defined in order to assess the potential **carry-over of a MI:**

reactivity, solubility, volatility, and any additional physical process designed to eliminate impurities e.g. chromatography.

Score assigned on the basis of the **physicochemical properties** of the **MI relative** to the process conditions.

These are then simply multiplied together to determine a 'purge factor' (for each stage)

The overall purge factor is a multiple of the factors for individual stages.

Predicted purge is then compared to required purge (this being based on the safety limit and initial level introduced into the process)

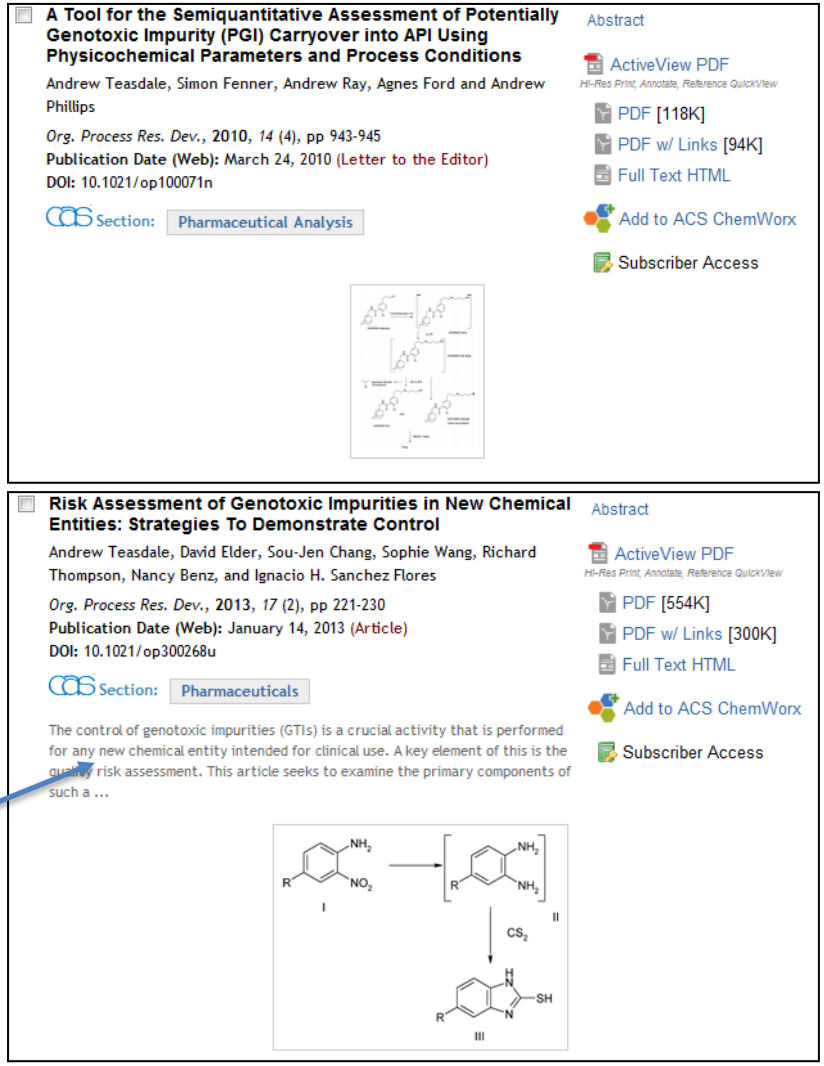
Purge Prediction Scoring System

- Scoring system based on basic principles – referred to as "paper" assessment because not automated (manual calculation via spreadsheet)
  - Reactivity shown to have largest effect
  - Other factors especially solubility would also influence purging.
  - Scoring system originally designed to be conservative
    - On validation this was experimentally observed

Physicochemical Parameters	Purge Factor
Reactivity	Highly Reactive = 100
	Moderately reactive = 10
	Low Reactivity / un-reactive = 1
Solubility	Freely Soluble = 10
	Moderately soluble = 3
	Sparingly Soluble = 1
Volatility	Boiling point >20^{0}C below that of the reaction/ process solvent = 10
	Boiling point +/- 10^{0}C that of the reaction/ process solvent. = 3
	Boiling point >20^{0}C above that of the reaction/ process solvent = 1
Ionisability – relates to liquid / liquid extraction	Ionisation potential of GI significantly different to that of the desired product [2]
Physical Processes – chromatography	Chromatography – GI elutes prior to desired product = 100
	Chromatography – GI elutes after desired product = 10
	Others evaluated on an individual basis.

Control Option 4
How do I apply this in practice?

- The principle of relating the physico-chemical properties of the mutagenic impurity to the chemical process is defined in the concept of purge factor calculations.



- OPR&D paper referenced directly in ICH M7

AZD9291 mesylate Control Strategy

- Osimertinib mutagenic impurities control strategy was carried out fully in line with ICH M7

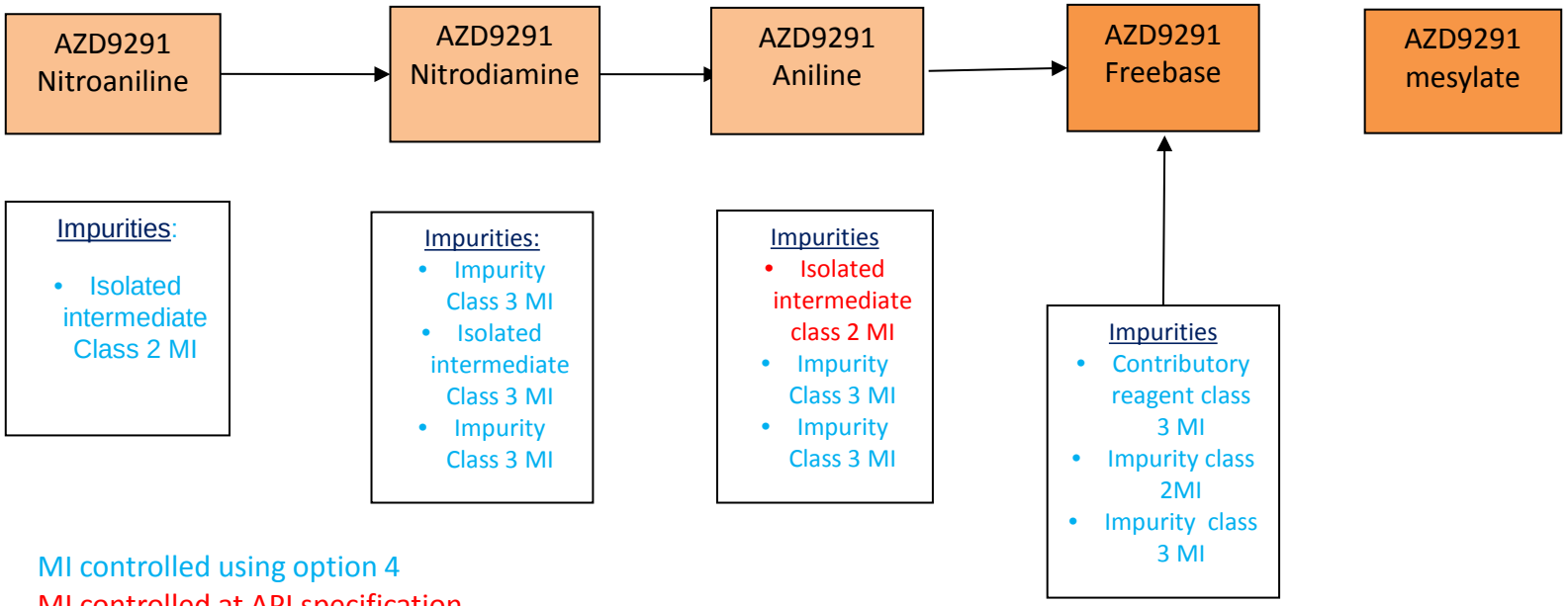
- SAR analysis on 34 potential impurities was carried out
  - From this analysis 10 potential impurities are shown as having alerting sub structures upon expert analysis. (Class 3)

- 3 of these impurities were tested and found to be Ames positive (class 2 MI)

- As per ICH M7 8.1 option 4 purge factor calculations were carried out on all 10 impurities

- Of the 10 impurities 9 were found to be purged to well below the TCC calculated for Osimertinib

AZD9291 mesylate Control Strategy



MI controlled using option 4

MI controlled at API specification

Conclusions

- In some instances, i.e. ICH M7 new guidance actively supports accelerated development through key concepts:
  - Limits based on duration / patient population
  - Flexible control options
- In other areas pragmatism is vital, need to challenge well established concepts
  - Particularly true of impurity specifications where there may be limited data.
- Ultimately it is critical to keep sight on the need to deliver high quality, safe medicines to patients.
- A LOT TO GAIN THROUGH DIALOGUE

BACK UP SLIDE

Mirabilis regulatory workflow publication

ELSEVIER

Regulatory Toxicology and Pharmacology

Volume 90, November 2017, Pages 22-28

A consortium-driven framework to guide the implementation of ICH M7 Option 4 control strategies

Chris Barber [a], Vincent Antonucci [b], Jens-Christoph Baumann [c], Roland Brown [d], Elizabeth Covey-Crump [a], David Elder [e], Eric Elliott [f], Jared W. Fennell [g], Fabrice Gallou [h], Nathan D. Ide [i], Guido Jordine [h], Jeffrey M. Kallemeyn [i], Dirk Lauwers [j], Adam R. Looker [k], Lucie E. Lovelle [h], Mark McLaughlin [b], Robert Molzahn [l], Martin Ott [a], Didier Schils [m], Rolf Schulte Oestrich [c], Neil Stevenson [n], Pere Talavera [o], Andrew Teasdale [p], Michael W. Urquhart [n], David L. Varie [g], Dennie Welch [i]

Goal: establish framework to leverage purge predictions to inform selection of control strategy during development, which in turn informs both data collection and regulatory reporting recommendations

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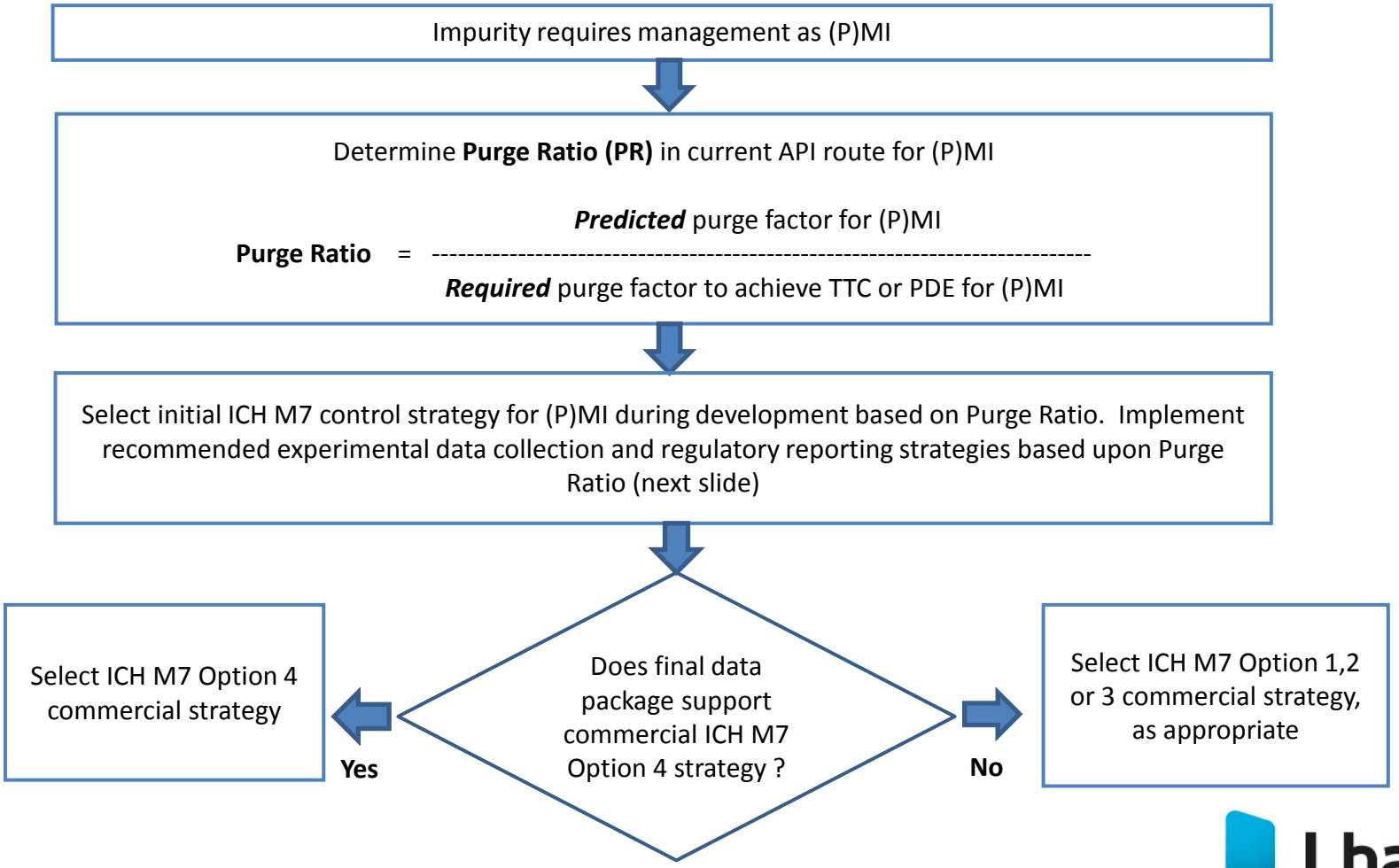
Mirabilis (P)MI Purge Prediction Decision Tree

Key premise: purge excess dictates data collection needs and regulatory reporting practices



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Example of calculation of Purge Ratio

Purge Ratio prediction of (P)MI "X" (a process reagent)

- Assume TTC is 100 ppm
- Assume charge (initial conc) is 1 eq or 10^6 ppm
- 10^4 purge factor (10^6 / 100 ppm) needed to achieve TTC
- Therefore to achieve a 10^3 Purge Ratio (i.e. three order magnitude more purge predicted than required to achieve TTC), Mirabilis must predict a 10^7 cumulative purge factor

$$\textbf{Purge Ratio} = \frac{\textbf{\textit{Predicted}} \text{ purge factor for (P)MI}}{\textbf{\textit{Required}} \text{ purge factor to achieve TTC or PDE for (P)MI}}$$

So how does one consistently apply the (P)MI Purge Ratio to lab workflows and regulatory reporting ?

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When Purge Ratio > 1000…

Data Collection Recommendations
Collection of additional experimental data not necessary to support scientific rationale for non-commercial or commercial API routes
Regulatory Reporting Recommendations
Report “unlikely to persist” or cumulative predicted purge factor and Purge Ratio for non-commercial API routes in regulatory submissions. Replace with summary of key elements of predicted purge factor calculations and Purge Ratio for commercial API routes in regulatory submissions

Option 4 recommended

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Example presentation in regulatory dossier when Purge Ratio > 1000 in commercial route

<insert chemical structure of (P)MI "X">	Point of introduction	Stage 2 of 5
	(P)MI TTC	50 ppm
	Assumed initial concentration and rationale for selection	10^6 ppm at start of Stage 2 because "X" charge is 1 equivalent
	Required Purge Factor to achieve TTC	2×10^4 = 10^6 ppm initial conc / 50 ppm TTC
	Predicted Purge Factor	2×10^8 (source Mirabilis software vx.x) Key factors: 1000x purge in Stage 2 driven by reactivity and solubility, purge in Stages 3-5 driven by solubility
	Purge Ratio	$1 \times 10^4 = 2 \times 10^8 / 2 \times 10^4$
	Control Strategy	Option 4

No supporting experimental data collection recommended when Purge Ratio is large

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