ICH M7: Situation at a Japanese Company

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Review: Key Actions in M7 Guideline

§ 5: Impurity Assessment

- What impurities need to be assessed? – actual, potential, degradation products

§ 6/7: Hazard Assessment / Risk Characterization

- Is the impurity mutagenic? QSAR + Ames
- What is the acceptable intake? (TTC, compound specific, less than lifetime exposures)

§ 8: Control

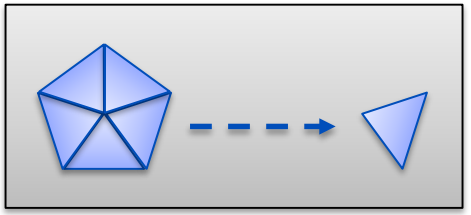
- Expectations, options for impurity control, lifecycle

Ref) ICH M7(R1) Training Material

Topics & corresponding ICH M7 Sections

Dev. Stage	Key Consideration Points	M7 §
Candidate Selection	> Risk Assessment of Degradation Products	[§5]
Clinical Development	> Understanding of Process and Impurity	[§5] [§6]
	> Development of Control Strategy	[§8]
Marketing Application	> Finalization of Hazard Assessment	[§6] [§7]

Assessment of Degradation Products



- Consideration Point
  - Degradation product stick throughout product lifecycle

- Difficulty
  - Select candidate with inherent concern or search another candidate?

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  - Predict and evaluate risk of degradation product during candidate selection to reduce concern in future development.
  - Study stability during development stage

Reference: Degradant Study

- Klainman et al. claim, that regardless of the chosen strategy, it is worth including into the safety assurance only major degradation products observed at significant levels in stress tests, accelerated or long-term stability studies, as this reflects the existence of degradation products that are most likely to be found in the products that currently are on the market.

- Industry … claim that the collective strategy should be based on a risk assessment, where the potential degradation products are identified and classified as relevant, addressed or irrelevant and as a result can be excluded from further analysis. The discussion concerning the aim of researchers' investigations and applicable stability tests is still opened.

Ref) Jamrógiewicz M et al., Recent breakthroughs in the stability testing of pharmaceutical compounds, TrAC, 2019; 111, 118-127.

Tasks for Mutagenic Degradant

- Consideration of potential cause and storage condition
  - Oxidation, Hydrolysis...
  - Heat, Moisture ...

- Inapplicability of purge discussion

- Analytical method for control development
  - High sensitivity procedure to evaluate TTC level
  - Data acquisition for control justification

Topics & corresponding ICH M7 Sections

Dev. Stage	Key Consideration Points	M7 §
Candidate Selection	> Risk Assessment of Degradation Products	[§5]
Clinical Development	> **Understanding of Process and Impurity**	[§5] [§6]
	> Development of Control Strategy	[§8]
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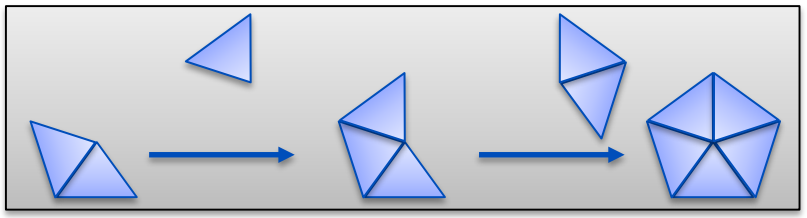
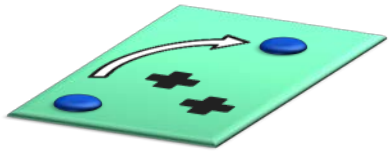
Understanding of Process & Impurity

- Consideration Point
  - Selection of process starting material [ICH Q11]
  - In silico impurity evaluation and in vivo follow up





- Difficulty
  - Update timing of in silico system and impact to former evaluation

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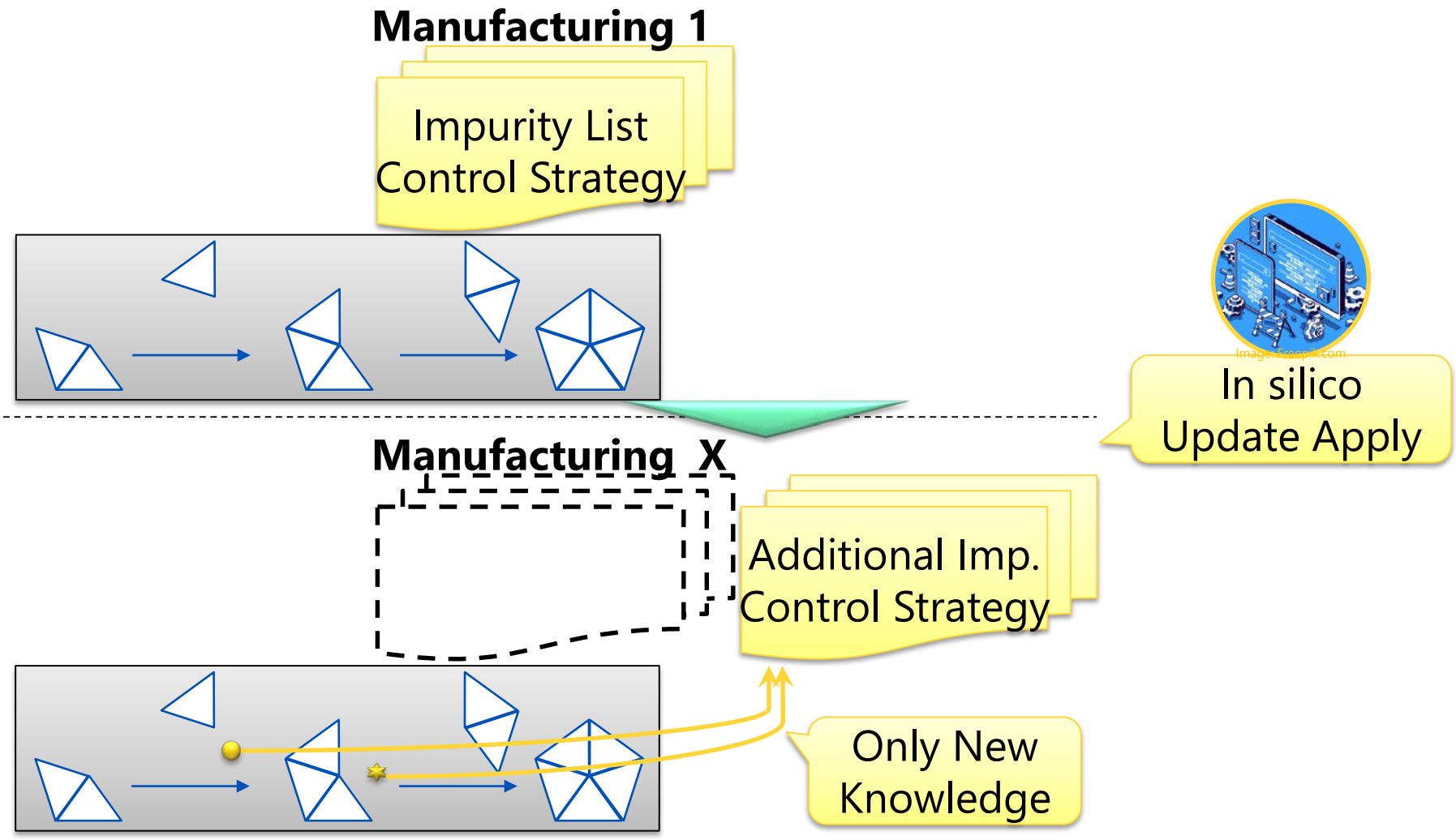
  - Reflect in silico system update with timely manner whenever possible

Typical Evaluation Procedure



Reference: Effect of in silico Update

- Most of the variation resulted in positive or equivocal predictions changing to equivocal or negative, respectively, with very few examples (on average 2%) of negative predictions changing to positive predictions.

- As a result of this analysis, we conclude that it is unnecessary to re-run a (Q)SAR prediction every time there is a version update unless there are specific reasons to do so, e.g., such as those presented below, which can be determined on a case-by-case basis.

Ref) Hasselgren C et al., Management of pharmaceutical ICH M7 (Q)SAR predictions – The impact of model updates, Regul Toxicol Pharmacol. 2020; 118, 104807.

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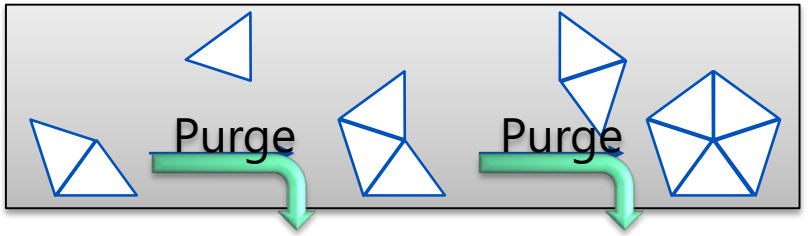
Development of Control Strategy



- Consideration Point
  - Efficient control point
  - Purge calculation
    with predicted and/or actual data

- Difficulty
  - Acceptability of purge calculation result and proposed control strategy

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  - Apply strategies with reference to some peer reviewed literatures
  - Introduce latest trends

Reference: Purge Factor

- Where the overall calculated purge factor would indicate the level of a GTI to be >100 times below the appropriate TTC limit, then no further action should typically be required.

Teasdale A et al., Risk Assessment of Genotoxic Impurities in New Chemical Entities: Strategies To Demonstrate Control, Org Process Res Dev, 2013; 17(2), 221-230.

- Purge Ratio (PR) = Predicted purge factor / Required purge factor

If PR ≥ 1000x	If 1000 > PR ≥ 100x	If PR < 100x
Collection of additional experimental data not necessary to support scientific rationale for non-commercial or commercial API routes	Collection of additional non-trace experimental data (solubility, reactivity, and volatility) recommended to support scientific rationale for both non-commercial and commercial API routes...	For non-commercial API routes, experimentally measure PMI purging, ..., to support scientific rationale. Note: Additional data are expected... For commercial API routes, detailed experimental fate & purge studies are expected to support a commercial Option 4 control strategy for all PMIs.

Barber C et al., A consortium-driven framework to guide the implementation of ICH M7 Option 4 control strategies, Regul Toxicol Pharmacol, 2017; 90, 22-28.

Reference: Option 4 Acceptability

- More recently, data was generated confirming the frequent application and acceptance of control option 4.
- Cross-industry data set provided evidence that the predictive purge factor approach provides conservative estimates when compared with experimental data points.

Ref) Borths CJ et al., Control of Mutagenic Impurities: Survey of Pharmaceutical Company Practices and a Proposed Framework for Industry Alignment, Org Process Res Dev, 2021; 25(4), 831-837.

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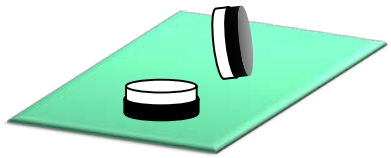
Finalization of Hazard Assessment

- Consideration Point
  - (Re)evaluation of hazard before marketing application



- Difficulty
  - Change in hazard assessment and impact to the control strategy

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  - Reevaluate impurities for commercial manufacturing process with latest knowledge

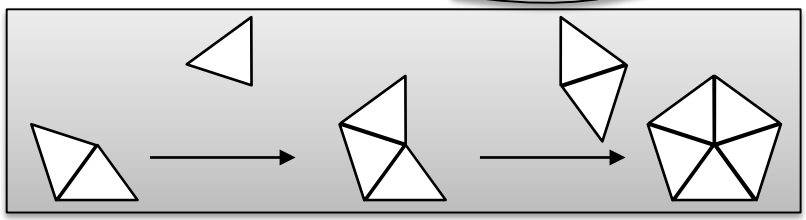
M7 Q&A (Step 2) Recommendation

- It is recommended that the sponsor re-run (Q)SAR predictions prior to the initial marketing application to ensure predictions reflect the most current data available. If the marketing application is later submitted in other regulatory jurisdictions, reassessment may be considered. As an example, in cases where there is reason to question the outcome of a negative prediction (e.g., an aromatic amine is present, but the model gave a negative prediction). Reassessment may also be considered if the predictions made for the initial global marketing application did not use a recent version of the software.

Typical Evaluation in Late Stage

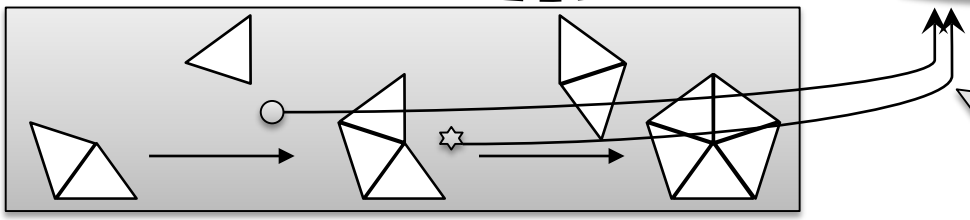
Manufacturing 1

Impurity List
Control Strategy



Manufacturing X

Additional Imp.
Control Strategy

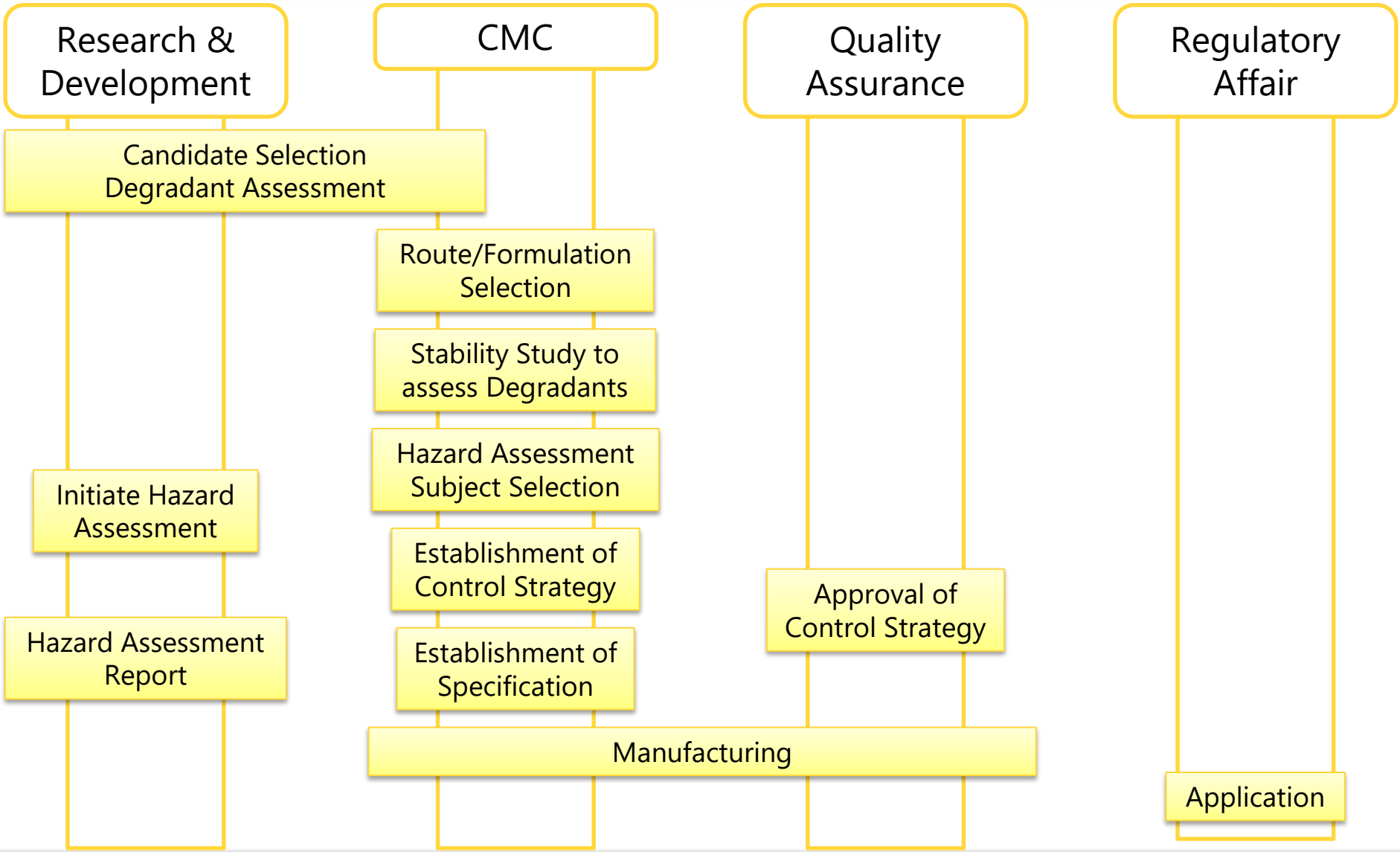


Only New
Knowledge

Toward Marketing App.

All Impurity List
Control Strategy

Summary of Shionogi Process



Other topics related to M7 (1/2)

- Change management of existing products
  - Benefit of change vs required effort for potential mutagenic impurity, suffering whether to apply new practice

- Marketing application to other country/region(s) as a new product
  - <Difficulty> Hazard reevaluation would be requested with latest knowledge, and that would affect quality control of current commercial products

Image: macrovector Freepik.com

Other topics related to M7 (2/2)

- Recall case in some commercial products
  Class 2 degradation product in epinastine
  - <Difficulty> Approach of retrospective evaluation

- Application to middle/large molecule pharmaceuticals
  - Key aspect (e.g. use of chemical reagents) should be taken into consideration, with reference to e.g. mRNA vaccine case.

Summary & Conclusion

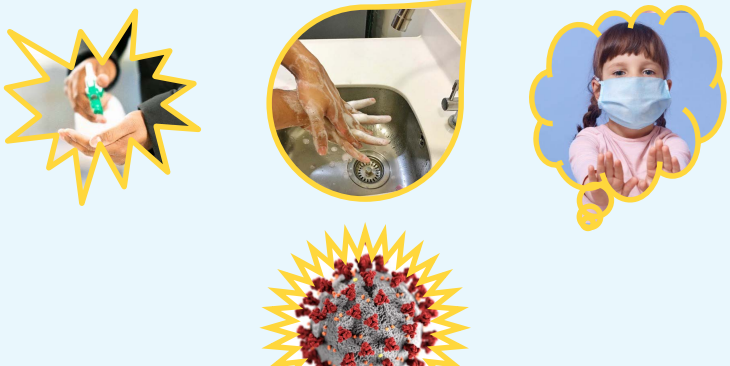
- From personal point of view;

- Incorporation of ICH M7 guideline in Japanese pharmaceutical industry progress consistently
  - Key aspects in M7 guideline;
  - ✓ Two (Q)SAR system
  - ✓ Control options 1 ~ 4 and utilization of impurity purge calculation

  - Since those are additional requests to ICH Q3A/B, it is a lot of load to small/middle companies, generic industries.

Thanks, especially to front-line medical service workers

Purge COVID by caring Reactivity, Solubility & Volatility(Diffusivity)!



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