

# The Case-By-Case Regulatory Factor: What Does It Mean For Small Molecule Development?



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# Learning Objectives

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- After this presentation, you will understand:
  1. The changing regulatory dogma (system of belief)
  2. How to interpret the 'case-by-case' approach
  3. Integrated designs can maintain scientific integrity

# Content

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- Government Support
- Regulatory Harmonization
- Non-Clinical Package Planning
- Integrated-Design Validation Study

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# Government Support

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- **Promote Drug Research and Development**
  - Grant Sources
  - Research Climate
  - Encourage Treatments for Rare Diseases
- **Provide Regulatory Guidance to Developers**
  - Domestic Regulatory Criteria
  - Global Regulatory Criteria
- **Protect Public from Injury**
  - Approval Process
  - Post-Market Surveillance
  - Withdrawal Process

# Government Support

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- **International Conference on Harmonisation (ICH)**
  - ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.
  - The focus of ICH has been on the technical requirements for medicinal products containing new drugs.
- **ICH Members**
  - European Commission - European Union (EU)
  - European Federation of Pharmaceutical Industries and Associations (EFPIA)
  - Ministry of Health, Labour and Welfare, Japan (MHLW)
  - Japan Pharmaceutical Manufacturers Association (JPMA)
  - US Food and Drug Administration (FDA)
  - Pharmaceutical Research and Manufacturers of America (PhRMA)
- **ICH Observers**
  - The World Health Organisation (WHO)
  - The European Free Trade Association (EFTA)
  - Health Canada

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# Regulatory Harmonization

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## ICH M3(R2): Synthetic Produced Drugs (Oral Administration)

### Past (Traditional)

- Genetic Toxicology (3 tests)
- Pharmacokinetics (2 species)
- Acute Toxicology (2 species)
- Subacute Toxicology (2 species)
- Safety Pharmacology (4 tests)
- Subchronic Toxicology (2 species)
- Developmental and Reproductive Toxicology (2 or 3 species)
- Chronic Toxicology (2 species)
- Subchronic Mouse (DRF)
- Carcinogenicity (2 species)

### Present (Case-by-case)

- Same
- Same
- MTD-DRF (2 species)
- Same
- hERG + 3 Integrated *in vivo*
- Same
- Same
- Duration changes
- Subacute Transgenic Mouse ?
- Rat + Transgenic Mouse ?

# Regulatory Harmonization

## Guidance for Industry<sup>1</sup>

### **M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals**

#### **II. PHARMACOLOGY STUDIES (2)**

Safety pharmacology and pharmacodynamic (PD) studies are defined in ICH S7A (Ref. 5). The core battery of safety pharmacology studies includes the assessment of effects on cardiovascular, central nervous, and respiratory systems, and should generally be conducted before human exposure, in accordance with ICH S7A and S7B (Refs. 5 and 6). When warranted, supplemental and follow-up safety pharmacology studies can be conducted during later clinical development. Consideration should be given to inclusion of any in vivo evaluations as additions to general toxicity studies, to the extent feasible, in order to reduce animal use.

# Regulatory Harmonization

Reintegration of cardiovascular, neurological, and respiratory evaluations in the toxicology studies has stimulated some controversy in the industry.

- When is it acceptable to integrate safety pharmacology in the pivotal repeated dose studies?
- The concern is that practices implied under S7A/B may be diluted when integrated into a repeated dose study.
- A “first-tier and follow-up” approach has significant merit because many small molecules present no meaningful adverse safety characterization information in an independent safety pharmacology study.
- There is hesitancy from the industry to make this change, but regulatory agencies routinely accept the integration of safety pharmacology into the pivotal repeated dose studies for small molecules.

# Regulatory Harmonization

- ICH M3(R2) compared to ICH S6 (Biotechnology-Derived Products)

## Small Molecule

- Genetic Toxicology (3 tests)
- Pharmacokinetics (2 species)
- MTD-DRF (2 species)
- Subacute Toxicology (2 species)
- hERG + 3 Integrated *in vivo*
- Subchronic Toxicology (2 species)
- Developmental and Reproductive Toxicology (2 or 3 species)
- Chronic Toxicology (2 species)
- Subchronic Mouse (DRF)
- Carcinogenicity (2 species)

## Biologic

- No relevance
- Same (RS)
- MFD-DRF (Relevant species; RS)
- Same (RS)
- No hERG + 3 Integrated *in vivo*
- Subchronic Toxicology (RS)
- Same (RS)
- Duration changes (RS)
- May not be needed
- May not be needed

# Regulatory Harmonization

## Small Molecule (Other evaluations)

- In vitro metabolism
- Formulation support (HPLC)
- Bioanalytical support (ISR)
- ADME
- Local tolerance (Always needed but rarely thought of)
- Expanded Immunotoxicology
- Efficacy
- Juvenile Animal Toxicity
- Phototoxicity
- Abuse Liability

## Biologic (Other evaluations)

- Immunogenicity
- Formulation support (HPLC ?)
- Bioanalytical support (ISR)
- Low relevance (Catabolism/food)
- Local tolerance (Understood because of administration route)
- Same
- Same (Add Imagery)
- Same
- Tissue-cross reactivity (fading)

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# Non-Clinical Package Planning

# Non-clinical Package Planning

- **Indication**
  - Strong case-by-case considerations
- **Treatment Duration**
  - Strong case-by-case considerations
- **Novel Target**
  - Full characterization needed
- **First-in-Class**
  - Full characterization needed
- **New Therapeutic for Familiar Target**
  - Full characterization should be considered
- **Change in Route or Formulation**
  - Strong case-by-case considerations
- **Biosimilar**
  - Strong case-by-case considerations

## My 'Case-By-Case' Interpretation:

Please take the time to consider various key attributes of your potential pharmaceutical before developing a non-clinical plan.

After you conduct some preliminary non-clinical experiments, please take the time to consider how the findings may change your non-clinical plan.

It is possible that you may need additions to your non-clinical plan, but it is also possible that you may have planned to provide excess redundant information, which may not be appropriate for animal welfare (3R's).

Therefore, please use a step-wise scientific approach for the design of each non-clinical support phase for your potential pharmaceutical.

# Non-clinical Package Planning

- Drug A is a small molecule for subchronic oral administration
  - Indication (broad-spectrum chemotherapeutic)
  - Treatment Duration (full preclinical characterization not needed based on duration)
  - Novel Target

## Non-Clinical Safety Package

- Genetic Toxicology (3 tests)
- *In vitro* Metabolism
- Pharmacokinetics (2 species)
- MTD-DRF (2 species)
- Subacute Toxicology (2 species)
- hERG + 3 Integrated *in vivo*
- Subchronic Toxicology (2 species)
- Developmental and Reproductive Toxicology (2 species)
- ADME

## Case-by-Case Considerations

- Independent Safety Pharmacology
- Expanded Immunotoxicity
- Other

# Non-clinical Package Planning

- Drug B is a biologic for subchronic intravenous administration
  - Indication (cancer)
  - Treatment Duration (full preclinical characterization not needed based on duration)
  - Novel Target (but conserved across species)

## Non-Clinical Safety Package

- Pharmacokinetics (2 species)
- MTD/MFD-DRF (2 species)
- Subacute Toxicology (2 species)
- No hERG + 3 Integrated *in vivo*
- Subchronic Toxicology (2 species)
- Developmental and Reproductive Toxicology (2 species)
- Immunogenicity
- No Tissue Cross Reactivity

## Case-by-Case Considerations

- Independent Safety Pharmacology
- Expanded Immunotoxicity
- Other

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# Integrated-Design Validation Study

# Integrated-Design Validation Study

## Surgical and Drug Treatment Assignments by Experimental Group

Group	Surgery	Lead Placement	Pressure Catheter Placement	Drug Treatment
1	-	NA	NA	17.8 mg/kg
2*	+	JET- Lead II	Femoral Artery	17.8 mg/kg
3*	+	JET-Lead II / CCTP – Lead II, EPI	Internal Iliac	0 mg/kg
4*	+	JET-Lead II / CCTP – Lead II, EPI	Internal Iliac	17.8 mg/kg

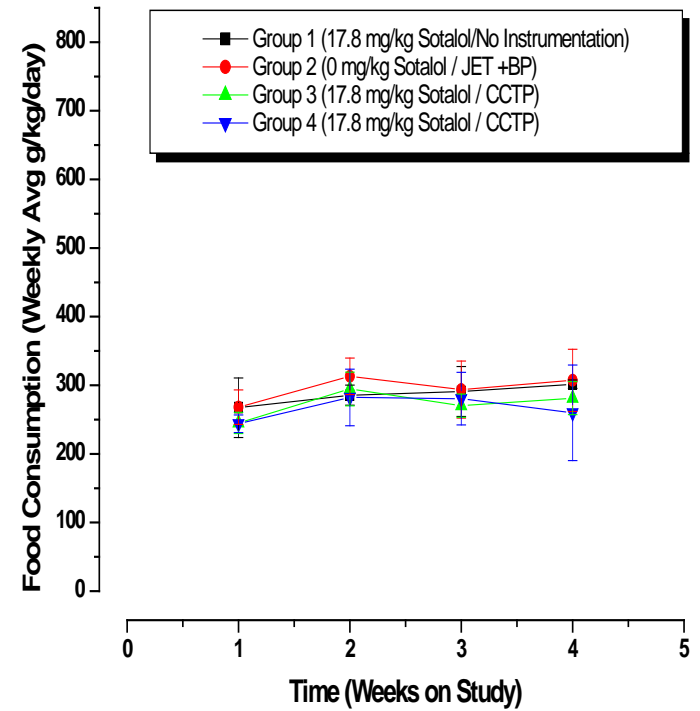
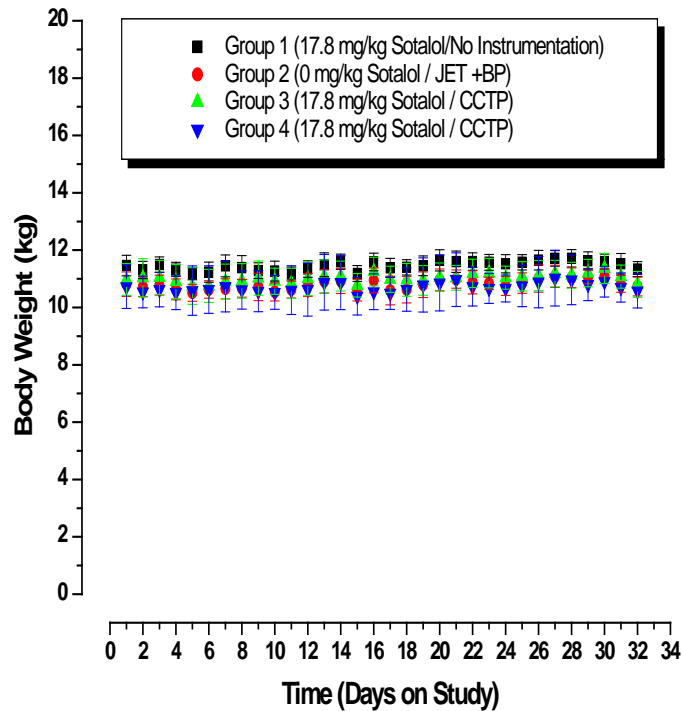
+ Performed

- Not Performed

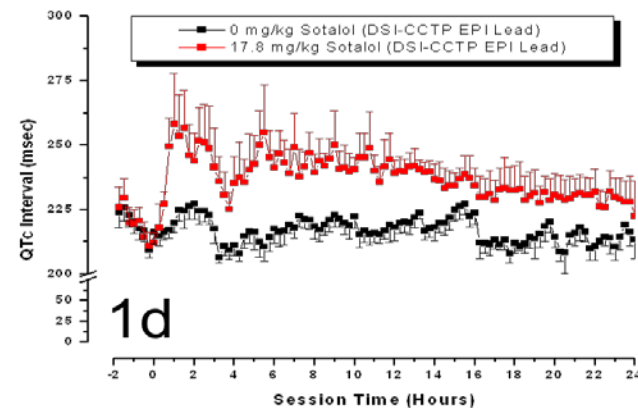
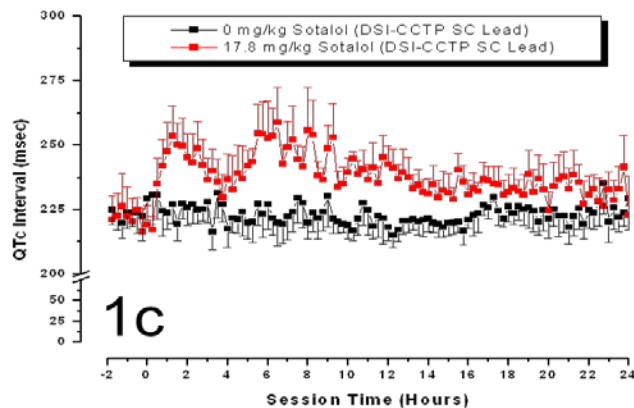
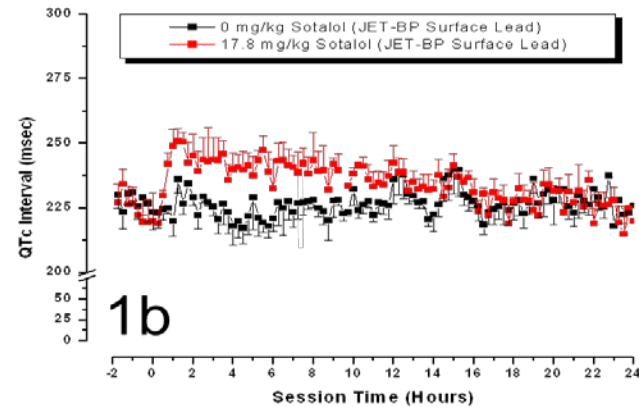
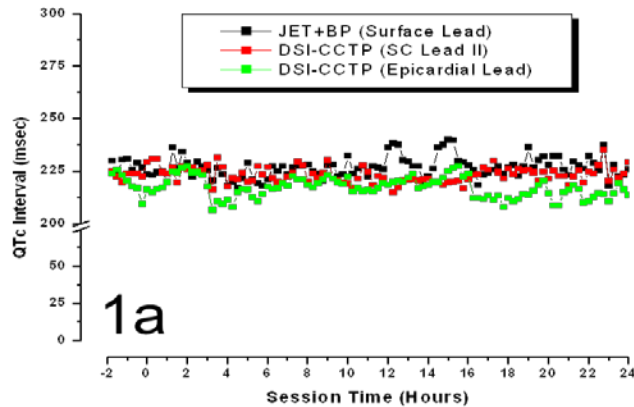
\* In addition to Lead II and Epicardial ECG evaluation enabled by the fully-implanted CCTP device, ECG was also monitored by JET with (surface) multi-electrode configuration

NA – Not Applicable

# Integrated-Design Validation Study



# Integrated-Design Validation Study



# Integrated-Design Validation Study

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- No surgical effects on body weights, food consumption, clinical observations, clinical pathology, organ weights or macroscopic evaluations
- Localized surgical effects observed at implantation sites (including subcutaneous, vascular, abdominal and epicardial sites)
- Drug-related cardiovascular effects detectable under all collection conditions

# Integrated-Design Validation Study

The maximum increase in  $\Delta QTc$  values observed were as follows:

- Restrained “Snapshot” (Surface Lead): +18.49 msec (+8.28%)
- JET with BP (Surface Lead): +29.0 msec (+12.4%)
- CCTP-DSI (SC Lead Placement): +38.8 msec (+16.4%)
- CCTP-DSI (Epicardial Lead Placement): +44.5 msec (+18.8%)

Both external and implanted telemetry techniques hold a most obvious advantage of capacity to characterize change over time (i.e., drug effect onset, maximal expression, and resolution)

# Learning Objectives

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- You should now have a basis to understand:
  1. The changing regulatory dogma (system of belief)
  2. How to interpret the 'case-by-case' approach
  3. Integrated designs can maintain scientific integrity

# Concluding Remarks

- It is key to understand how the pharmacology of your therapeutic can translate into toxicity or exaggerated pharmacology.
- Case-by-case means case-by-case (Science and technology over tradition).
- Do not assume that your scientific justifications will satisfy all agency countries (any change from recommended non-clinical safety testing should be discussed with the agency).
- The trade-offs between signal quality, methodology, animal welfare, and cost are worthy of consideration in determining the path forward on any given small molecule or biopharmaceutical program.
- Integrated study designs are viable options that produce acceptable data for determination of cardiovascular alterations.