Considerations for an Integrated Nonclinical-Clinical Risk Assessment

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Opportunity for New ICH E14/S7B Q&As

- **While at adoption ICH E14 suggested a QT interval evaluation independent of ICH S7B results …**
- **Both documents highlight the need for integration of information in a manner which is informative as a totality of evidence**
- **Current ICH activities are directed at scenarios where the nonclinical data are informative in clinical study implementation and evaluation**
- **How can an integrated nonclinical–clinical risk assessment be informative for clinical development, regulatory decision making and labelling ?**

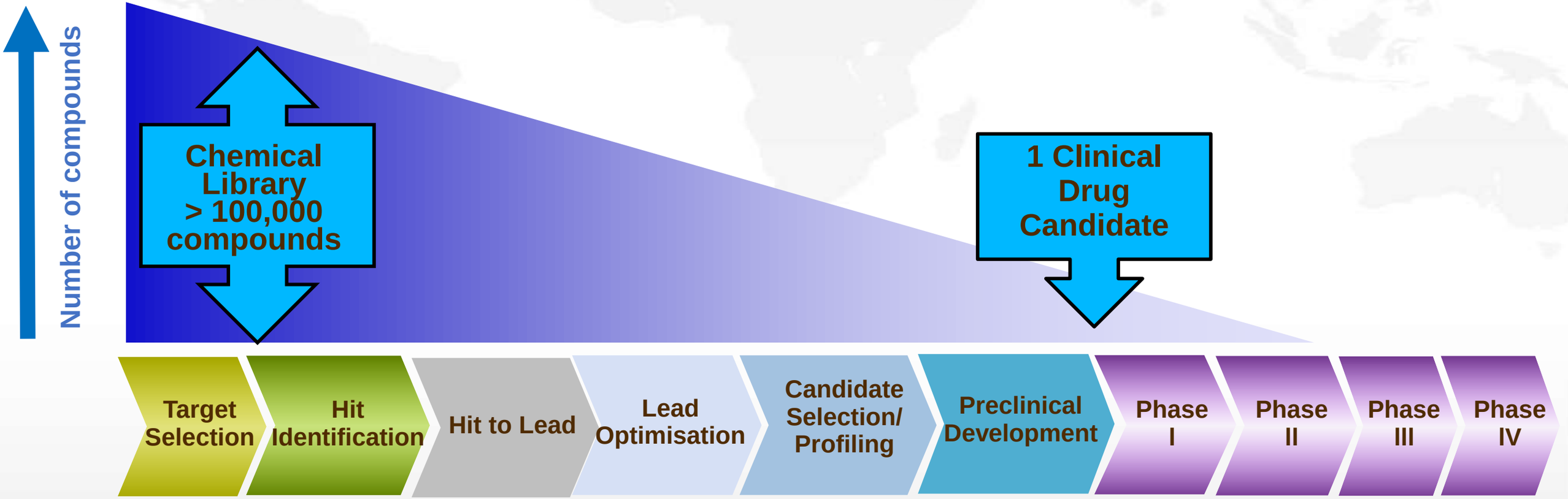
Evolution of the QTc/Torsades de Pointes (TdP) Landscape in Drug Development Pipeline Over the Last 20 Years

- **Shift in portfolio modalities entering drug development**
- **Increase proportion of non-small molecule candidates entering development (e.g., Biotechnology-derived products)**
- **Increase proportion of oncology products**
- **Increase usage and acceptance of Concentration-QTc (conc-QTc) modeling as a substitute for the clinical 'Thorough QT' (TQT) study**
- **Increase proportion of TQT negative; nowadays most TQT are negative**
- **Gradual reduction in QT/TdP Adverse Events (AEs) incidence in the FDA Adverse Event Report System (FAERS)***

Mullard, NRDD, 2020; Park *et al.,* Int J Cardiol; 2013; Park *et al.,* BJP 2018; * Pharmapendium search 29th September 2020

The Drug Discovery & Development Process

- **Prototypical workflow for a small molecule program**

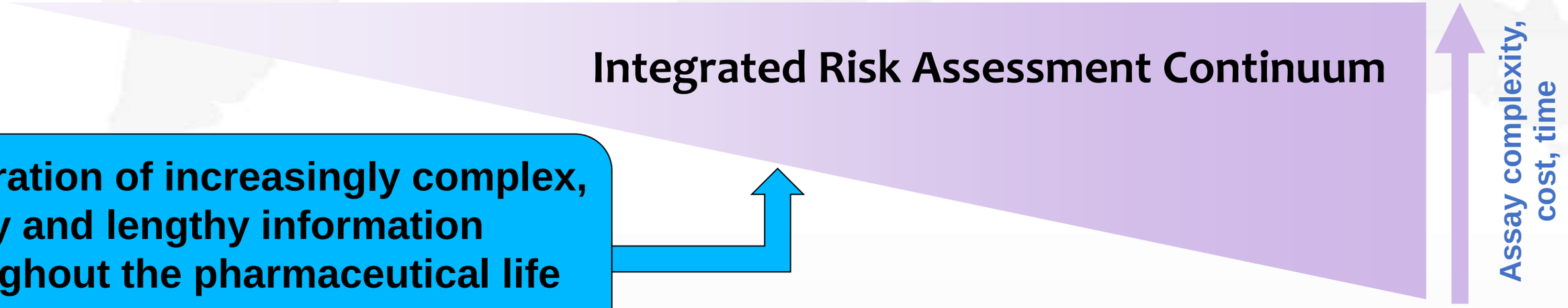


- **Lengthy, costly process with low success rate**

Value Proposition and Anticipated Impact of the New E14/S7B Q&As

- **Use high quality nonclinical data to:**
  - Make better informed decision earlier in drug development
    - By streamlining the drug development process by reducing or eliminating the burden on clinical studies
  - Inform clinical development and reduce the need for dedicated TQT
    - By supplementing phase 1 ECG evaluation when exposure margin is insufficient to waive positive control in concentration-response analysis (E14 Q&A 5.1)
  - Change regulatory decision and labelling
    - By supplementing QT assessment when a specific TQT study cannot be conducted (E14 Q&A 6.1)

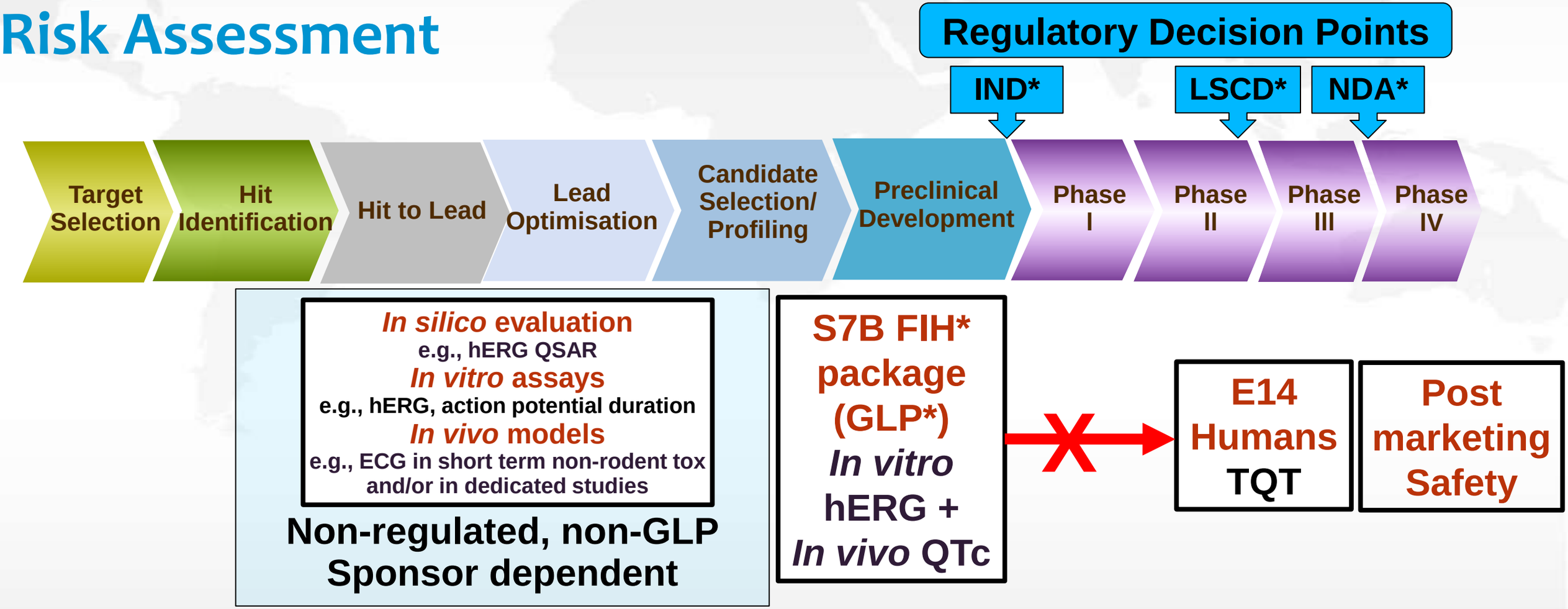
Integrated Risk Assessment (IRA) Concept



Integration of increasingly complex, costly and lengthy information throughout the pharmaceutical life cycle

Benefit / risk concept depending upon disease indication, patient population, standard of care, etc.

Original (Post-2005) Components of a QT (Non) Integrated Risk Assessment

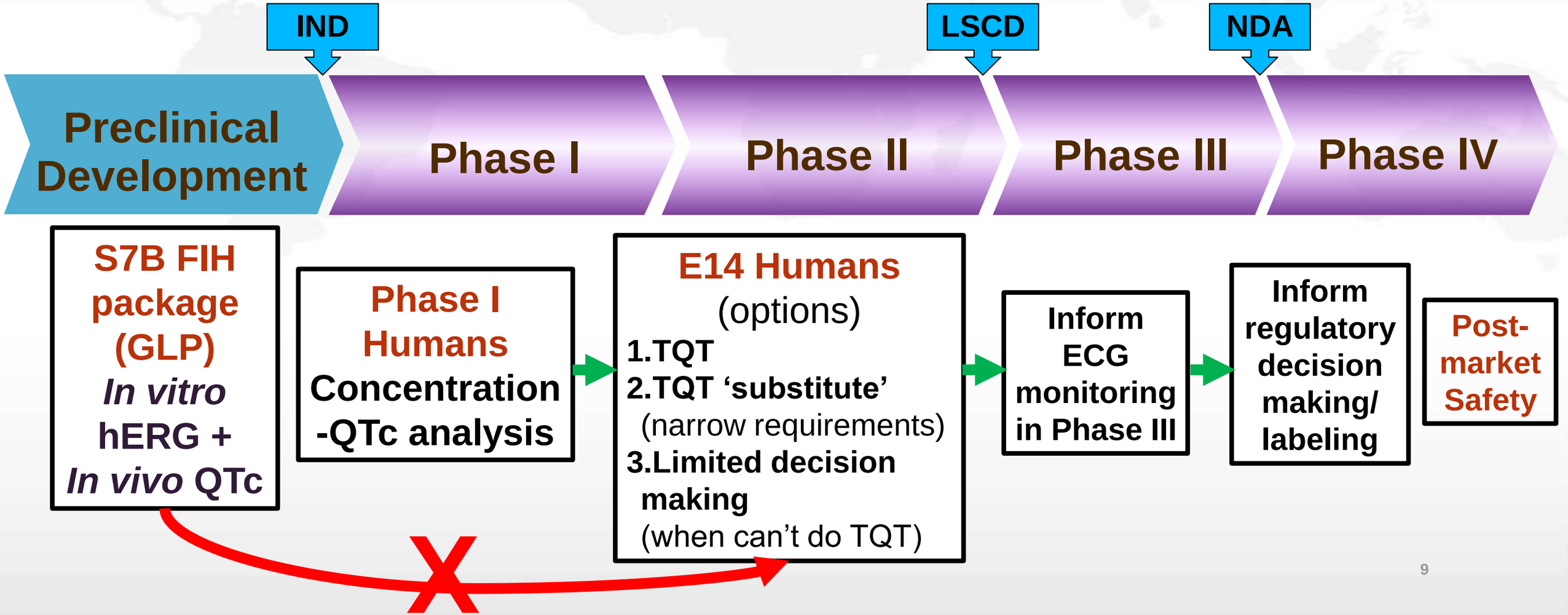


Abbreviations: FIH - First In Human; GLP - Good Laboratory Practice; IND - Investigational New Drug; LSCD - Late Stage Clinical Development; NDA - New Drug Application or equivalent in non-US regions

Original (Post-2005) Components of a QT (Non) Integrated Risk Assessment

- **Regulatory decision points are fixed in time relative to clinical development phases**
- **Originally S7B and E14 information not explicitly linked and not considered as part of a nonclinical-clinical IRA but they were also largely focused on different regulatory decision points**
- **Goal of the new Q&As: To inform on delayed ventricular repolarization, QTc prolongation and TdP risk in early and late clinical development, based on the totality of evidence**

Current (Post-2015) Components of a QT (Non) Integrated Risk Assessment



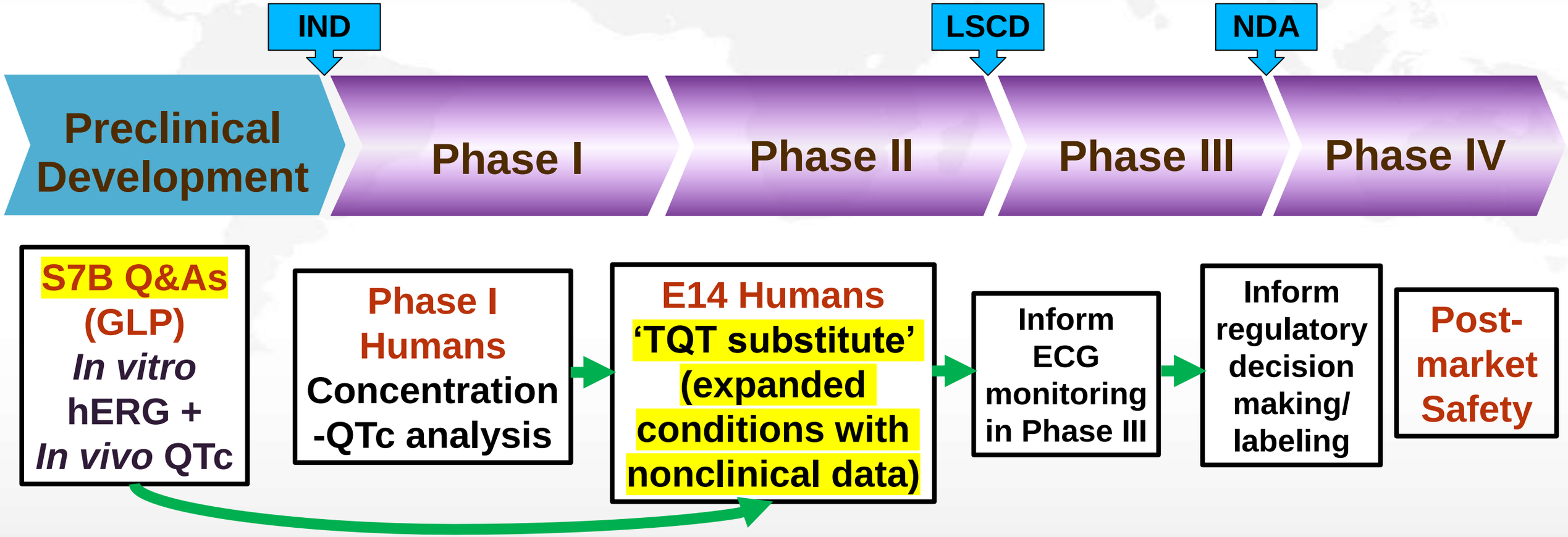
Current (Post-2015) Components of a QT (Non) Integrated Risk Assessment

- **Phase 1 concentration QTc analysis to enable for a TQT 'substitute'; although under strict conditions with narrow requirements.**
- **However, nonclinical (S7B) and clinical (Concentration QTc analysis, E14) information still not explicitly considered as part of an nonclinical-clinical integrated risk assessment**

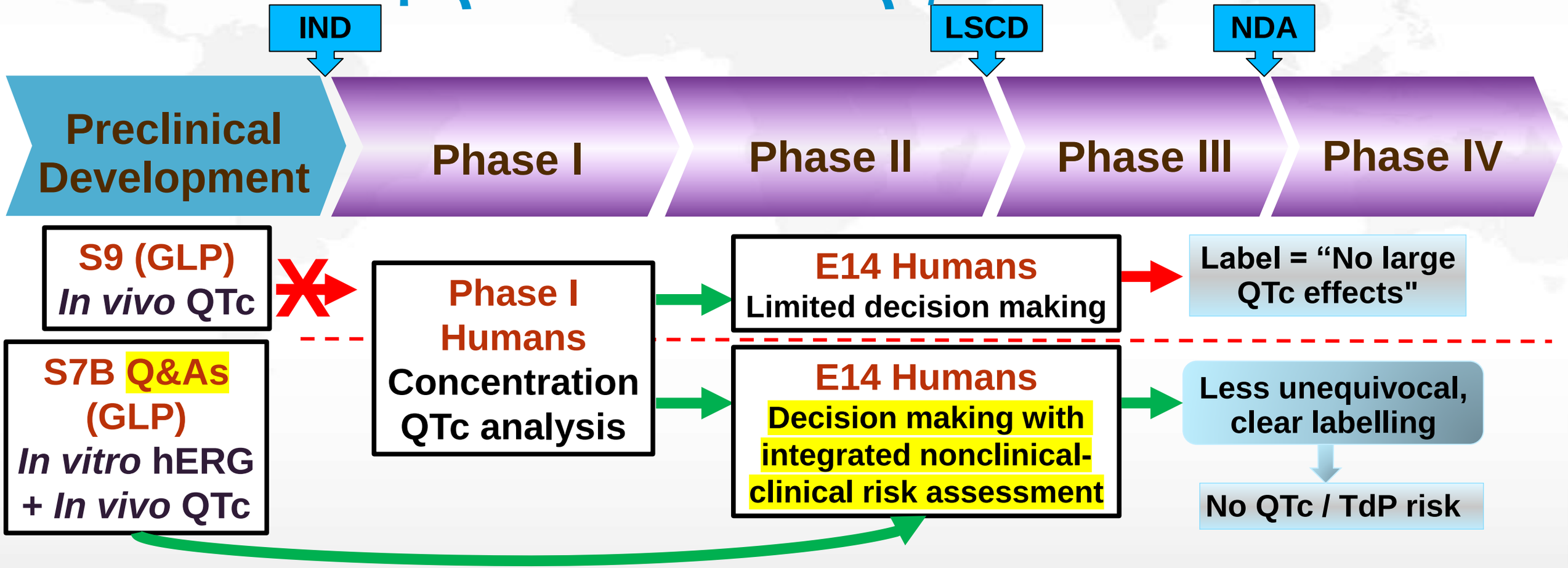
Operationalizing the Proposed ICH E14/S7B Q&As

- **Q&As concept paper states:**
  - "Considering the impact of these 'nonclinical' recommendations on clinical situations where current E14 methodology is problematic.
  - For example, clinical QT assessments that are confounded by issues such as heart rate changes, inability to test a supratherapeutic concentration, and absence of a placebo group, etc."
- **Use of an integrated nonclinical-clinical risk assessment to impact clinical ECG monitoring under:**
  - Q&A 5.1 => i.e. use of clinical Conc-QTc modeling when maximum therapeutic exposure has not been fully covered clinically
  - Q&A 6.1 => i.e. under scenarios where a placebo-controlled comparison is not possible (e.g., Oncology)
  - *Potentially other circumstances, Yet To Be Defined => e.g., low systemic exposure drugs; highly selective drugs*

Components of a QT/TdP Fully Integrated Risk Assessment Under New E14 Q&A 5.1 with Supporting Nonclinical Data



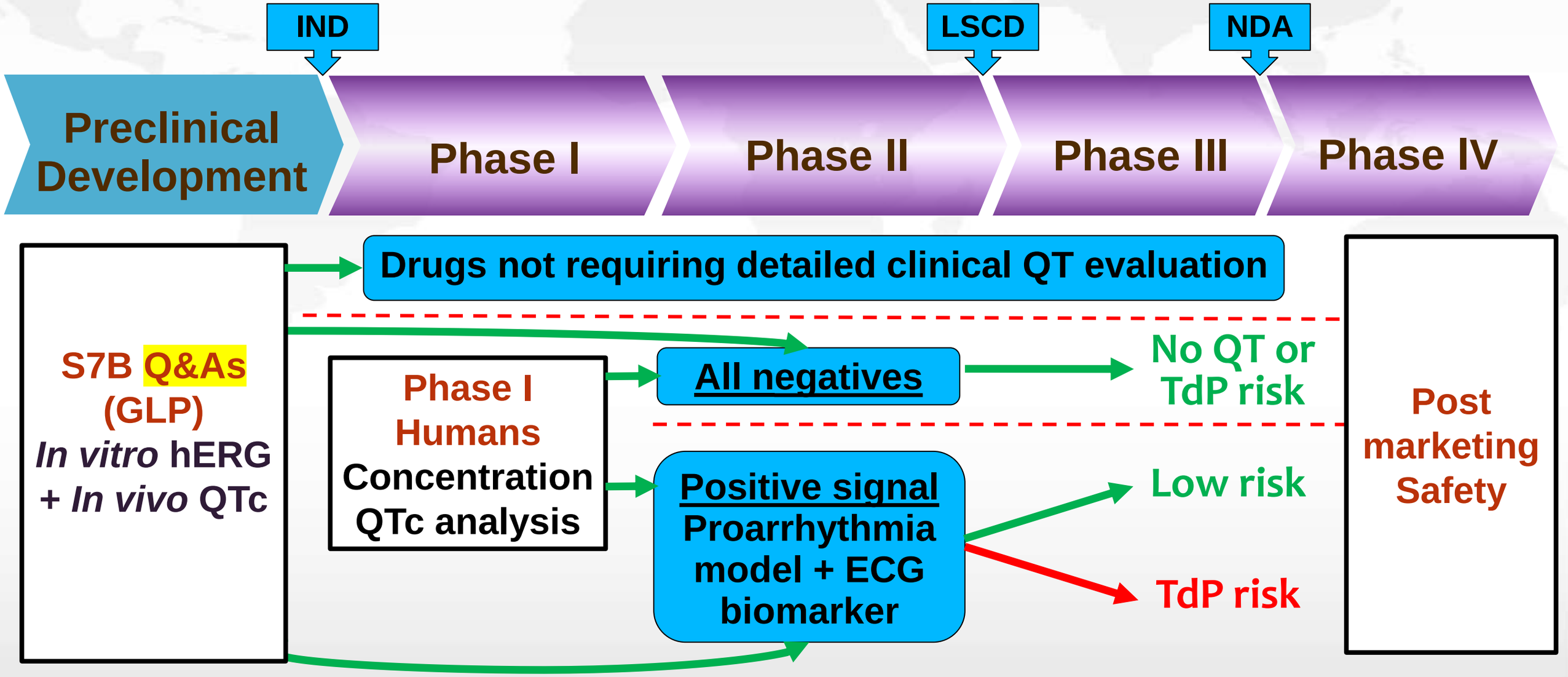
Components of a QT/TdP Fully Integrated Risk Assessment under New E14 Q&A 6.1 When TQT/Substitute Not Possible



Proposed Components of a QT Fully Integrated Risk Assessment

- **'Current' S7B remains adequate to support First In Humans Regulatory Decision Point (i.e., initial IND submission)**
- **S7B Q&As to offer an opportunity to further reduce clinical QT/QTc monitoring under certain circumstances based on the totality of evidence under**
  - Q&A 5.1 to use double-negative nonclinical data to supplement phase 1 ECG evaluation when exposure margin is insufficient
    => Reduce TQT clinical studies
  - Q&A 6.1 to supplement QT assessment when a specific study cannot be conducted
    => Change regulatory decision making and labeling

QT Integrated Risk Assessment – Future State ?



QT Integrated Risk Assessment – Future State ?

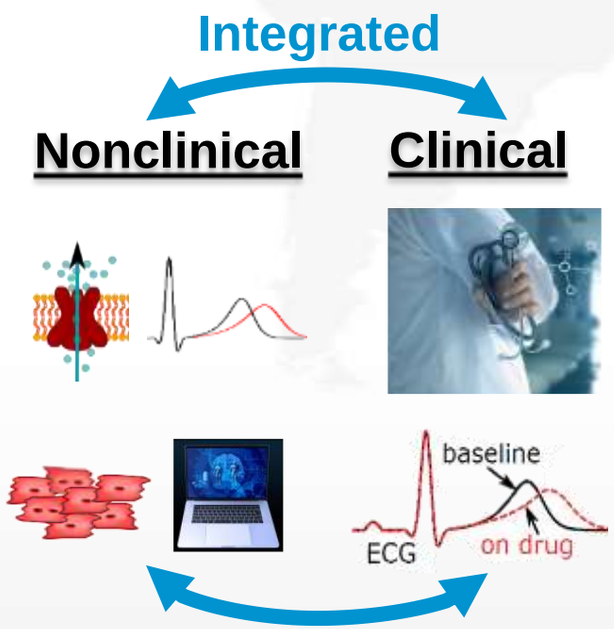
- **Can low risk drugs that might not require detailed clinical QT assessment be defined ?**
- **Can nonclinical-clinical QT/TdP integrated risk assessment be further optimized for other scenarios ?**
- **Can we refine the use, impact of proarrhythmia models and ECG biomarkers data to inform decision making and labelling for QT prolonging drugs ?**

Summary

- **The regulatory decision points are fixed in time relative to clinical development phases**
- **Originally, S7B and E14 information not explicitly linked and not considered as part of a nonclinical-clinical integrated risk assessment but they were also largely focused on different regulatory decision points**
- **The 2015 Q&As conc-QTc and now the 2020 Q&As do offer opportunities to make data collection and integration more efficient, focused and impactful**
- **Alternative development pathways exist for mAbs and oncology agents**
  - Q&A 6.1 provides option for oncology to reduce clinical burden and impact label
  - Could the mAbs approach be expanded to other modalities?

Day 1 Schedule

E14 Scenarios and Integrated Risk Assessment



- ✓ **Background, Motivation for and Overview of the New Q&As for ICH E14 and S7B**
  - ✓ **David Strauss, *FDA, United States***
- ✓ **Revised E14 Q&As and Presentation of Examples to Highlight the Impact of Nonclinical Data on Clinical Development and Interpretation**
  - ✓ **Christine Garnett, *FDA, United States***
- ✓ **S7B Integrated Risk Assessment Q&As**
  - ✓ **Zhihua Li, *FDA, United States***
- ✓ **Considerations for an Integrated Nonclinical-Clinical Risk Assessment**
  - ✓ **Jean-Pierre Valentin, *EFPIA***
- ➢ ***Discussion of Questions Received from the Q&A Pod***
  - **Facilitators: David Strauss, *FDA, United States* and Derek Leishman, *PhRMA***
  - **All Speakers and Flora Musuamba, *EC, Europe*; Colette Strnadova, *Health Canada, Canada*; Charles Benson, *EFPIA***

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Thank you!

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