EU Variations system

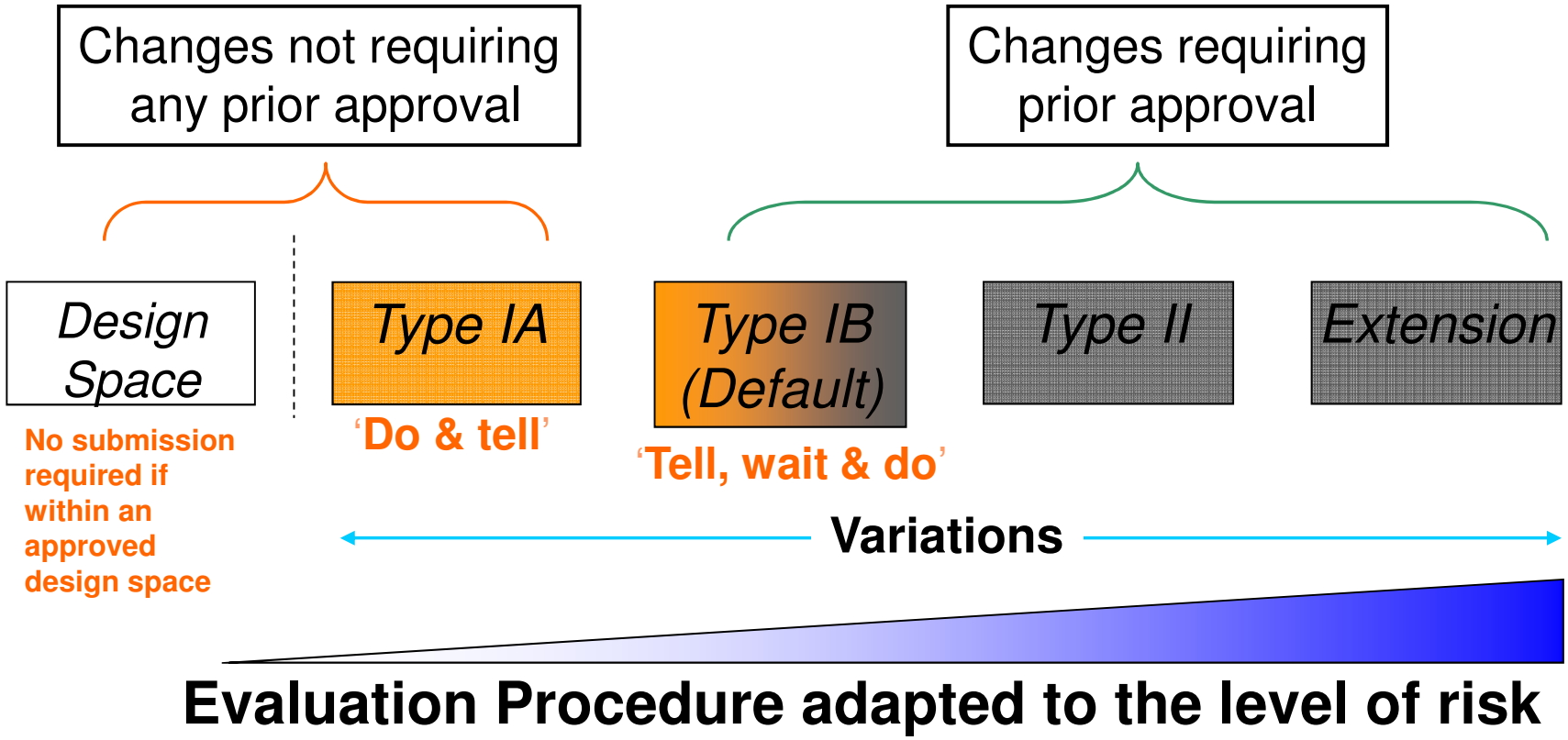
EU legislation (Regulation)

- Changes already classified on a risk based basis (underpinned by a very detailed classification guideline)

- Additional flexibility – Post Approval Change Management Protocol (PACMP)
  - justify downgrading in type of required variation
  - no restrictions to the nature of changes
  - limit (Type IB) regarding level of downgrading for biopharmaceutical products.

EU Variations System

Summary - Types of Variations



Design Space

B.II.g) *Design Space and post approval change management protocol*

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures		1, 2, 3	II
b) Test procedures for excipients/intermediates and/or the finished product.		1, 2, 3	II

Documentation

1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.

2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

Managing changes related to Design Spaces

Process description – regulatory commitment.

How is a Design Space actually presented in respect of CPPs and nCPPs?

1. How you classify an **extension** of a Design Space (Type II)? – possible interpretation as being only applicable to widening of CPPs.

Changes to nCPPs handled differently (minor changes, possibly Type IA)

Need clear transparency in dossier in respect to CPPs vs nCPPs

2. Use of Post Approval Change Management Protocol (always possible anyway)