Stability data and attribution of retest/shelflife

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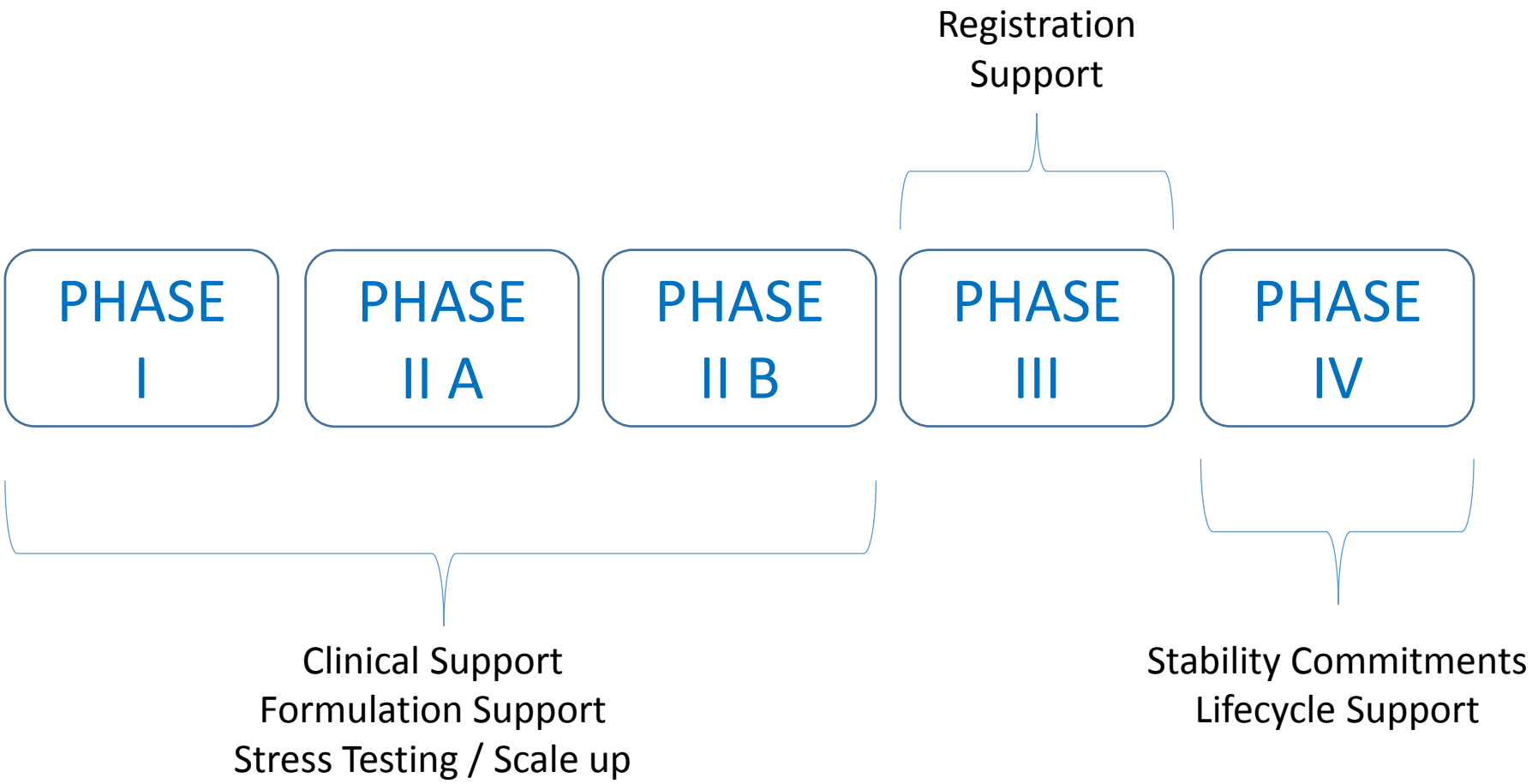
ICH Guidelines

- **Q1A (R2)** – Stability testing of New Drug Substances and Products
- **Q1B** – Stability Testing: Photostability Testing of New Drug Substances and Products
- **Q1C** – Stability Testing for New dosage Forms
- **Q1D** – Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
- **Q1E** – Evaluation of Stability Data
- **Q1F** – Stability Data package for Registration Applications in climatic Zones III and IV

Why do we need stable products ?

Stability Evolution



Stability is defined as :

- **…** resistance to **chemical** change or to **physical** disintegration

  Merriam-Webster

- **…** The capacity of a drug substance or a drug product to **remain within specifications** established to ensure its identity, strength, quality, and purity **throughout the retest period or expiration dating period**, as appropriate.

  FDA

- **…** evidence on how the quality of a drug substance or drug product **varies with time** under the influence of a variety of **environmental factors** such as temperature, humidity, and light, and **to establish a retest period** for the drug substance or a shelf life for the drug product and recommended storage conditions.

  ICH Q1A (R2)

Stability study types

- Long term
  - «normal» target storage conditions
- Intermediate
  - Stability condition which is designed to moderately increase the rate of degradation
- Accelerate
  - Stability condition which can be used as a potential worst case predictive condition for the long term conditions
- Stress testing
  - Intentional degradation by various chemical and non-physical stressing conditions
- Photostability
  - Determination of light impact on the stability of the product

API Stability:
Tests and acceptance criteria

Specifications: test attributes susceptible to change:

- Appearance (description)
- Degradation (related substances)
- Assay
- Enantiomer
- Plus others susceptible to change, e.g. LOD

Methods:

- If same as in API specs, cross-reference
- If different, provide methodology and validation data for impurity and assay methods
- Methods should be stability-indicating

API Stability:

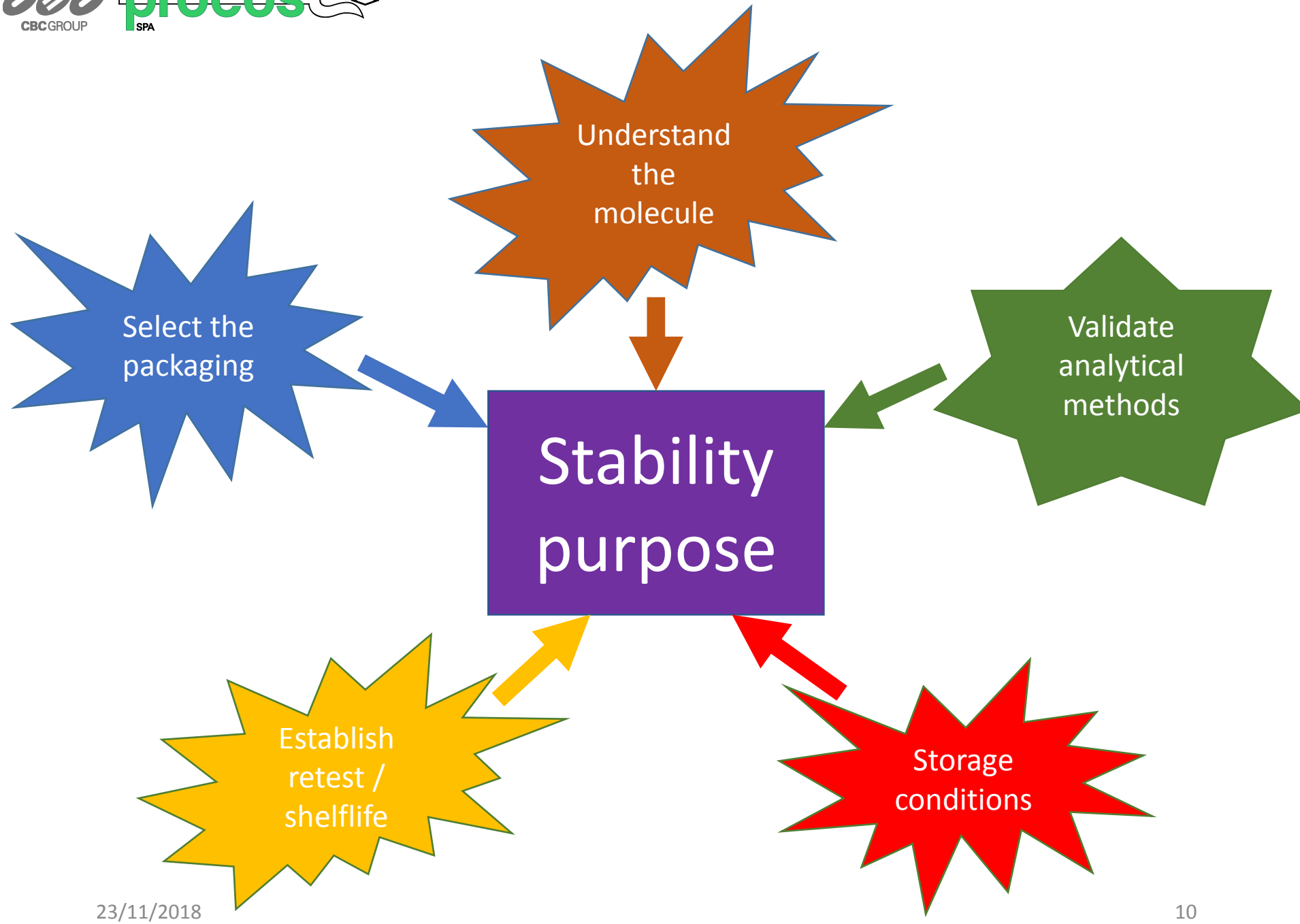
Tests and acceptance criteria

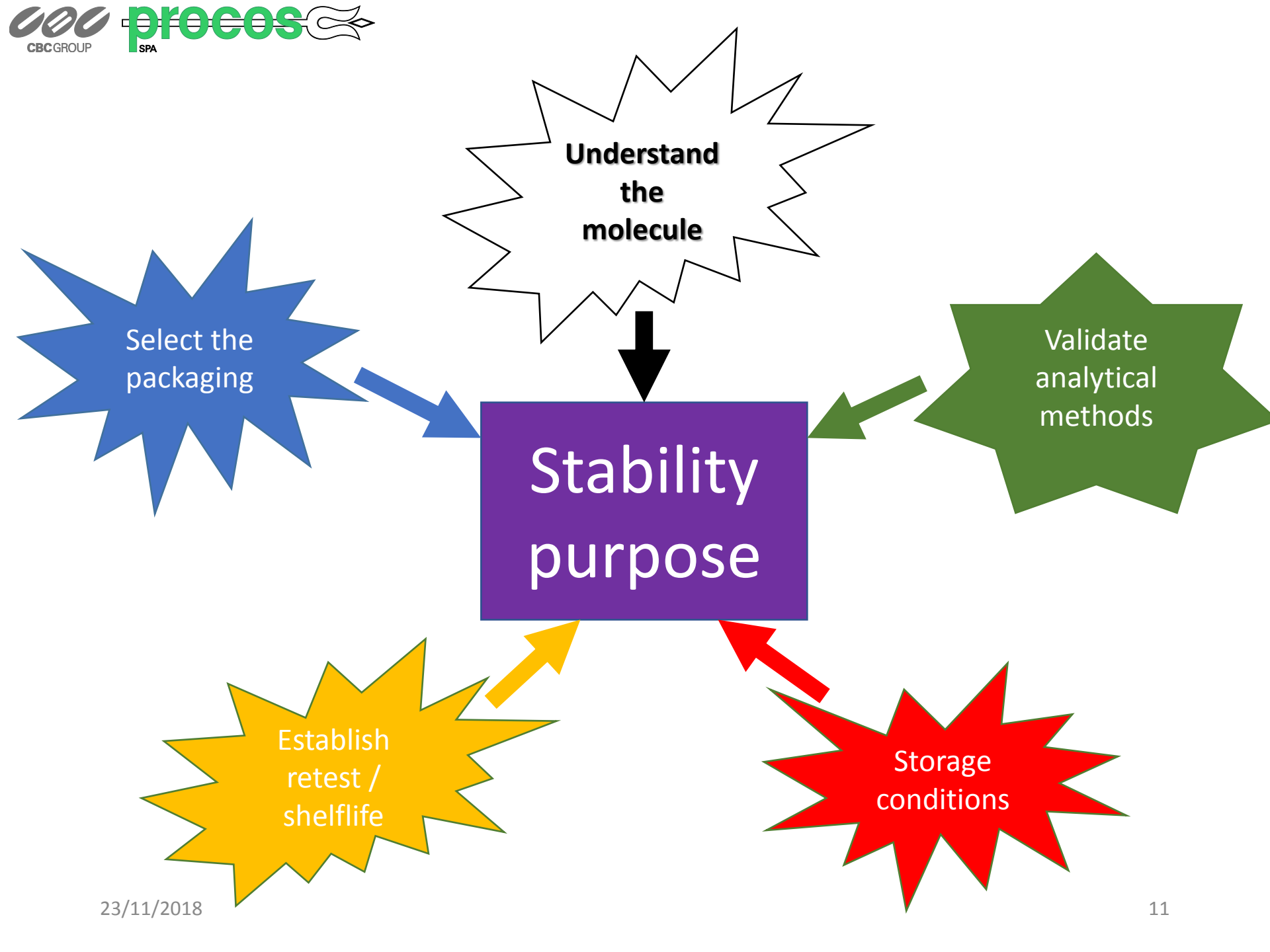
Other parameters to be monitored

- The API has low solubility and micronized, and the FPP is low dose. **PSD i**s critical.

  PSD stability should be monitored for potential increase in particle size (due to discreet particles or particle agglomerates).

- For a low solubility API, if there is evidence that polymorph stability may be an issue, **polymorphic form** should be monitored during stability studies**.**


Understand the molecule
Select the packaging
Validate analytical methods
Stability purpose
Establish retest / shelflife
Storage conditions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Understand the molecule:
Stress Studies

Stability testing under conditions exceeding those used for accelerated testing. Used to:

- establish the inherent stability characteristics of the molecule
- establish the degradation pathways
- identify the likely degradation products
- validate the stability indication power of the analytical methods
- formulation development, manufacturing process development

Stress Studies

Approach for Assessment: DO

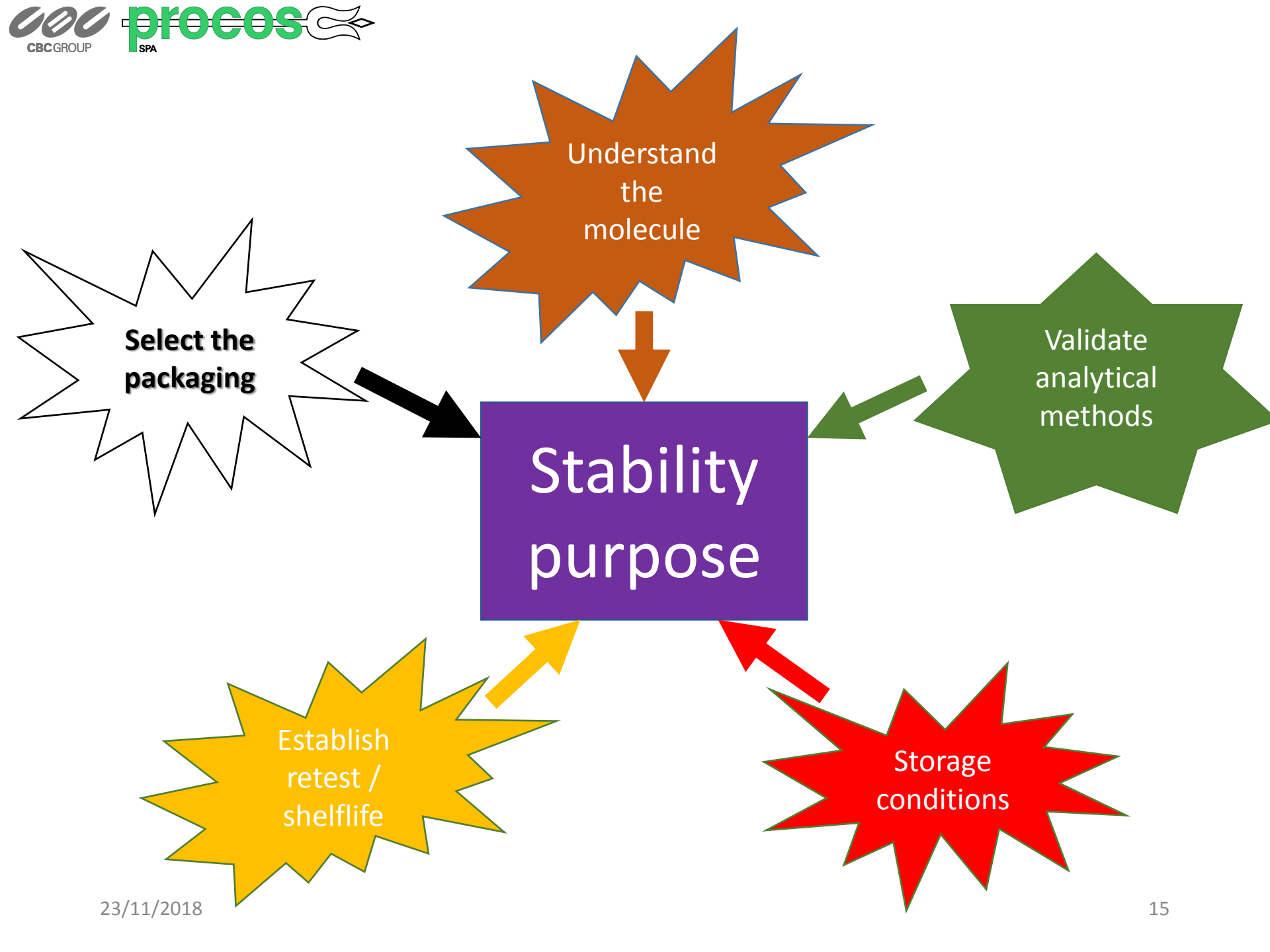
- Check if data is provided, either generated by supplier/applicant or from literature references
- Check compendial statement, e.g “protect from light”.
- Check the extent of degradation
  - ✓≈10% → adequate degradation
  - ✓little or no degradants : verify if conditions are "harsh" enough. If yes, the API is considered stable.
- Conclude on the degradation pathways, stability nature of the API

Stress Studies

Approach for Assessment: DON'T

- Spend excessive time with degradants generated in stress studies if they are not formed in practice

The impurities/degradants that must be closely investigated are those appearing when stored at long-term and accelerated conditions at greater than (or approaching) the identification threshold (the limit of individual unknowns, 0.1%)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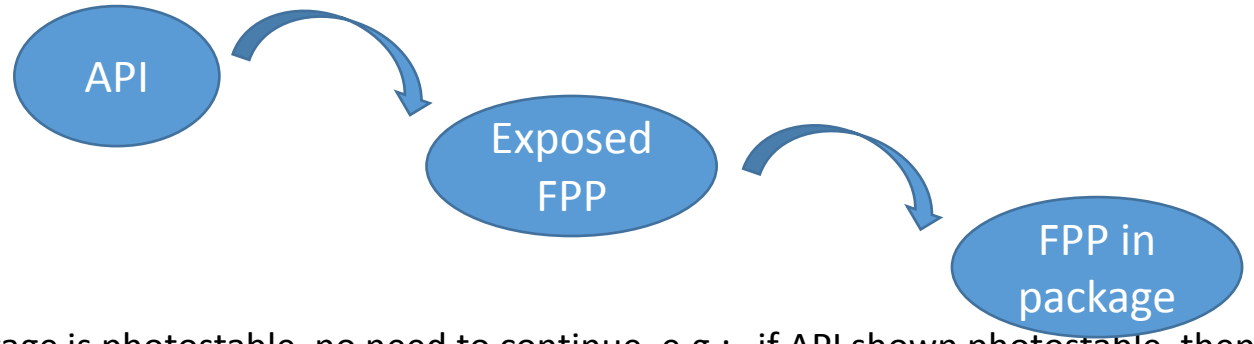
Select packaging:
Photostability Studies

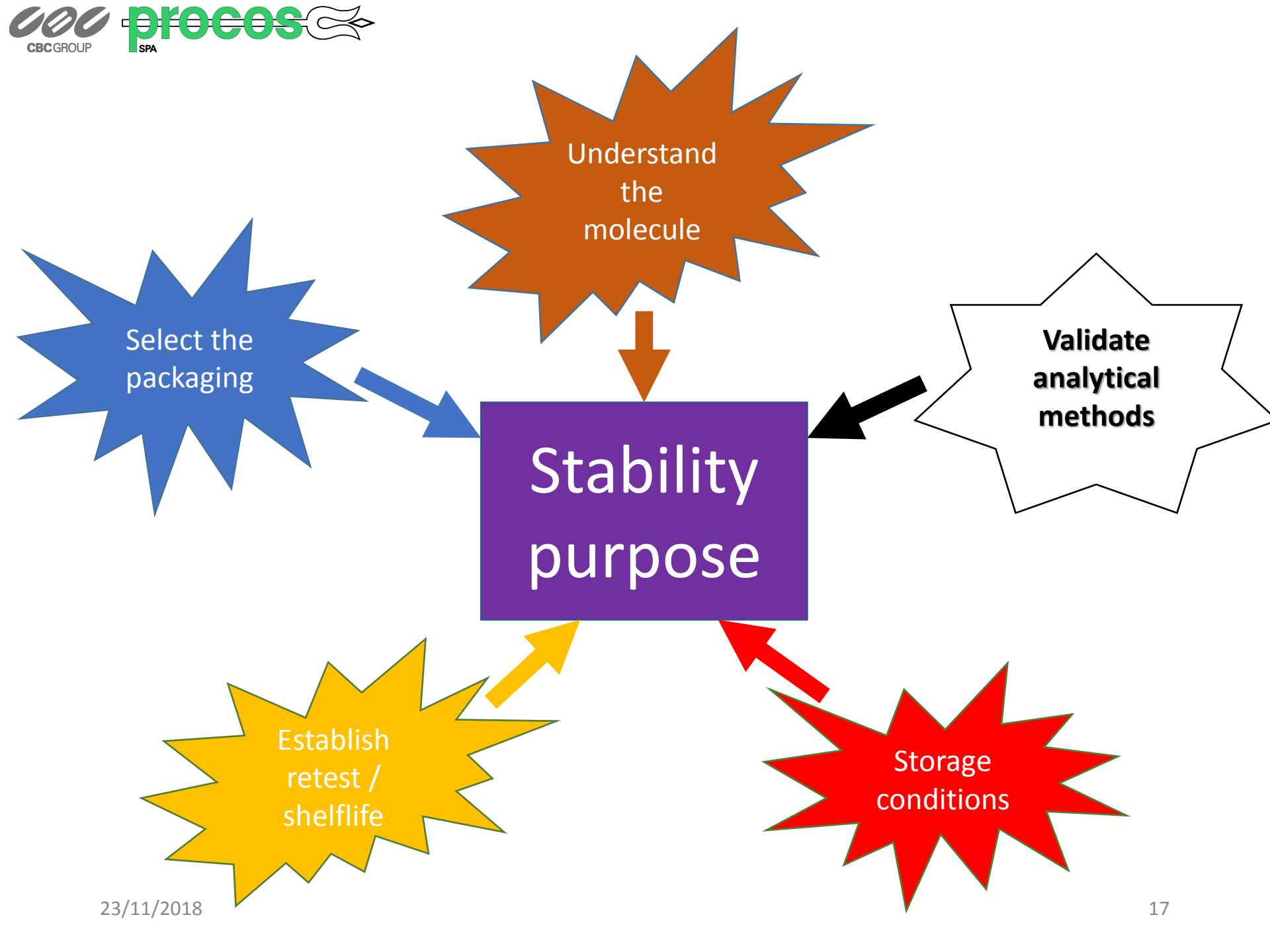
- Photostability Studies should be conducted on at least one primary batch; see ICHQ1B.

Test progressively:



If any stage is photostable, no need to continue, e.g.: if API shown photostable, then FPP testing is not necessary

Either photostability should be demonstrated or light protection of packaging demonstrated (light transmission data, e.g. USP <661>)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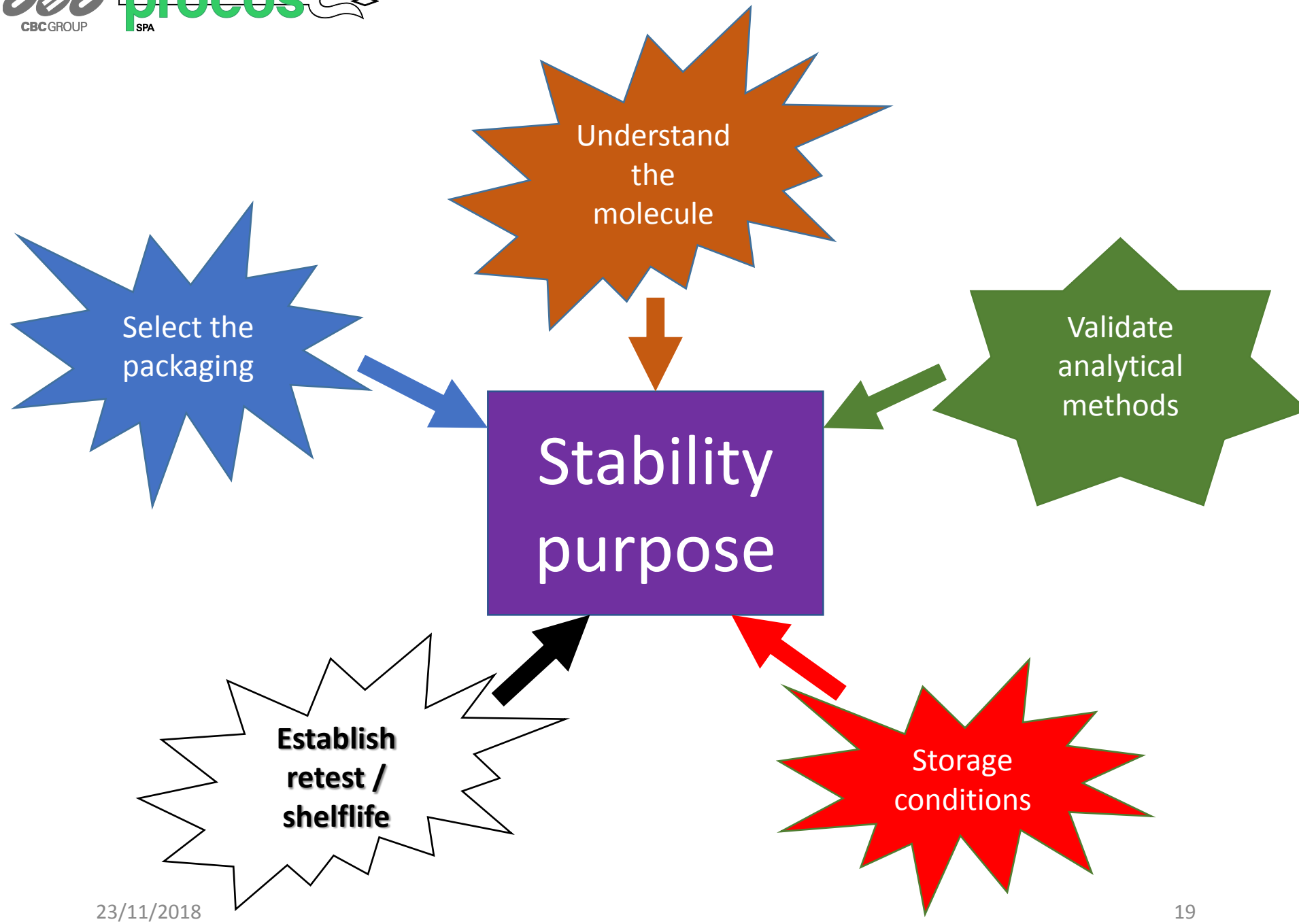
Validate analytical methods:
Stability indicating method

- This is a chicken and egg problem
  - need analytical methods to analyze stability data
  - need stability information to validate methods
- Start with preliminary method based on what is known of drug substance
  - can determine content of drug substance, can separate the known or expected degradants
- Use preliminary method to analyze stress stability studies
  - evaluate ability of method to separate degradants i.e the specificity --confirm peak purity, mass balance
- Use this information to modify/improve method
- Stability studies and analytical method development work together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Established retest period:
Extrapolation

Extrapolation: Extend the retest period or shelf life beyond the period covered by available long-term stability data

- A retest period or shelf life granted on the basis of extrapolation should always be verified by additional long-term stability data as soon as these data become available (commitments).
- Extrapolation is guided by the flow chart in the guideline

Established shelflife acceptance criteria

Summary of the stability results

Example: 40°C±2°C/75%±5%RH, 6 Months. 202357, 203089, 203763

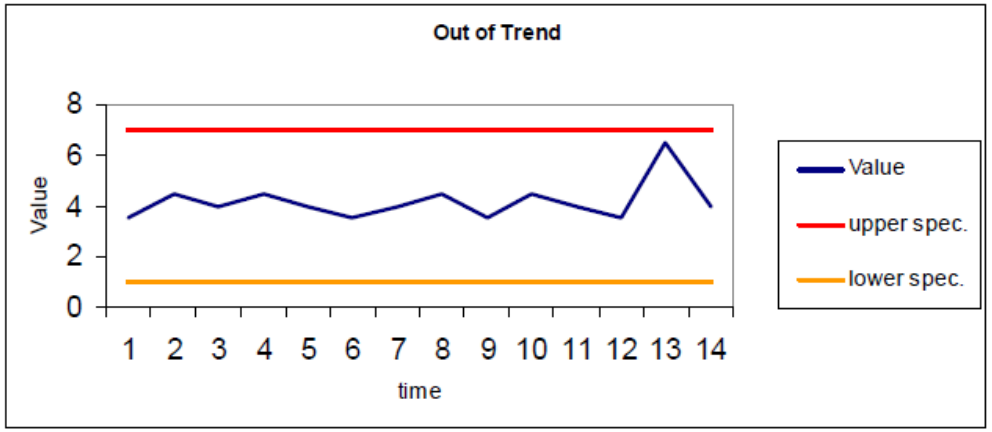
Test	Results
Description (…)	Meets specification
Moisture (NMT 0.5%)	**State range of values or highest value, trend** 0.1-0.48%, slight increasing trend. For batch 203089, 0.48% at 6 Month.
Impurities Imp A: NMT 0.5% Imp B: NMT 0.3% Any unkown individual: NMT 0.2% Total imps: NMT 1.5%	**State range of values or highest value, trend (**for quantitative methods**)** Imp A: 0.08 % to 0.32%, increasing trend Imp B: Up to 0.23%, no trend Any unknown indi: up to 0.11% , no trend Total imps: 0.34%- 0.82%, increasing trend
Assay (90.0%-110.0%)	**State range of values or lowest value, trend** 97.8-100.2%, no trend

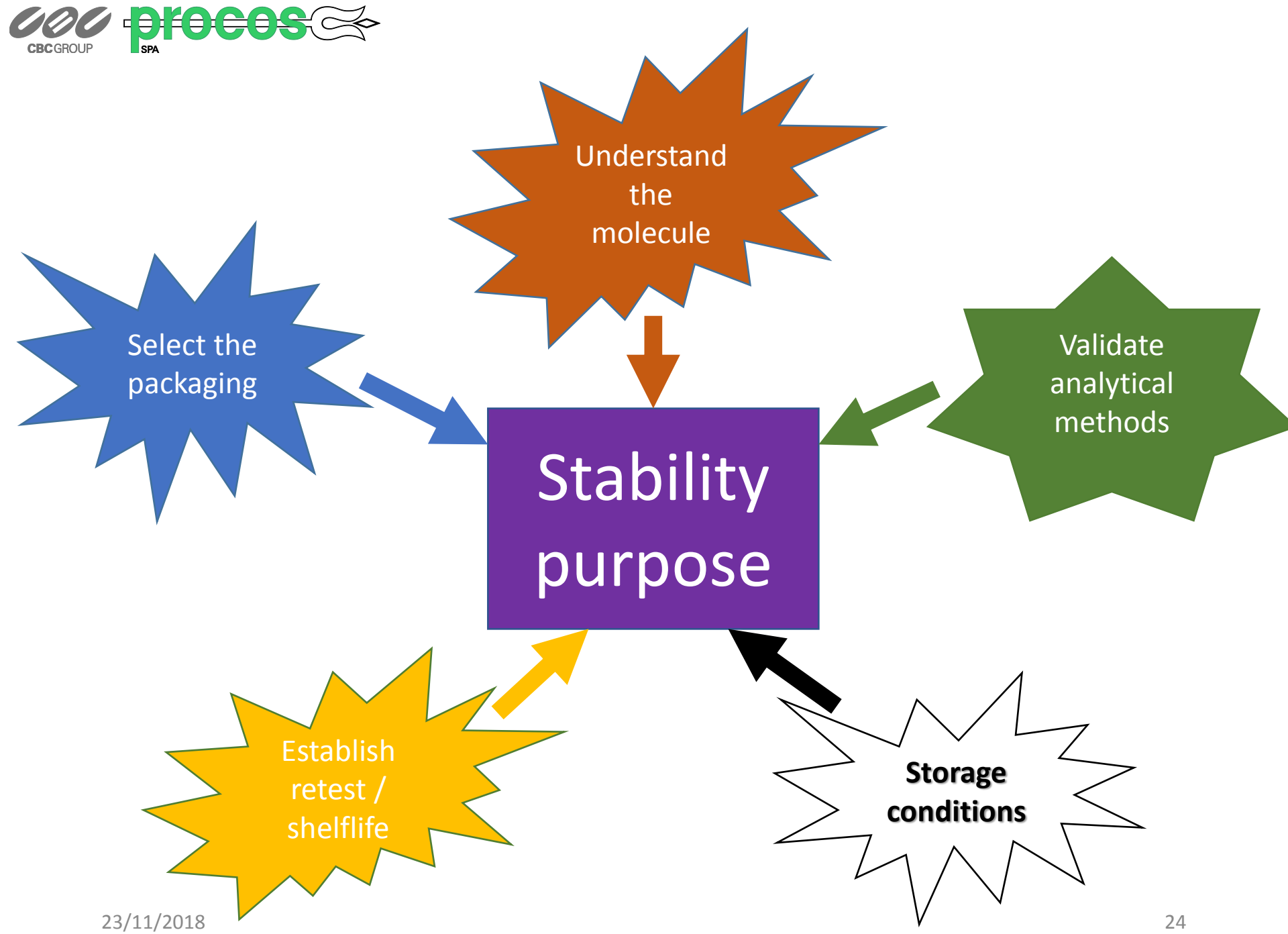
Note: When summarizing, the limits should be included in the stability summary

Established shelflife acceptance criteria

Trends, Significant changes, OOS

- Variation: means you won't usually have a perfect linear trend (analytical variability, sample uniformity)
- Trends: if the majority of stations show a trend (downward, upward), consider it a trend.
- OOT: analytical value outside our experience but within the specification (no OOS)
- OOS: analytical value outside of the registered specification

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Established API Storage conditions:
Statements/Labelling

Recommended labelling statements for active pharmaceutical ingredients (APIs)

Testing condition under which the stability of the API has been demonstrated	Recommended labelling statement[a]
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure of accelerated)	"Do not store above 25 °C"[b]
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"[b]
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

b :"protect from moisture" should be added if applicable

Holding time Studies

Summary of acceptable holding times

A **maximum processing time** of one month (30 days) is acceptable without validation. (industry standard)

Any **holding time** for an intermediate or the bulk product >30 days must be supported by stability studies.

Example #1

Data are provided over the retest period at long-term conditions.

Data at accelerated conditions are not available.

- The applicant states that accelerated data are not necessary because long-term data cover the whole proposed retest period.

Is it acceptable?

- **Answer:**

✓ Accelerated data are not only to support extrapolation, they are also to cover excursions outside the long-term storage conditions.

✓ Accelerated data are always required to support a retest or shelf-life period

Example #2

Data are provided for 12 months at 30◦C/75% and 6 months at 40◦C/75%.

- No significant change is noted.
- No/little change and variability.
- How long could shelf life be granted?

- **Answer:**

✓ A provisional shelf-life of 24 months (12 months + 12 months) can be assigned.

✓ Storage statement “Do not store above 30◦C”.

✓ Commitment to continue the stability study should be provided

Example #3

Data are provided for 18 months at 30◦C/75% and 6 months at 40◦C/75%.

- Significant change is noted at 40◦C/75% at 6 months time point.
- Data at 30◦C/75% are in compliance with the specification without significant trends.
- There is no intermediate storage condition (i.e. 30◦C/65%).

How long could shelf life be granted?

- **Answer:**

✓ A shelf-life of 18 months can be assigned. The shelf-life is based on real time data due to significant change observed at accelerated conditions.

✓ Storage statement “Do not store above 30◦C”.

✓ Commitment to charge additional batches to stability studies


➢API Stability is
➢A large concept including many tools
➢Science-based approach supported by a Regulatory framework
➢Knowledge to prevent failures

Thank you very much

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