mRNA Therapeutics: Last Chance for Platform Methods?

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Joining Forces to Advance the Quality of mRNA Therapeutics

4/23/2025

mRNA technology as broad toolkit

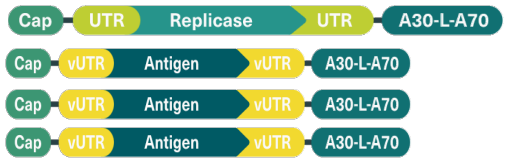
Multiple mRNA formats

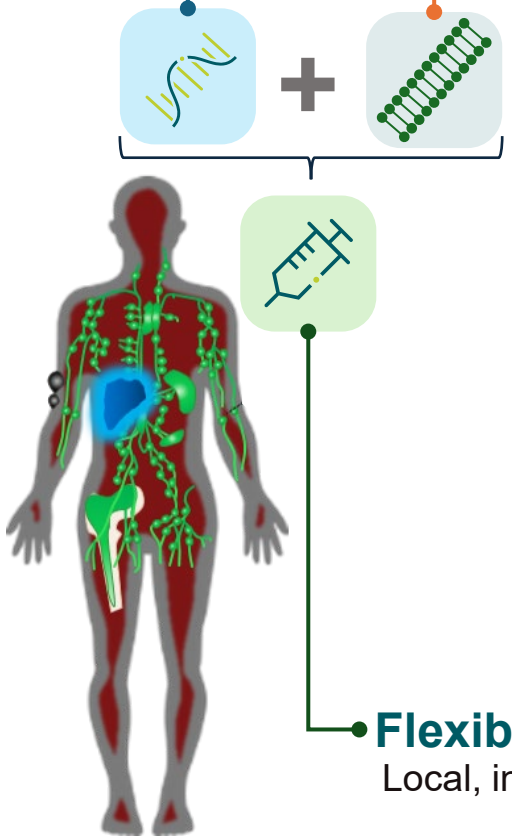
Backbone-optimized
uridine mRNA (uRNA)

Backbone-optimized
nucleoside-modified mRNA (modRNA)

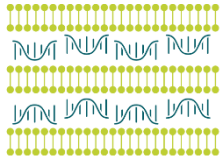
Self-amplifying mRNA (saRNA)

Trans-amplifying mRNA (taRNA)

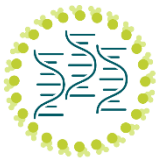




Delivery formulations



Lipoplex (LPX)



Lipid nanoparticles (LNP)

Polyplexes

Flexible delivery routes

Local, intratumoral, tissue-specific, or systemic

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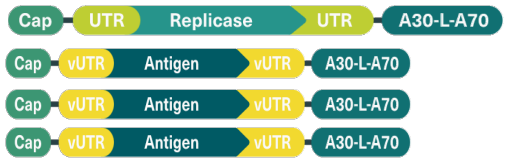

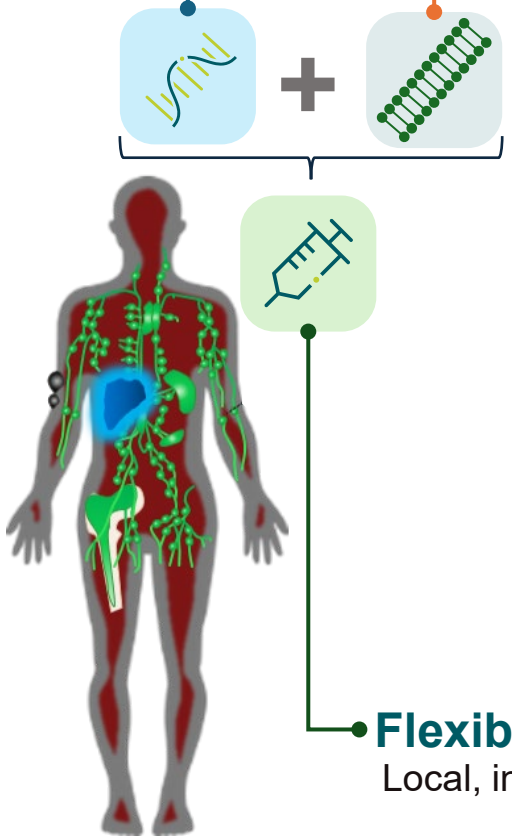

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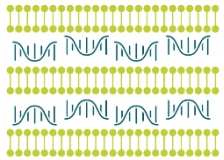

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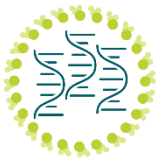

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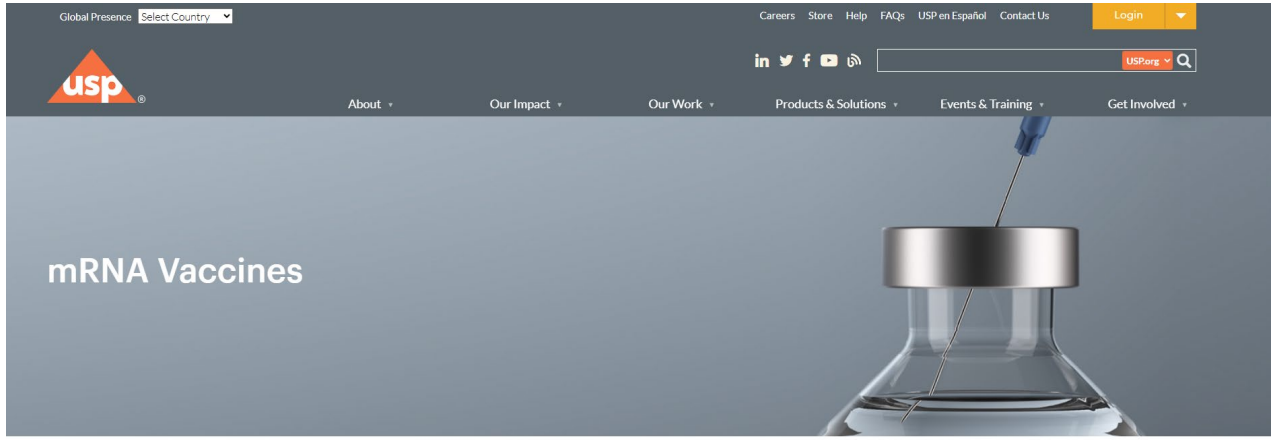
Each mRNA format is optimized for specific applications

Advances in mRNA guidelines



Public consultation on new general texts on mRNA vaccines in Pharmeuropa 36.2

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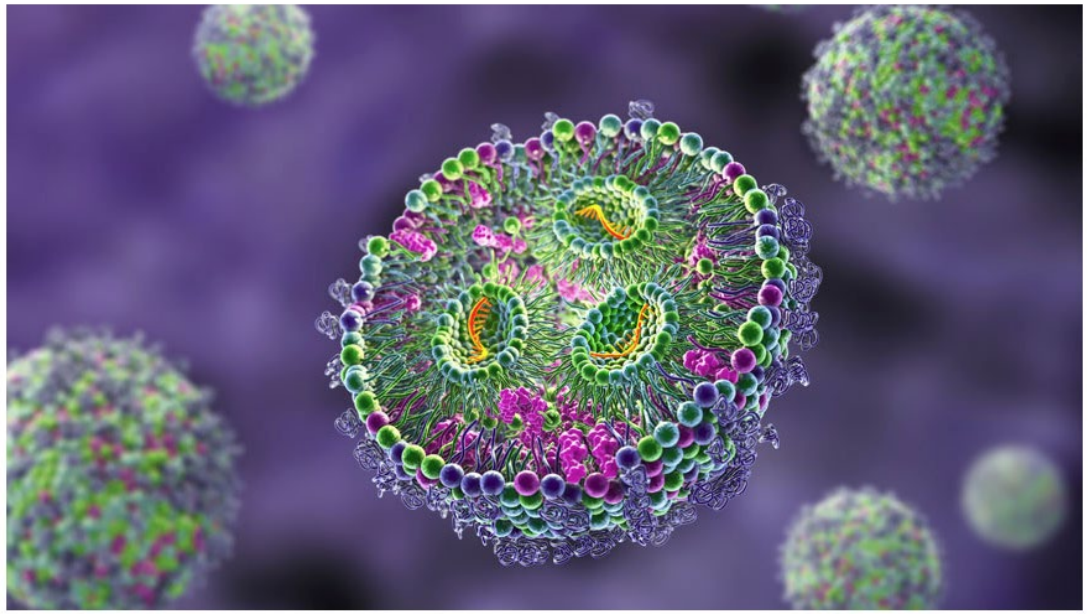

The success of mRNA technology in the vaccine space, has triggered ongoing efforts of developments in regulatory guidelines and industry standards. In response to this emerging field, initiatives have been launched by both the United States Pharmacopeia (USP)[1] and the European Pharmacopoeia (Ph. Eur.)[2].

[1]https://www.usp.org/mrna, visited 11th of February
[2]https://www.edqm.eu/en/-/public-consultation-on-new-general-texts-on-mrna-vaccines-in-pharmeuropa-36.2, visited 11th of February

Considerations on the analytical platform concept

The Concept of Platform Analytical Procedures

Definition from ICH Q2 (r2) and USP1220

"A platform analytical procedure can be defined as a multi-product method suitable to test quality attributes of different products without **significant change** to its operational conditions, system suitability and reporting structure. This type of method would apply to **molecules that are sufficiently alike** with respect to the attributes that the platform method is intended to measure."

The concept of platform analytical procedures is addressed in ICH Q2 (R2)[1] guidance as well as ICH Q14[3] guideline and draft USP 1220[2]

[1]https://www.ema.europa.eu/en/ich-q2r2-validation-analytical-procedures-scientific-guideline,visited 11th of February
[2]https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/gc-1220-pre-post-20210924.pdf, visited 11th of February
[3]https://www.ema.europa.eu/en/ich-q14-analytical-procedure-development-scientific-guideline, visited 11th of February

What is new in ICHQ2 (R2), ICHQ14 and draft USP1220?

Knowledge driven validation strategy: Scientific and Risk-based approaches throughout the entire analytical life cycle

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Risk scoring (based on knowledge/data)
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E2E Approach from development to Routine and through subsequent adaptations

Development is key to generate knowledge that can be leveraged in validations and for routine testing
→ Routine testing increases knowledge basis over time

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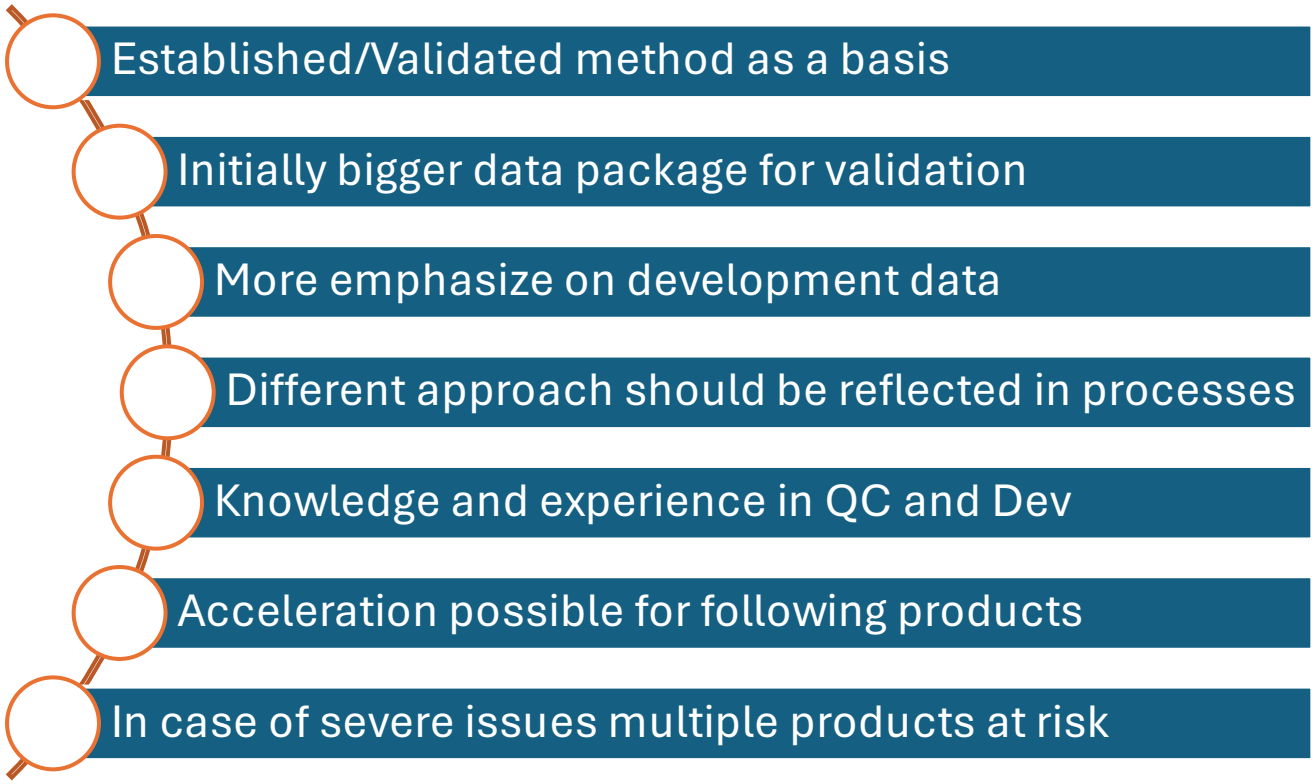
General considerations on platform analytical procedures



Prior knowledge/data

Establishment of the design space

Point to consider for Inspections

E2E approach

Power comes over time → data

Constant knowledge generation - LCM

Development and method understanding

The **class** of mRNA-based products and link to platform

- We define the **class** of mRNA-based products as using exogenous mRNA to express a pharmaceutically active protein
- Each **mRNA platform** within this **class** uses a specific **mRNA format** combined with a certain **formulation**;
  - thus, within each **platform** we would like to use **prior knowledge** gained from our experience using the same type of **mRNA format** and **formulation**;
- In addition, there are some aspects that are common to all **mRNA platforms** and thus apply to the whole **class** of mRNA-based therapeutics and vaccines.

Generic analytical CMC aspects for the **class** of mRNA-based products

All mRNA-based therapeutics and vaccines are chemically similar, and all are manufactured by a cell-free enzymatic process, commonly called *in vitro* transcription, that uses a DNA template, an RNA polymerase and nucleoside triphosphate building blocks; thus, there are some **generic analytical CMC aspects applying to all**; examples include:

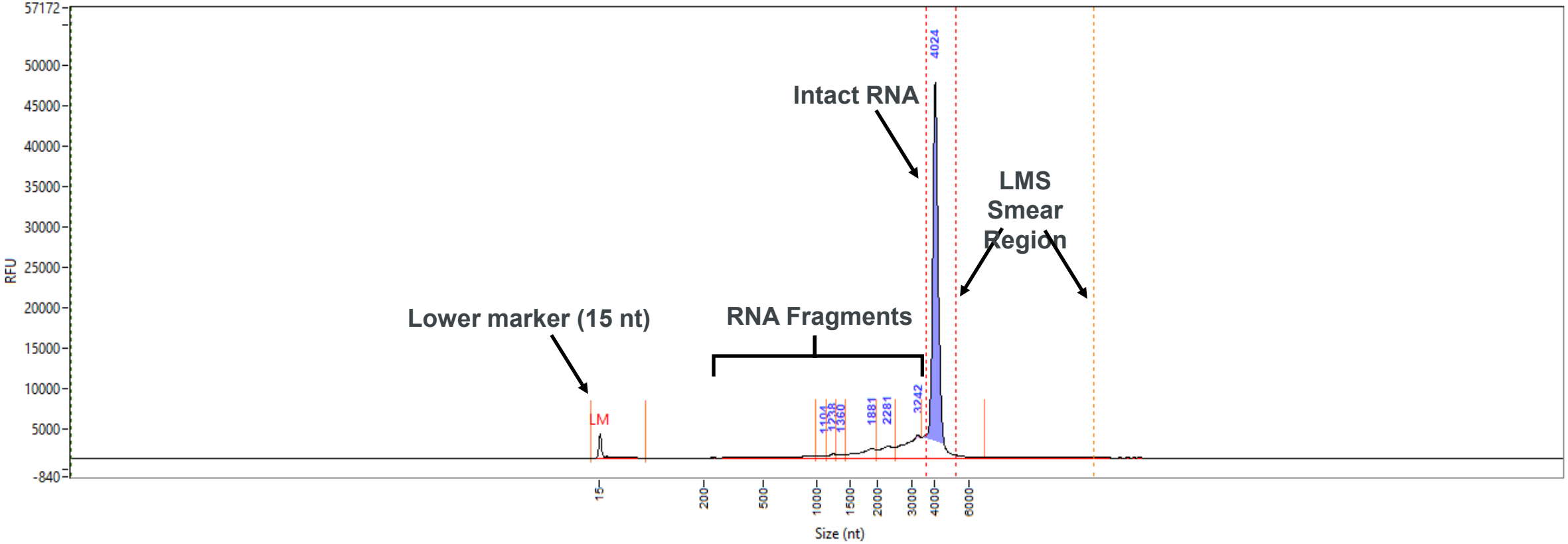
- The **identity of the mRNA**, i.e., its sequence, is defined by the DNA template; this is well documented in the scientific literature and has been verified by BioNTech for all mRNA types used until now → this **prior knowledge** should be considered, e.g., for identity testing
- The **same platform formulations** are used → **prior knowledge** should be considered, e.g., matrix effects and sample preparation for analytical testing
- The **same set of starting and auxiliary materials** is used → this **prior knowledge** should be considered, e.g., for definition of the control strategy, the release panel and ability of analytical methods to detect impurities
- The **main degradation pathway for mRNA** is hydrolysis of the phosphate-ribose backbone; based on BioNTech experience and as published in the scientific literature, this happens within a certain range in a statistical manner per nucleotide and time → this **prior knowledge** should be considered, e.g., for product characterization and with regards to stability indicating methods as well as physicochemical methods

Capillary Electrophoresis (CE) as an Example for a platform analytical procedure

Example for an mRNA platform analytical procedure:

- Method development as well as validation covers the use of **non-modified mRNA** (i.e., containing A, C, G, and U) and **modified mRNA** (i.e., N1-Methyl-Pseudouridine) with different **cap-structures** as well as **5' and 3' UTR** sequences and a **poly(A)-tail** developed for high efficacy as the **mRNA format → mRNA sequence space**
- As of now, this **platform analytical procedure** has been applied for **more than 15 antigens (monovalent and multivalent)**; the corresponding mRNAs range from less than 1000 to up to 5000 nucleotides with a certain variation in the relative sequence composition (ratio of A/C/G/U)
- Essentially the **same platform formulations (LNP or LPX)** are used. Sample preparation may differ based on formulation and concentration. The core of the analytical method remains unchanged **→ mRNA formulation space**
- Thus, this **mRNA analytical platform procedure** applies to the whole **class** of mRNA-based therapeutics including vaccines covered within the **analytical design space** defined during method development and validation.

Exemplary data



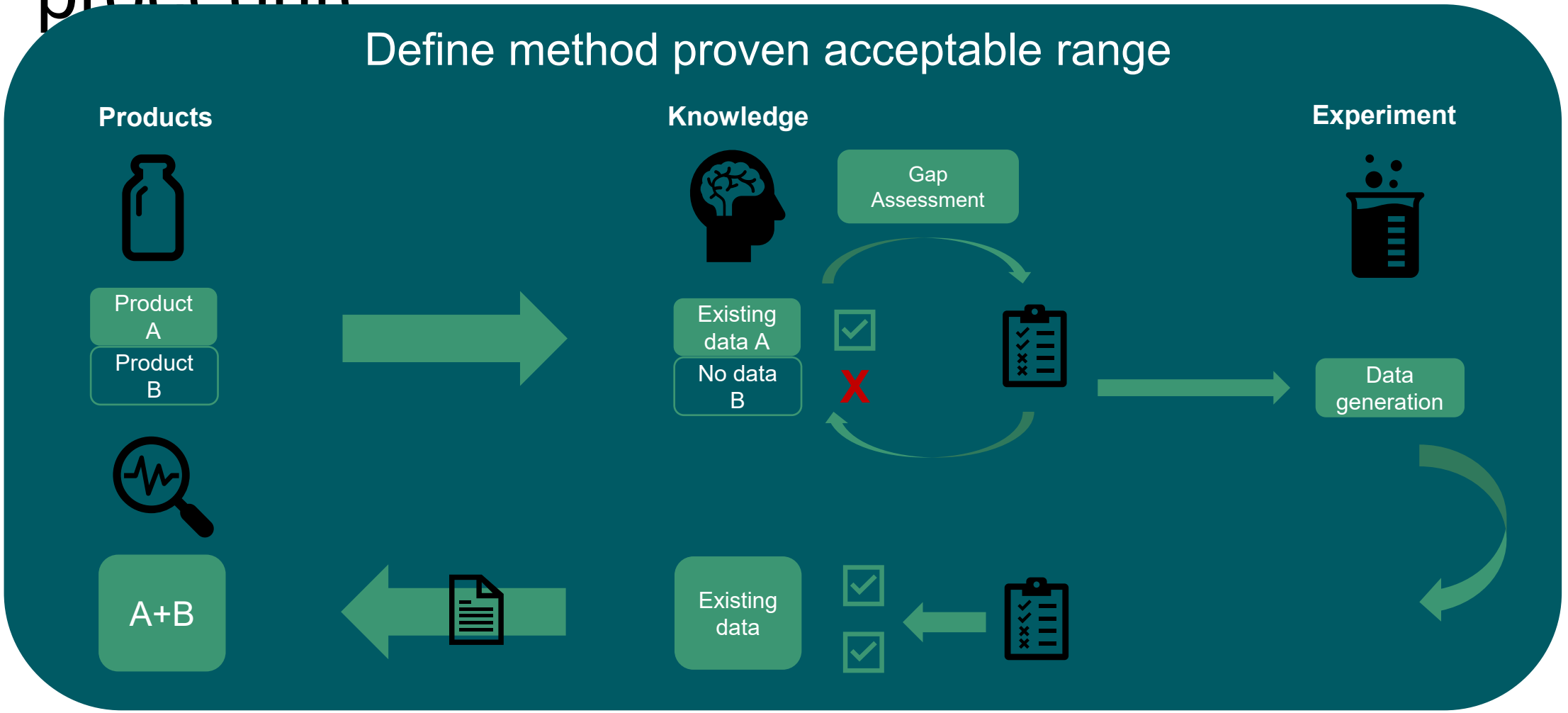
- **RNA fragments**: smaller fragments, fragmented and/or depredated product
- **Main peak:** target mRNA of the product
- **Late Migrating species (LMS):** Aggregates or other impurities that elute after the main peak

Concept for platform analytical procedure validation

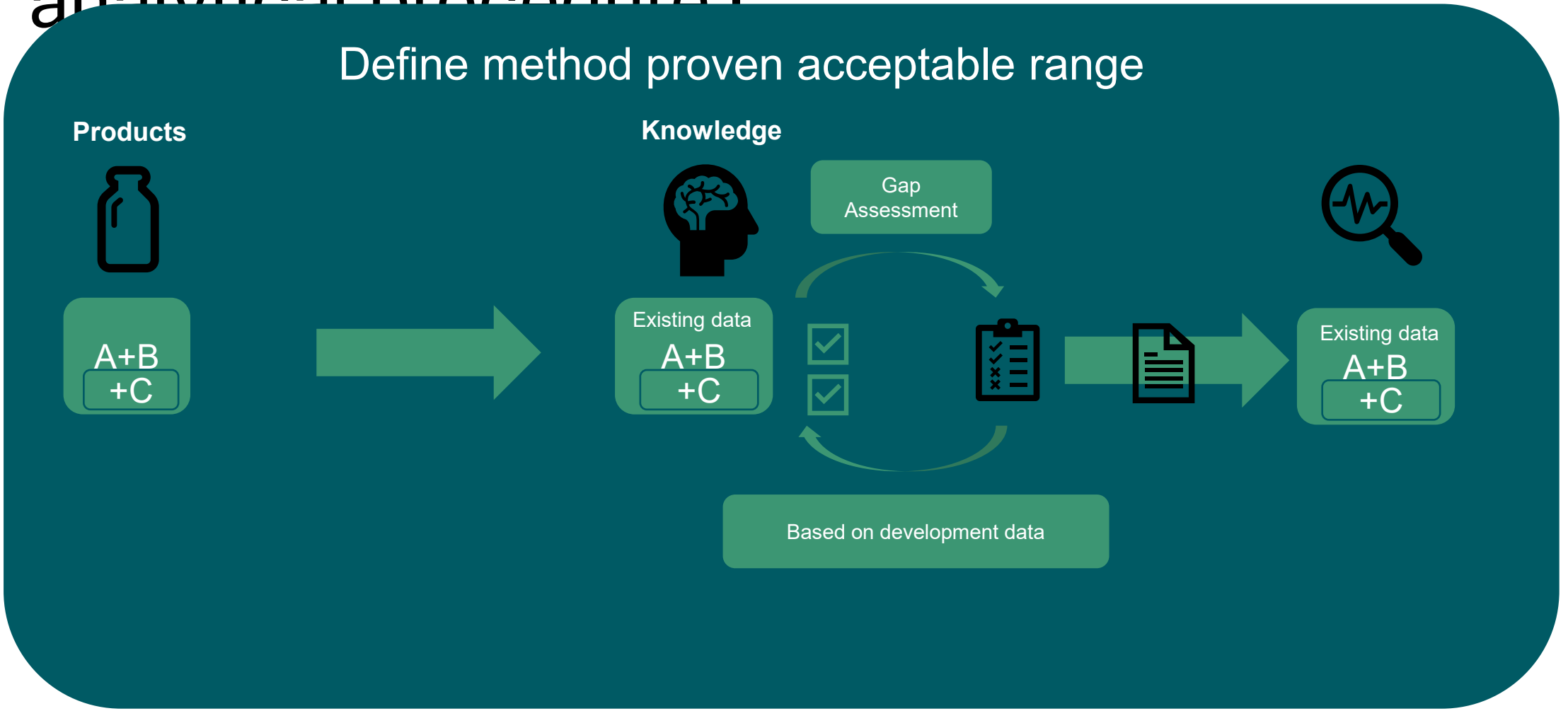
To enable faster analytical development of new candidates **the platform analytical validation** is covering

- ❑ a certain **analytical design space** with the corresponding **mRNA sequence space and formulation space**
- ❑ reduced **platform analytical validation** for new LNP/LPX based mRNA products based on platform analytical data
  - After assessment of the changes and their impact on method performance additional **RNA formats and formulations** could be onboarded with a risked based approach leveraging prior analytical data and experience
  - No significant changes to the core of the **platform analytical procedure** (evaluation/assessment)
  - Define critical validation criteria i.e. Accuracy for different purity and degradation levels - **Existing knowledge** from development can be leveraged

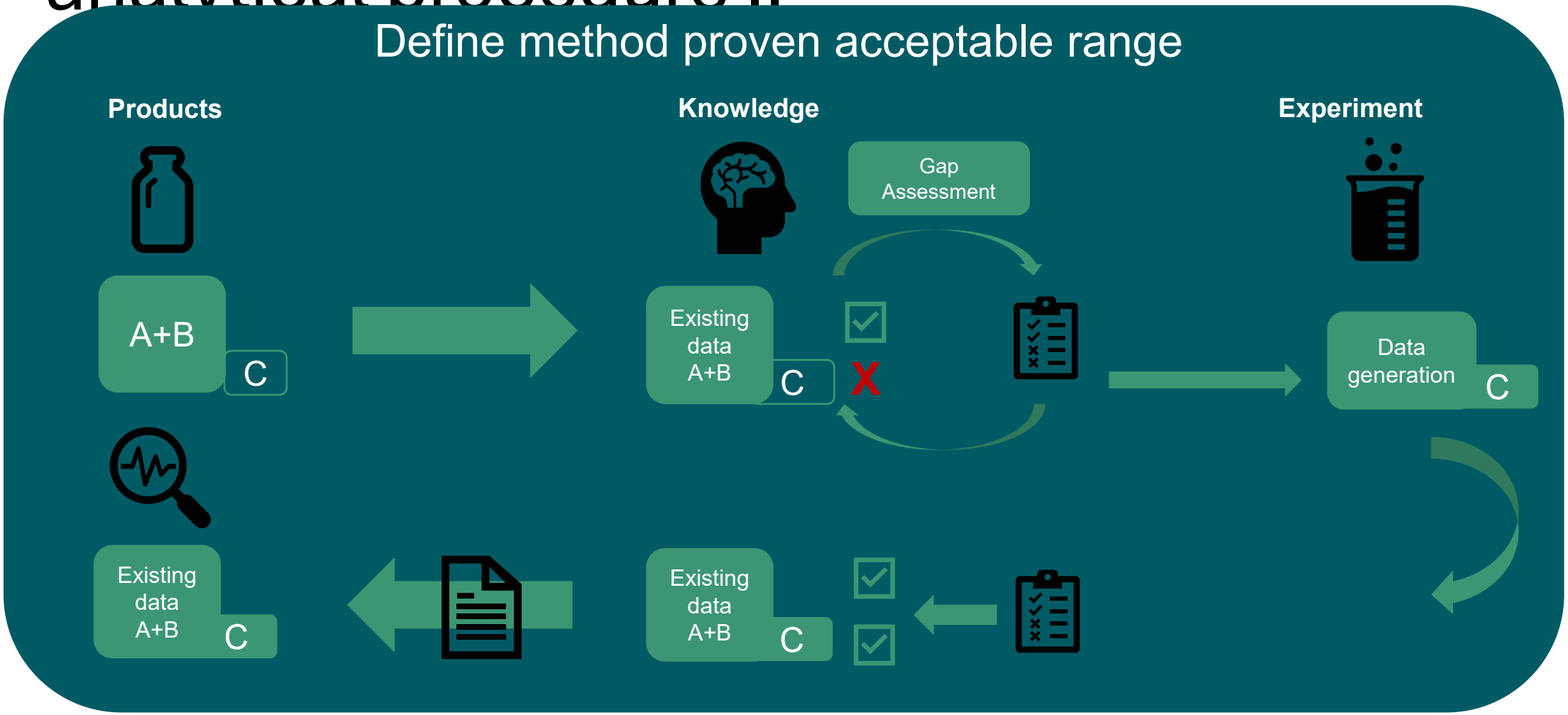
Establishment of new platform analytical procedure



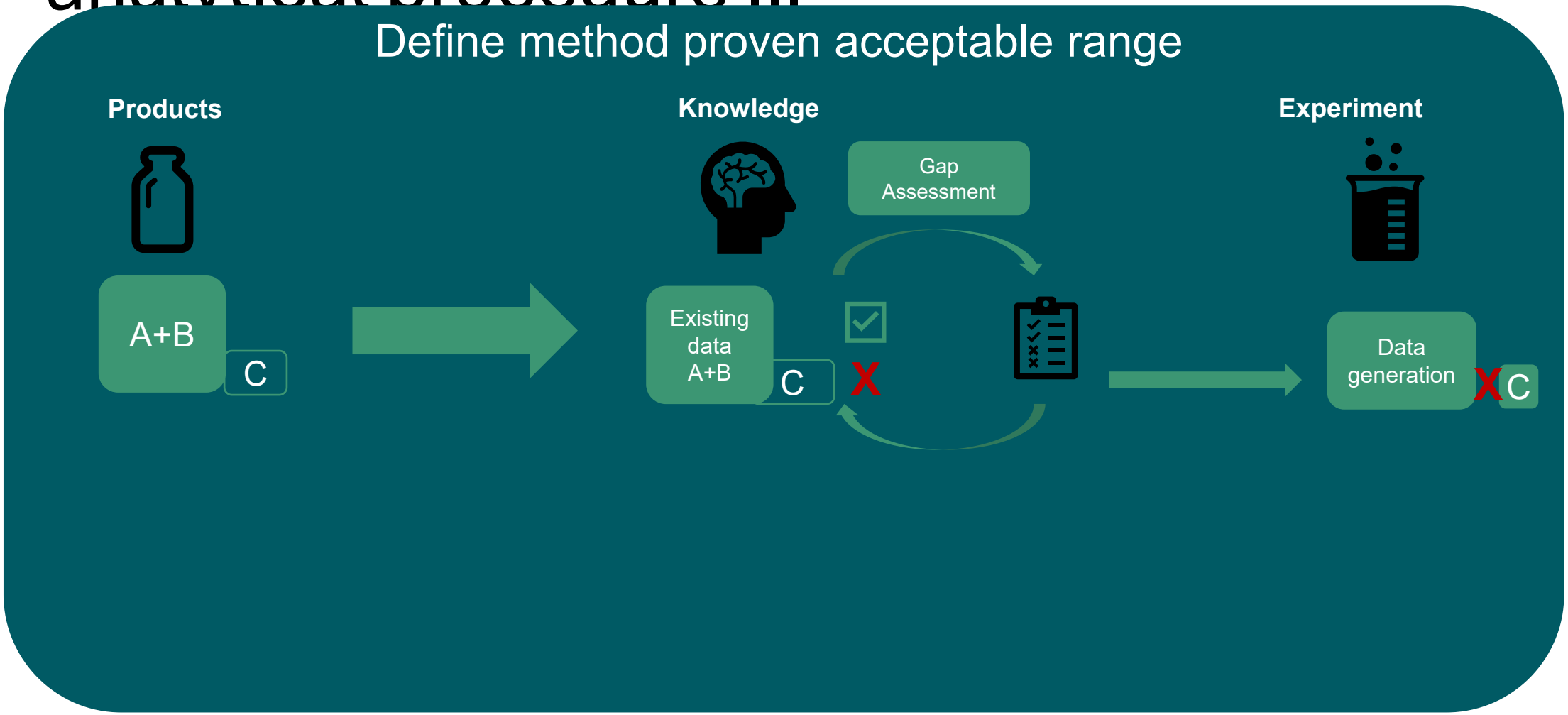
Onboarding of new product to platform analytical procedure I



Onboarding of new product to platform analytical procedure II



Onboarding of new product to platform analytical procedure III



Summary

- The **class** of mRNA-based therapeutics and vaccines favors **platform analytical procedures** due to the similar molecular properties of different mRNA molecules and the “conserved” manufacturing process
- Platform analytical procedures are a powerful tool to **improve method performance** by leveraging prior analytical knowledge and ensuring **constant lifecycle management**
  - Improved robustness/method understanding through extensive knowledge and big datasets
- For following products platform analytical procedures enable faster development in a **compliant manner** guaranteeing method performance and quality
  - Disclaimer analytical platform concept may not be applicable to all analytical methods

Thank you