Post-approval CMC changes with matrix approach

Decock Marie, Kaoukab Raji Abdelmoughit and Sennvik Kristina (Global Regulatory Affairs, CMC)
GSK Vaccines, Rue de l'Institut 89, 1330 Rixensart, Belgium

INTRODUCTION

Importance of post-approval CMC changes for vaccines

- Foster **continuous improvement** and **innovation**
- Meet **regulatory requirements**

Multi-product CMC changes

- Impact on **multiple products**, e.g. transfer of manufacturing facilities, changes in primary containers, raw materials...
- Increased **complexity** and **timings** (supply to the patient)

Reduced design strategies

- Ensure a **robust evaluation** of multi-product changes, applying **scientifically-based** rationales
- Allow a **reliable** and **timely** access to vaccines
- Result in a **reduction** of the overall number of **replicate runs/batches** required for evaluation
- **Project-dependent** and **fit-for-purpose**

Bracketing

Process extremes are representative of intermediate conditions (e.g. volume)

Matrixing

A subset of samples for all factor combinations is selected for evaluation (e.g. stability)

Batch N ₀	Testing time-points (months)							
	0	3	6	9	12	18	24	36
101	X	X			X	X		X
102	X		X		X		X	X
103	X			X	X		X	X

METHOD

Family grouping and selection of representatives

- Grouping into **families** based on manufacturing process, technology, product nature and composition
- Family representative(s) selected based on **worst-case** considerations (based on process complexity, product composition...)
- **Consistency batches** are manufactured for the family representative(s)
Additional consistency batch(es) may be manufactured for **other family members**
- Prior product and process knowledge is **high**

Examples

- Matrix applied directly to the **process** under evaluation, e.g. *multi-product facility transfer*
- Matrix applied to generate **supportive data** to validate a previous manufacturing step, e.g. *change in purification equipment of antigen bulk (G)*
Bulk (DS): 3 consistency batches with new purification equipment

- **Registered** products
- **Well-established** consistency and stability profiles
- **Classical** process qualification of facilities and equipments
- **Personnel** is trained according to internal procedures

WHAT DOES NOT CHANGE

- **Manufacturing processes**
- **Testing** (QC, stability) and **release**
- **Operational parameters** e.g. transfer time, holding time

Matrix approach by family grouping

Grouping of products into **families** and selecting **representatives** for validation based on **worst-case** considerations

	Products	N ₀ batches	
		0/1	3
Family 1	1A (member)	X	
	1B (member)	X	
	1C (member)	X	
	1D (representative)		X
	1E (member)	X	
Family 2	2A (representative)		X
	2B (member)	X	
	2C (member)	X	

RESULTS **WHO, EMA, FDA and Health Canada** (WHO – “Guidelines for procedures and data requirements for changes to approved vaccines”, October 2014)

Validation

- Must consider **multiple parameters** (product characteristics, process, equipment, presentation...)
- Must be supported by **strong scientific rationales**
- Approach need to meet **internal company requirements**
- Data obtained for the family representatives are applicable to the **whole** family grouping

Regulatory

- Matrix approach not always accepted by **local authorities**
- Family representative(s) may not be **registered** in every country
Additional data may need to be provided (commercial lots)
- **Single-source** countries, **manufacturing routes**
- Changes in the **regulatory environment**

- CONCLUSIONS**
- The matrix is an **alternate risk-based streamlined approach** to reduce the number of consistency batches applying **scientifically-based rationales**
 - The matrix approach allows **robust validation together with optimized project timelines**
 - Progress still needed to fully embed the concept in **regulatory guidelines**

This work was sponsored by GlaxoSmithKline Biologicals SA. All authors have declared the following interests: Decock Marie, Kaoukab-Raji Abdelmoughit and Sennvik Kristina are employees of the GSK group of companies.