CMC Statisticians – the backbone from Development to Lifecycle Management

Bianca Teodorescu 22-10-2025

Inspired by **patients**.
Driven by **science**.

Our company in a nutshell

Global biopharma company

1928

Solid science heritage

Revenue €6.15B*

Sustainability as business approach

Listed on Euronext Brussels

Our areas of focus

Neurology

Immunology

Our world

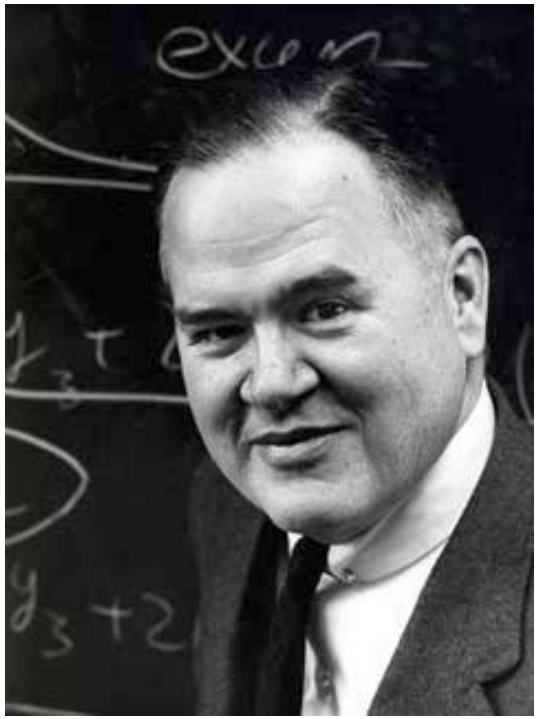
Presence in 36 countries*

>3.1M patients accessed our solutions*

~9,300 employees*

R&D spend 29% of revenue*

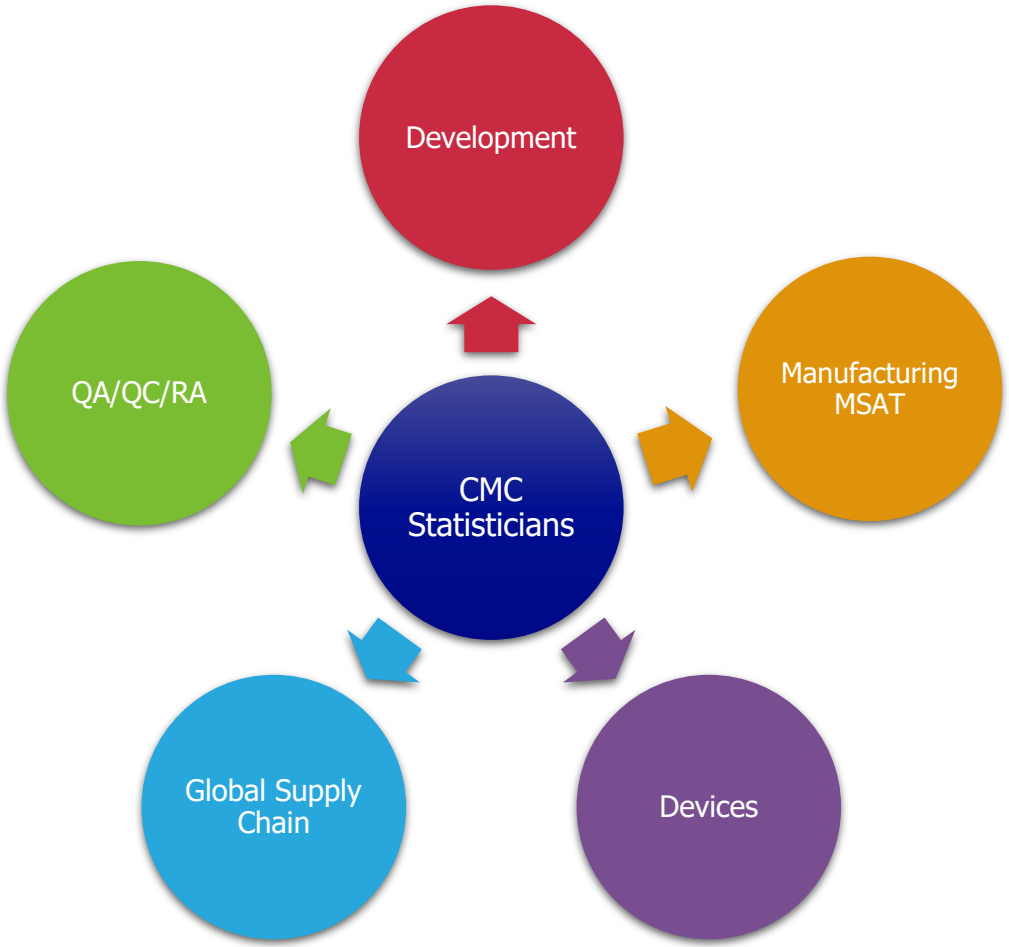
*Source: Integrated Annual Report 2024



"The best thing about being a statistician is that you get to play in everyone's backyard"

J.W.Tukey

CMC backyard – Patient Supply



Transversal group across Development & Commercial

Pharma | Biologicals | Gene Therapy

CMC STATISTICIANS partner with scientists to **design** and **optimize** drug substance and drug product **manufacturing processes**, develop and validate analytical methods, and enhance existing processes and products. They **provide statistical expertise** to troubleshoot issues, ensure robust solutions, and **actively contribute to regulatory submissions** by preparing documentation and **addressing Health Authority questions** during review.

QA= Quality Assurance; QC= Quality Control; RA= Regulatory Affairs; MSAT= Manufacturing Science & Technology

Quality by Design & Statistics

Quality by Design (QbD) ICHQ8(R2): A **systematic approach to development** that begins with **predefined objectives** and emphasizes product and process understanding and process control, **based on sound science** and **quality risk management**.

Statistical analysis: A systematic, objective-driven process that **applies sound scientific principles** to the collection, organization, interpretation, and presentation of data **under uncertainty (risk).** It is designed to extract meaningful insights, test hypotheses, and support data driven decision-making by employing appropriate statistical methodologies aligned with the **predefined study objectives**.

Roles within the CMC Statistics Team

CMC Statistical Sciences
Mission & Vision:

Ensure Sound Statistical Decisions at all levels of the organization across product/process lifecycle

CMC STATISTICS

Product Support

- Dedicated **CMC Stat Product Lead** that drives the CMC statistical strategy for CMC development & commercial activities of the product
- Accelerate drug development processes and launches
- Provide tools, methodologies and processes to ensure optimal statistical support and statistical practices harmonization.

Training & Compliance

- Develop, maintain, and give statistical trainings to scientists across CMC departments
- Create & maintain Guidelines/SOPs
- Participation to conferences & Publications

Automatization & Tools

- Develop, maintain, and optimize statistical tools and automation initiatives/applications to drive programming/analysis efficiency and consistency across CMC Statistical Sciences & CMC departments.
- Provide technical support for use & maintenance of statistical tools (R/SAS/JMP/Python)
- Assess other statistical tools as per request

Advanced Analytics

- Lead and manage product-specific Advanced Analytics (AA) projects
- Maintain close collaboration, exchange and support with CMC Product stats streams
- Provide big data and advanced statistical expertise and solutions to improve the performance and resilience of commercial manufacturing & supports the implementation of outcomes and solution
- Coordinate Data Engineering services for AA projects and solutions

The backbone

Target Product Profile (TPP)

CMC Statistical Sciences

CMC STATISTICS

Clinical (incl pre-clinical)

CMC

Quality by Design (QbD) (ICH Q8)

Phase I

Phase II

Phase III

First Submission

Approval

Phase IV

Safety & Efficacy

Quality Target Product Profile (QTPP)

Critical Quality Attributes (CQA)

Critical Process Parameters (CPP)

Control Strategy (CS)

Lifecycle Management

Process Development

- Development and optimisation of process
- Scale Down Model (SDM) verification
- Process Characterization Studies (PCS)
- PAR & CPP determination
- Process Comparability

Analytical development

- Bioassays & Phys-chem Methods
- Method Robustness
- Method Validation
- Method Bridging

Stability & Shelf-life

- Provisional and final commercial specifications
- Room Temperature allowance

Devices

- Dose accuracy
- Fill volume
- Reliability studies
- BLGF

RA

- Prepare submission dossier
- Response to questions during submissions

QA/QC

- Investigations

Manufacturing

- Hold-up studies/Investigations
- Process optimization (Advanced Analytics)
- MSAT support

Post-approval changes

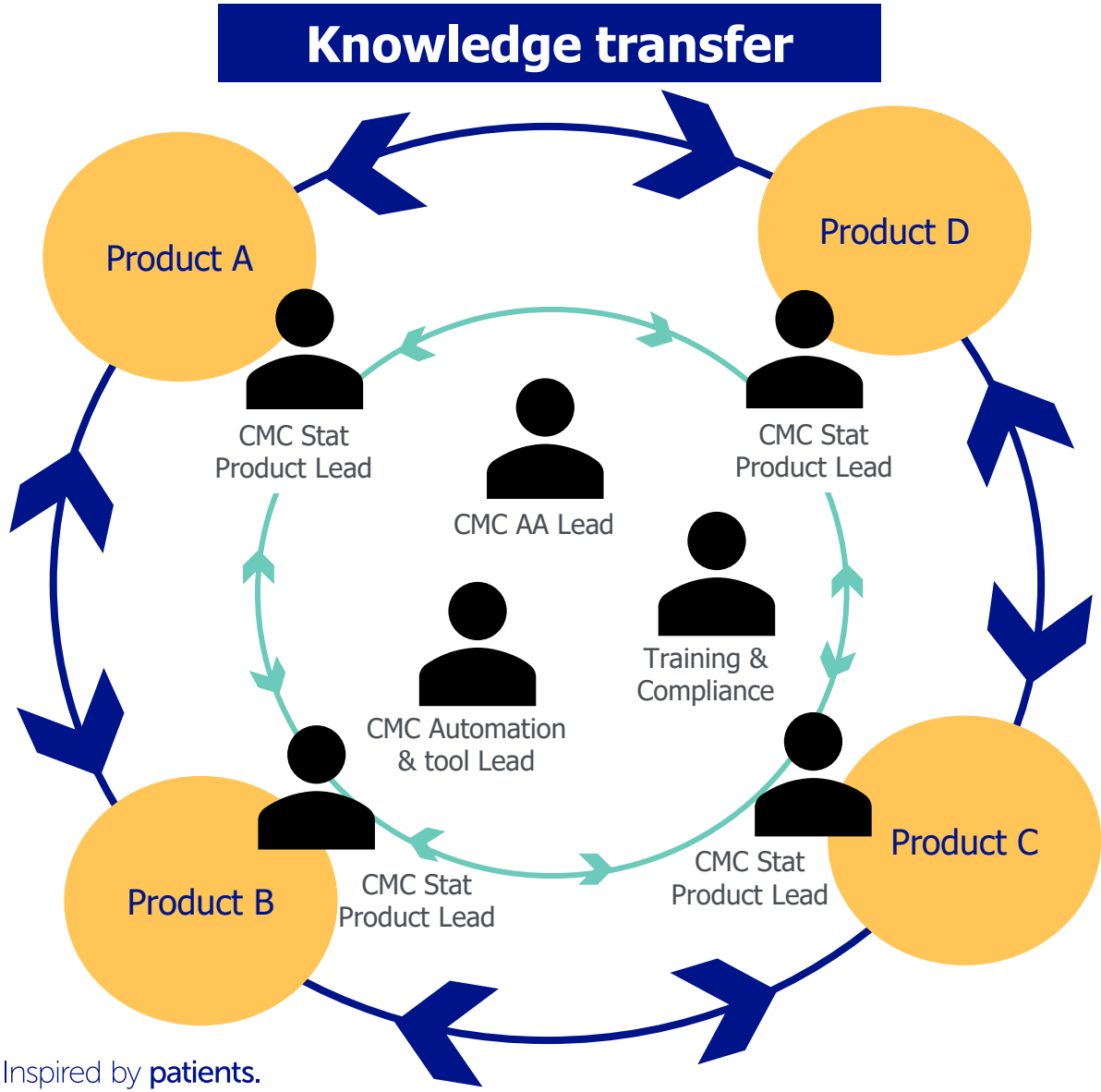
- Comparability studies
- 2G methods
- Shelf-life extension
- Specifications setting 2G

Monitoring & control

- Control limits for Market complaints monitoring
- Control limits for Microbiological environmental activities
- CPV (Continuous Process Verification)
- Annual Stability Trending

PAR= Proven Acceptable Ranges ; BLGF = Break Loose Gliding Force

Ways of working



Resources centralized in one group, leading to:

- **Common group dedicated to Pharma/Biologicals & Gene Therapy**
- **Efficient use of resources**
- **Increased reactivity** to unplanned demands due to the higher pool of resources
- **Harmonization of practices**
- Possibility of **learning and growth** for all team members (vs isolation in a group)

Case Studies

Process Characterization Studies (PCS) for Upstream Process (USP)

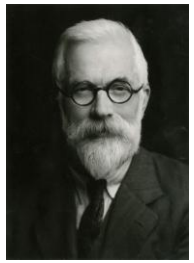
PAR & CPP determination for USP

Product A

- Not involved in the design of the PCS
  - OFAT studies
  - Sources of variability not taken into account: e.g.different analytical runs, batches, ref std
  - Statisticians asked to analyse already generated data
- **Model:** only **main effects** of process parameters
- **Output**:
  - Individual ranges
  - No information on interactions between process parameters
  - Confounded effects
  - Less flexibility

Product B

- **Involved** in the PCS **design**:
  - Proper DoE
  - Specifities of the design accounted for (runs, batches, ref std)
- **Model: main effects, interactions and quadratic effects** between process parameters
- **Output:**
  - Design space
  - Information on interactions and quadratic effects
  - More flexibility



"To consult the statistician after an experiment is finished is often merely to ask him to conduct a postmortem examination. He can perhaps say what the experiment died of."

Sir Ronald Fisher

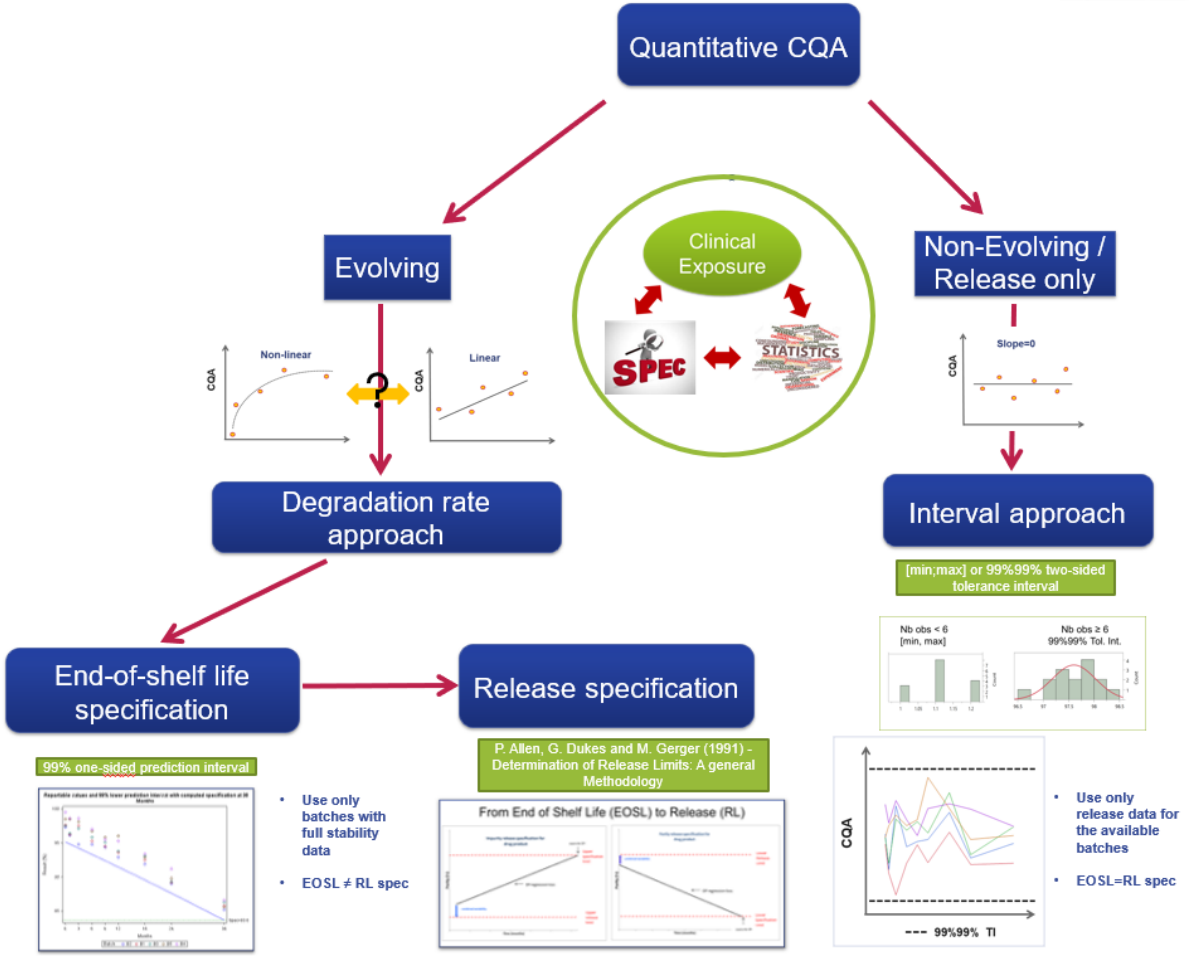
A **collaborative effort** between process, analytical, quality, regulatory, and statistical experts to ensure that **more robust solutions** are implemented to **ensure manufacturing flexibility.**

PAR= Proven Acceptable Ranges ; CPP=Critical Process Parameters

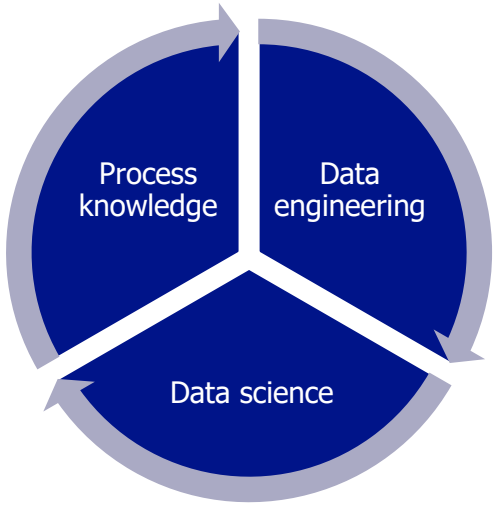
Justification of Commercial Specifications

For a given Shelf-life, Room Temperature allowance and current data set (current manufacturing process), CMC Statistics team:

- Computes what the desired EOSL specification should be
- Computes probability of being Out-of-Specifications



Advanced Analytics for Commercial Biomanufacturing



Driver: Increase supply resilience for a mature biopharmaceutical process

Objectives: Increase productivity (DS/batch) and run rate (batch/year), Advanced Analytics acting both as a change vector and an enabler for the other pillars of the program

Project mode: agile approach, lean team (~4 FTEs), matrix organization, entirely in-house, using in-house Digital Technologies platforms

Team structure: data engineers, statisticians and process experts (transversal across internal manufacturing, CMC development and digital technology)

Constraints: Enact change within limits of the regulatory dossier, small-scale experiment resources limited

Output: An increase in productivity of **more than 15% (beyond initial expectation)**

Priority 1a: Short-term business impact
Identify and drive implementation of change controls leading to significant productivity and financial gains

Priority 1b: Long-term business impact
Develop long-term measures to maintain sustainable performance (through ways of working, automation, industrialization, reporting and documentation)

Priority 2: Develop and sustain expertise
Serve the needs of the people creating short- and long- term impact through advanced analytics (data engineering/data science/statistics experts)

Priority 3: Develop and sustain data users
Serve the needs of the wider community through facilitated access to data, knowledge and ad-hoc solutions (process experts and specialists)

*Slide from Alexandre Super, first presented at BioTalkUS

Take home message

- **Do's: Discuss the study design, objective and needs** in terms of data assessment **before initiating any new study** (plan meeting preferably to avoid discussing study design through document reviews). **Involve the stat team from the start** and define together whether stat support is required and confirm Roles & Responsibilities (R&Rs).

- **Don'ts:** involve stat team after protocol issuance or when data are already available/processed as it is **challenging to provide support** when the study **design did not originally consider the statistics perspective**.

- **What we bring to the table:**
  - A holistic view (dev to commercial)
  - Different backgrounds besides statistics: chemistry, bioengineer, mathematician
  - Data science expertise
  - Impartial view
  - Passion for understanding what the other CMC departments are doing to better help them

- **What is needed for long term success:**
  - CMC Statisticians as a core stakeholder of CMC projects
  - Clear definition of R&R
  - Management support
  - Organizational visibility
  - Resources proportional to the requests

Take home message

« We recommend that you consult with a statistician before discussing the study design and statistical approach with FDA »

FDA, Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products, 2023

Acknowledgments

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Thanks. Any feedback?