Captured between “scientific truth” and “formal correctness”

Building up worlds first pharma Good Manufacturing Practice Dioxin Lab

Kay Kelterer
Kay Kelterer Environmental Consulting,
Lohe 25a, 21217 Seevetal, Germany
info@kaykelterer.de

Entry 0: The client's wish is our order

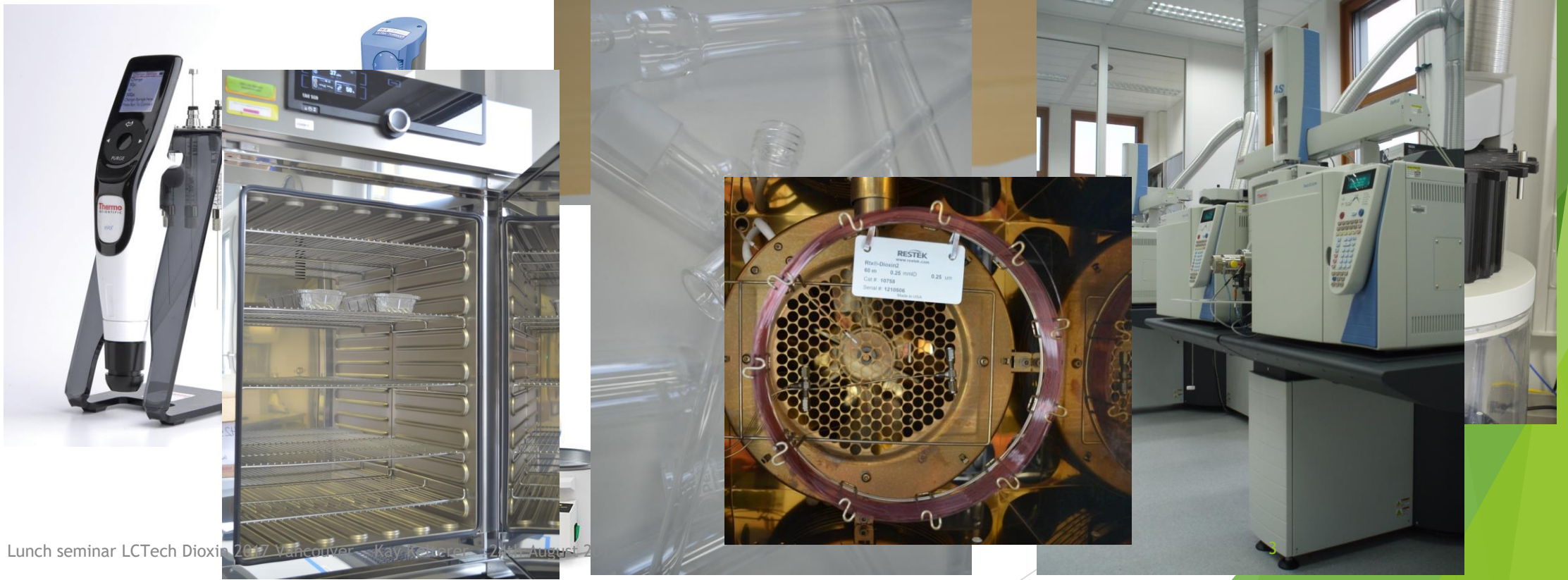
- Eurofins got request from client for PCDD/F, PCB and PBDE analysis in Fish oil under cGMP

- Eurofins group decision: "We take the experts for dioxin analysis from EF 'GfA Lab Service' and implement a GMP dioxin lab at EF 'Dr. Specht Laboratorien'. GfA is the competence center for dioxin analysis and at Dr. Specht they have running analysis for pesticides under a GMP quality system. After one year the lab will be switched back to 'GfA Lab Service'. Any volunteers?"

The Customer is King

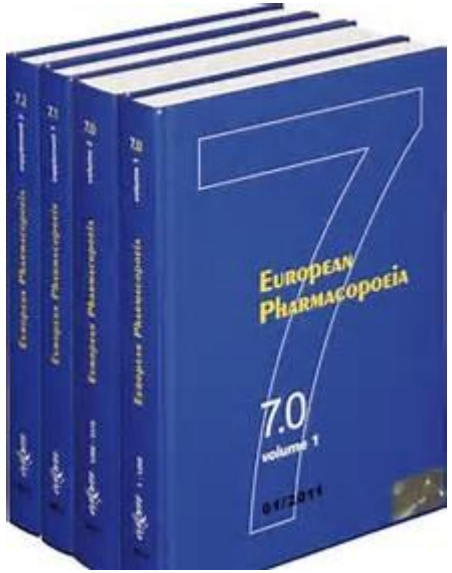
Entry 28: What do we need?

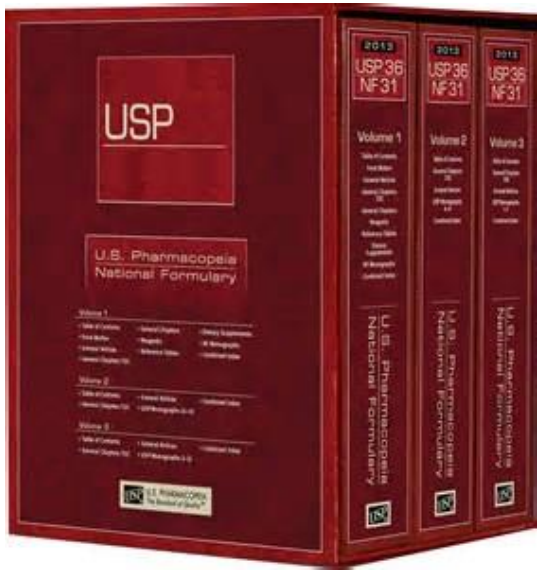
- What do we need? → Room, equipment, staff and we need to know what GMP really means.



Entry 52: GMP what does it mean?

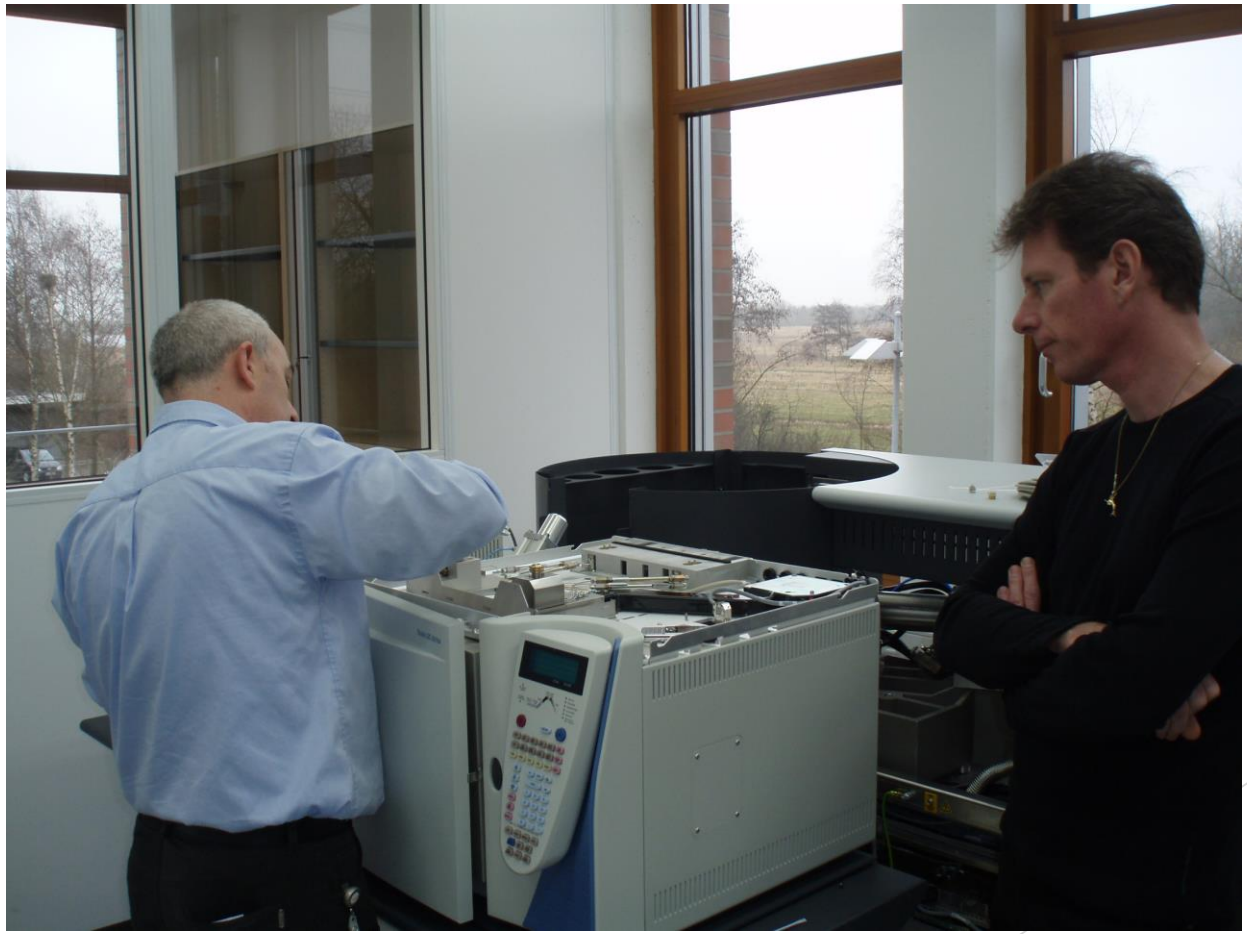
- GMP training…
- GMP stands for “**G**ive **M**ore **P**aper”





Entry 101: The two big toys arrived!

- DFS with IQ/OQ



Entry 138: Reading regulations and requirements.

- What‘s in the fine print of the clients request?
  - One Method in accordance to US Pharmacopoeia (USP) and European Pharmacopoeia (EP)
  - USP → Method: US EPA 1613 and US EPA 1668
  - EP → Method: according to EU regulation for food

EUROPEAN PHARMACOPOEIA 07/2012:1250

OMEGA-3-ACID ETHYL ESTERS 90

Omega-3 acidorum esteri ethylici 90

PRODUCTION

The content of dioxins and dioxin-like PCBs (polychlorinated biphenyls) is controlled using methods and limits in accordance with the requirements set in the European Union or other applicable regulations.

USP 35 *Official Monographs* / Omega-3 4111

Omega-3-Acid Ethyl Esters

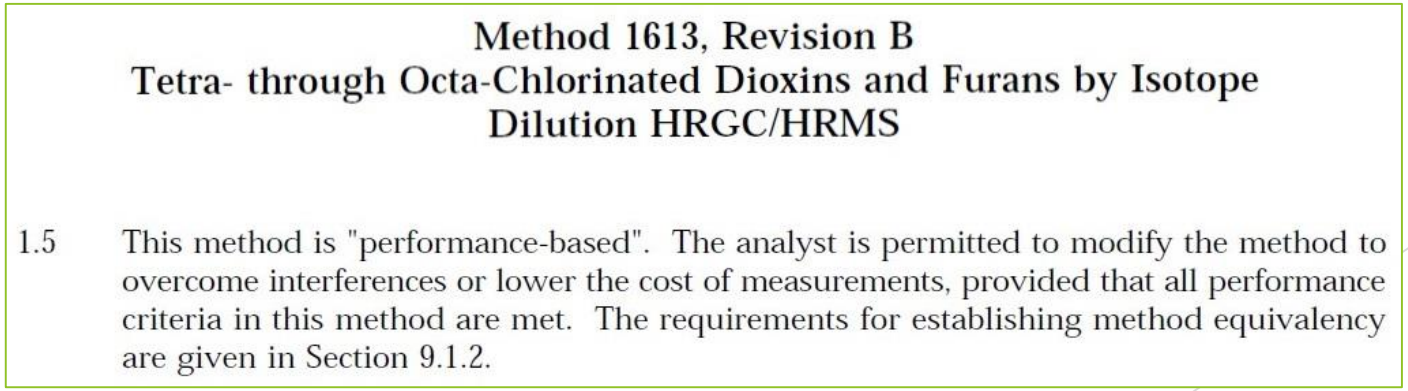
- **LIMIT OF DIOXINS, FURANS, AND POLYCHLORINATED BIPHENYLS (PCBS):** Determine the content of polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) by method No. 1613 revision B of the Environmental Protection Agency. Determine the content of polychlorinated biphenyls (PCBs) by method No. 1668 revision A of the Environmental Protection Agency. **Acceptance criteria:** The sum of PCDDs and PCDFs is NMT 1 pg/g of WHO toxic equivalents. The sum of PCBs (polychlorinated biphenyls, IUPAC congeners PCB-28, PCB-52, PCB-101, and PCB-118, PCB-138, PCB-153, PCB-180) is NMT 0.5 ppm.

Entry 138: Reading regulations and requirements.

- US EPA methods intentionally made for environmental samples! How does omega-3 ethyl ester fits into it and how we can reach the requested limits?
- EU Regulation requests ISO 17025 but our German GMP authority requested a stringent separation between ISO and GMP analysis
- QA criteria / method requirements from US EPA method vs. EU regulation (e.g. separation efficiency, use of ^{13}C labelled standards)

Entry 153: Finalizing the methods and the corresponding documents.

- Most important sentence in US EPA methods: “This method is ‘performance-based’.
  - We end up with documents for US EPA 1613 and 1668 listing all “amendments” with explanations and link to our method validation
- Exceptions for EU regulation
  - Again a document with explanations for the exceptions
- Method development and validated with client material (Omega-3 ethyl ester 90)



Method 1613, Revision B
Tetra- through Octa-Chlorinated Dioxins and Furans by Isotope Dilution HRGC/HRMS

1.5 This method is "performance-based". The analyst is permitted to modify the method to overcome interferences or lower the cost of measurements, provided that all performance criteria in this method are met. The requirements for establishing method equivalency are given in Section 9.1.2.

Entry 180: „It's alive“ or we have created a monster

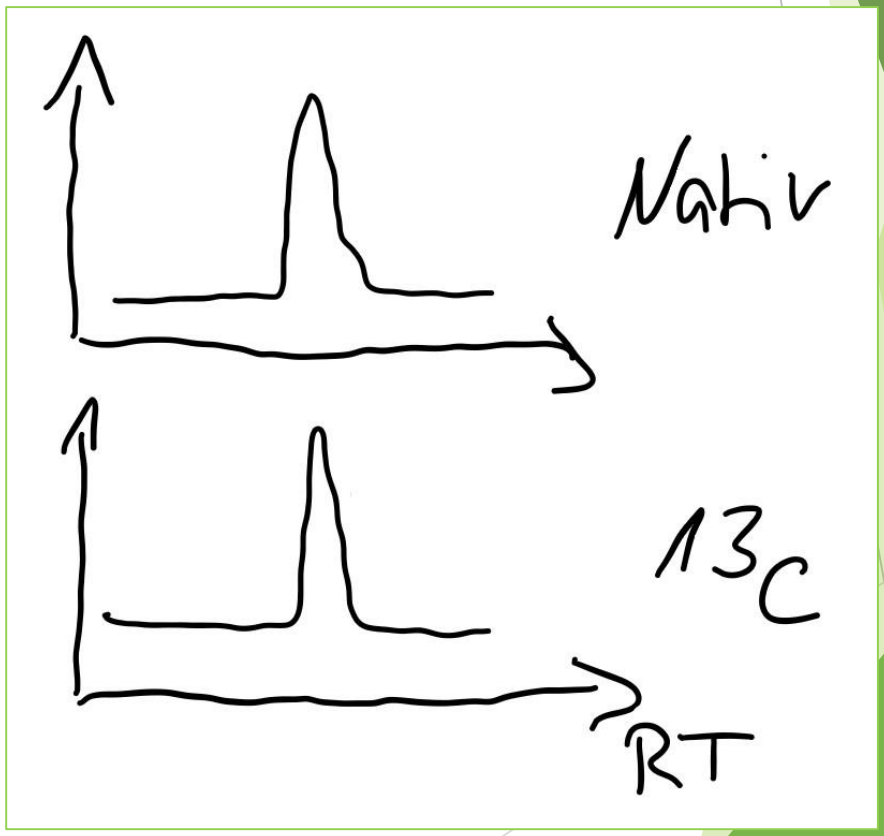
- Real samples arriving: “Hurray”

- Sample material: “Omega-3 EE 90”; “Omega-3 EE 60”; “crude fish oil”; “semi-refined fish oil”; “Omega-3 TG”; …

- GMP requirement: Method validation or verification needed for every change in the method or of sample material

Entry 180: „It's alive“ or we have created a monster

- Handling of interferences…
- BDE resolution 10.000 run on 60m column
- Many unimposing steps take much more time and effort e.g. lot control for solvent mixtures or preparation of adsorbents (carbon or coated silica)



Entry 209: Next time we do better

- First read the fine prints → declare all framework requirements
- Design qualification! Done and document before ordering equipment/software
- Source out lot control to supplier as much as possible
- Reduce manual handling (documentation and repeatability)

Thanks for your attention

Special thanks to my former colleagues from GMP dioxin team of Eurofins