

# WFI Beyond: metal control that lasts – every ICH Q3D element still below limit at the T18 stability point

The Water for Injection with elemental impurities controlled **beyond compendial** – acceptance set at half the ICH Q3D limit, and the stability data that shows the metal floor stays put, from research to GMP.

By Sarah Gierl, Head of R&D, PAN-Celltech · TP-08 · Rev 1.0 · 14 Oct 2026 · elemental impurities in WFI Beyond, stability-confirmed · [Download the PDF](#)

## Key takeaways

- Water is the base of every buffer, medium and final formulation – so its metal profile sets the elemental-impurity ceiling for the whole process, and in an injectable trace metals cannot be argued away downstream.
- PAN-Celltech tests WFI Beyond for all **24 ICH Q3D elemental impurities** by **ICP-MS** (Ph. Eur. 2.4.20 / USP <233>) – and this paper adds the dimension a release value cannot: **stability**.
- **Thousands-fold margin:** every ICH Q3D element lands far inside its limit – most below the method's limit of quantification – so the metal headroom for your process is set at the water layer.
- At the **T18 long-term stability time point (18 months)**, every element was **below its limit** – most below the quantification limit – with **no out-of-specification result**.
- **Container-independent:** confirmed in both **PET and PETG** single-use containers, across the 500 mL and 1000 mL formats.
- Lead sat at its limit of quantification ( $\leq 0.10 \mu\text{g/L}$ , well under the  $500 \mu\text{g/L}$  ICH limit); every other ICH Q3D element was below it.
- This underpins the metal-control cornerstone of **WFI Beyond** with stability evidence, not just a release snapshot.

The metal control PAN-Celltech reports at release does not drift over shelf life: at the T18 stability time point, in both PET and PETG, every ICH Q3D element stays below limit – most below the quantification limit.

**In brief.** Controlling elemental impurities in the water is a cornerstone of WFI Beyond: all 24 ICH Q3D elements measured by ICP-MS on every lot – a first for a water. This paper adds what a release certificate cannot show on its own: that the profile holds. GMP-released elemental-impurity reports at the T18 long-term stability time point, across the 500 mL and 1000 mL formats of WFI Beyond in PET and PETG show the full ICH Q3D panel, still below limit at T18, most below the quantification limit, with no OOS result. The metal floor beneath an injectable is not just low at release; it stays low.

## 1. Why elemental impurities start with the water

ICH Q3D sets limits for 24 elemental impurities in a drug product, because trace metals are not inert: they catalyse the oxidation and aggregation of proteins and the hydrolysis of RNA, and in a parenteral they cannot be removed once the product is filled. Water is the base of every buffer, every medium and the final formulation, so the water's metal profile sets the ceiling for everything built on it. Answer the elemental-impurity question at the water layer, and it does not have to be re-argued at every downstream step.

That is why PAN-Celltech measures the **full ICH Q3D panel by ICP-MS** on WFI Beyond – 24 elements, to Ph. Eur. 2.4.20 and USP <233>, reported on the Certificate of Analysis. A release value proves the water left the line clean. The question this paper answers is the next one a regulator and a QA team ask: *does it stay clean?*

***Answer the elemental-impurity question at the water layer – with the whole ICH Q3D panel, measured and stable – and you do not have to argue it downstream, for the entire process built on that water.***

## 2. The study – what was tested

Elemental-impurity reports were confirmed by an external, ISO/IEC 17025-accredited GMP laboratory at the **T18** long-term stability time point (18 months from production), across the 500 mL and 1000 mL formats of WFI Beyond in PET

and PETG single-use containers. Each report runs the full 24-element ICH Q3D panel by ICP-MS.

| Format (Art. No.)   | Container | Time point | Outcome                  |
|---------------------|-----------|------------|--------------------------|
| 1000 mL · CT-981000 | PET       | T18        | All below limit · no OOS |
| 1000 mL · CT-981000 | PETG      | T18        | All below limit · no OOS |
| 500 mL · CT-981500  | PET       | T18        | All below limit · no OOS |
| 500 mL · CT-981500  | PETG      | T18        | All below limit · no OOS |

Method: ICP-MS to Ph. Eur. 2.4.20 and USP <233>, to a validated method;  
assessment recorded as free of out-of-specification results and of test-relevant deviations.

### 3. Results – every element below limit, most below the quantification limit

Across both formats and both container materials at T18, **every parameter was below its applicable limit**. The great majority were below the quantification limit; lead was at its limit of quantification; every other element was below it. The table below shows the applicable limit and the result at T18 (highest value observed across the formats and container materials – most elements below the quantification limit).

| Element                                                       | ICH Q3D(R2) limit [µg/L] | Beyond-compendial limit [µg/L] | LOQ [µg/L] | Result at T18 [µg/L] |
|---------------------------------------------------------------|--------------------------|--------------------------------|------------|----------------------|
| <b>Class 1 – Human toxicants (evaluation always required)</b> |                          |                                |            |                      |
| <b>Arsenic (As)</b>                                           | ≤ 1,500                  | ≤ 750                          | 0.30       | < 0.30               |
| <b>Cadmium (Cd)</b>                                           | ≤ 200                    | ≤ 100                          | 0.04       | < 0.04               |
| <b>Mercury (Hg)</b>                                           | ≤ 300                    | ≤ 150                          | 0.06       | < 0.06               |
| <b>Lead (Pb)</b>                                              | ≤ 500                    | ≤ 250                          | 0.10       | ≤ 0.10               |
| <b>Class 2A – High probability of occurrence</b>              |                          |                                |            |                      |
| <b>Cobalt (Co)</b>                                            | ≤ 500                    | ≤ 250                          | 0.10       | < 0.10               |
| <b>Nickel (Ni)</b>                                            | ≤ 2,000                  | ≤ 1,000                        | 0.40       | < 0.40               |
| <b>Vanadium (V)</b>                                           | ≤ 1,000                  | ≤ 500                          | 0.20       | < 0.20               |
| <b>Class 2B – Low probability of occurrence</b>               |                          |                                |            |                      |
| <b>Silver (Ag)</b>                                            | ≤ 1,500                  | ≤ 750                          | 0.20       | < 0.20               |
| <b>Gold (Au)</b>                                              | ≤ 30,000                 | ≤ 15,000                       | 2.0        | < 2.0                |
| <b>Iridium (Ir)</b>                                           | ≤ 1,000                  | ≤ 500                          | 0.20       | < 0.20               |

| Element                                                       | ICH Q3D(R2) limit [µg/L] | Beyond-compendial limit [µg/L] | LOQ [µg/L] | Result at T18 [µg/L] |
|---------------------------------------------------------------|--------------------------|--------------------------------|------------|----------------------|
| <b>Osmium (Os)</b>                                            | ≤ 1,000                  | ≤ 500                          | 0.20       | < 0.20               |
| <b>Palladium (Pd)</b>                                         | ≤ 1,000                  | ≤ 500                          | 0.20       | < 0.20               |
| <b>Platinum (Pt)</b>                                          | ≤ 1,000                  | ≤ 500                          | 0.20       | < 0.20               |
| <b>Rhodium (Rh)</b>                                           | ≤ 1,000                  | ≤ 500                          | 0.20       | < 0.20               |
| <b>Ruthenium (Ru)</b>                                         | ≤ 1,000                  | ≤ 500                          | 0.20       | < 0.20               |
| <b>Selenium (Se)</b>                                          | ≤ 8,000                  | ≤ 4,000                        | 1.60       | < 1.60               |
| <b>Thallium (Tl)</b>                                          | ≤ 800                    | ≤ 400                          | 0.16       | < 0.16               |
| <b>Class 3 – Evaluation required for the parenteral route</b> |                          |                                |            |                      |
| <b>Barium (Ba)</b>                                            | ≤ 70,000                 | ≤ 35,000                       | 14.00      | < 14.00              |
| <b>Chromium (Cr)</b>                                          | ≤ 110,000                | ≤ 55,000                       | 22.00      | < 22.00              |
| <b>Copper (Cu)</b>                                            | ≤ 30,000                 | ≤ 15,000                       | 6.00       | < 6.00               |
| <b>Lithium (Li)</b>                                           | ≤ 25,000                 | ≤ 12,500                       | 5.00       | < 5.00               |
| <b>Molybdenum (Mo)</b>                                        | ≤ 150,000                | ≤ 75,000                       | 30.00      | < 30.00              |
| <b>Antimony (Sb)</b>                                          | ≤ 9,000                  | ≤ 4,500                        | 1.80       | < 1.80               |
| <b>Tin (Sn)</b>                                               | ≤ 60,000                 | ≤ 30,000                       | 12.00      | < 12.00              |

ICH Q3D(R2) limits are calculated per Section 7, Option 1 from the parenteral permitted daily exposures (PDE) in Table A.2.1: limit [µg/g] = PDE [µg/day] / 10 g/day; for aqueous solutions at 1.00 g/mL (20 °C), 1 µg/g corresponds to 1 mg/L, and the assumed daily intake is to be verified by the manufacturer of the finished medicinal product. Results are from GMP stability testing by an ISO/IEC 17025-accredited laboratory (Ph. Eur. 2.4.20 / USP <233>, ICP-MS). The beyond-compendial acceptance criterion is set at half the ICH Q3D compendial limit; LOQ is the method's limit of quantification, and a result below it is reported as "< LOQ".

## 4. Beyond the 24 – the oxidation metals copper and iron

Beyond the full ICH Q3D panel, PAN-Celltech additionally characterises the two metals that drive metal-catalysed oxidation (Fenton chemistry) in protein processes – **copper and iron** – and reports them in a dedicated oxidation-metals addendum to the Certificate of Analysis. Copper is covered within the ICH Q3D panel (Class 3); iron is beyond compendial, tested in neither the Ph. Eur. Water for Injection monograph nor ICH Q3D. The addendum supplements the CoA without replacing it.

## Oxidation-relevant trace metals for antibody processes

For monoclonal-antibody processes, two metals drive metal-catalysed oxidation (Fenton chemistry): copper and iron. PAN-Celltech reports both as a CoA addendum – copper within the ICH Q3D panel (Class 3), iron beyond compendial – and both come in below the limit of quantification, at release and at the T18 stability point. Both oxidation catalysts are controlled below quantification at the water source.

| Element            | Role in oxidation                   | Reference limit [ $\mu\text{g/L}$ ] | LOQ [ $\mu\text{g/L}$ ] | Result at release and T18 [ $\mu\text{g/L}$ ] |
|--------------------|-------------------------------------|-------------------------------------|-------------------------|-----------------------------------------------|
| <b>Copper (Cu)</b> | Most potent MCO catalyst (His/Met)  | 30000 (ICH Q3D, Class 3)            | 6                       | < 6                                           |
| <b>Iron (Fe)</b>   | Co-primary MCO catalyst; ubiquitous | 25000 (in-house ref.)               | 5                       | < 5                                           |

**What this means for antibody processes.** The two metals that catalyse antibody oxidation are controlled at the water source – iron beyond what the pharmacopoeia and ICH Q3D require. Building a monoclonal-antibody process on WFI Beyond removes trace copper and iron as an upstream contributor to oxidation, aggregation and the developability risks that surface late at CMC.

## 5. What it means

**Metal control that lasts.** A low elemental profile at release is expected; a low profile that holds to the T18 stability point is the evidence a filing actually leans on. It turns the release claim into a shelf-life claim: the metal floor beneath your buffers, media and final formulation stays where it was.

**Container-independent.** The profile held across the 500 mL and 1000 mL formats in both PET and PETG, so there is no meaningful leaching of ICH Q3D elements from the single-use container over the stability interval – a real question for ready-to-use water shipped in plastic, answered with data rather than assertion.

**It underpins the headline.** "All 24 ICH Q3D elements by ICP-MS – a first for a water" is a strong claim; this is the stability evidence beneath it. And because every buffer, medium and formulation is built on this water base, the controlled metal floor is inherited by the whole process built on it – the same argument the

WFI Beyond standard makes for endotoxin and nuclease control, now shown for elemental impurities over time.

## 6. Conclusion

Meeting a limit at release tells you the water left the line clean. Holding the whole ICH Q3D panel below limit at the T18 stability point – across both formats and container materials, with no OOS – tells you it stays clean. That is the difference between a specification and a guarantee you can build a process on, and it is the metal-control half of the beyond-compendial water standard, proven over time.

## Frequently asked questions

### What do the T18 stability reports show for elemental impurities? —

At the T18 long-term stability time point, all 24 ICH Q3D elemental impurities were below their applicable limit by ICP-MS, with no out-of-specification result. Most elements were below the quantification limit; lead was at its limit of quantification ( $\leq 0.10 \mu\text{g/L}$ , well under the  $500 \mu\text{g/L}$  ICH limit); every other ICH Q3D element was below it.

### Does the container material change the metal profile? —

No relevant difference was seen. The profile was confirmed across the 500 mL and 1000 mL formats in PET and PETG – so no meaningful leaching of ICH Q3D elements from the container was observed over the stability interval studied.

### How are the elements measured? —

By ICP-MS according to Ph. Eur. 2.4.20 and USP <233>, to a validated method. The limits shown are the validated-method specification (ICH Q3D-based), reported on the Certificate of Analysis.

### Which WFI Beyond articles does this cover? —

This paper covers both WFI Beyond formats – **1000 mL (CT-981000)** and **500 mL (CT-981500)**. The elemental-impurity data are taken from GMP stability reports at the T18 long-term stability point, across both formats in PET and PETG. The full 24-element ICH Q3D panel by ICP-MS (Ph. Eur. 2.4.20 / USP <233>) is reported per lot on the Certificate of Analysis.

### Where do the per-lot numbers come from? —

From each lot's Certificate of Analysis, tested and released against the defined panel. The values in this paper come from the cited GMP stability reports at the T18 time point.

## Related reading

- [Beyond Compendial – Applied to Buffers and Reagents](#) – the full impurity dossier mapped across the downstream portfolio.
- [WFI Beyond – Water for Injection beyond the monograph](#) – the water story behind the beyond-compendial standard.
- [Knowledge Hub](#) – case studies and technical papers, including [The Water in the Powder](#).

## Build your process on water controlled beyond compendial

Ask for the elemental-impurity data set, a representative Certificate of Analysis, or the WFI Beyond specification.

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Elemental-impurity data from GMP stability reports for WFI Beyond (CT-981000 and CT-981500); the same metal control is a defining attribute of WFI Beyond. T18 denotes the 18-month long-term stability time point of the ongoing stability study. Data: T18 (18-month) stability across the 500 mL and 1000 mL formats in PET and PETG; released GMP, no OOS. Manufactured to GMP in an EU Annex 1 facility (a capability, not a certification). TP-08 · Rev 1.0, 14 Oct 2026 – Classification: Public.