

The Water in the Powder

By Sarah Gierl, Head of R&D, PAN-Celltech · TP-05 · Rev 1.0 · 20 Oct 2026 · for manufacturers and users of cell-culture media powders · [Download the PDF](#)

Key takeaways

- A ready-to-use liquid medium is powder dissolved in water – roughly **99% water by mass**. Its impurity load therefore has two sources, not one: the powder, and the reconstitution water.
- For several impurity classes – **trace (elemental) metals, endotoxin, nucleases and organic carbon** – the water contributes directly. For trace metals the two simply add together in the final litre.
- The reconstitution water is the **unmeasured half**: the pharmacopoeial water monograph does not require elemental impurities to be reported, and in practice almost no one measures the water they dissolve powder in.
- You cannot control what you do not measure. A powder purified to the last part per billion, dissolved in uncharacterised water, has a final impurity load no one can fully account for.
- WFI Beyond is the water that arrives **already measured**: all 24 ICH Q3D elemental impurities by validated ICP-MS on the Certificate of Analysis – across two representative lots, all below the limit of quantification bar a single antimony reading at one fill start (below the limit of quantification by fill end), plus **iron** – the oxidation metal in no water monograph and not even in ICH Q3D – in a dedicated oxidation-metals addendum. Endotoxin more than 50x below the limit, nuclease-free, animal-component-free; backed by a filed FDA Type IV DMF (MF044505).
- Two audiences, one answer. **If you sell powder**: specify and document the reconstitution water, or have the powder converted to a documented GMP liquid. **If you use powder**: choose a characterised water and your final-medium impurity budget becomes known, not assumed.
- Said plainly: the water is the **unmeasured, uncontrolled variable** – not automatically the largest source. Which impurity classes your targets are about decides how much it moves the number.

You can purify a powder to the last part per billion. Then it is dissolved in water nobody measured – and half of the final medium's impurity story is written by that water.

In brief. Enormous effort goes into lowering the impurity load of cell-culture media powders, and the targets keep getting tighter. But a powder is only half of

what reaches the bioreactor. The medium a customer actually uses is powder *reconstituted in water* – and that liquid is about 99% water. So the impurity load of the final medium is the powder's plus the water's. For trace metals, endotoxin and nucleases the water contributes directly, yet the reconstitution water is almost never measured – ordinary Water for Injection is not required to report elemental impurities at all. This paper makes the case for treating the water as the second half of the impurity budget, shows what it looks like to measure it to a finished-drug standard (ICH Q3D, 24 elements by ICP-MS – plus iron, which no monograph lists), and sets out what both media-powder suppliers and media-powder users can do about it.

1. A medium is two ingredients, not one

Treat a ready-to-use liquid medium honestly and it is a mixture of exactly two things: a defined powder, and the water it is dissolved in. By mass the split is lopsided – a typical reconstituted medium is on the order of **99% water** and a few per cent solids. That single fact has a consequence that is easy to miss: the impurity content of the final medium is not a property of the powder alone. It is the sum of what the powder brings and what the water brings.

For some impurity classes that sum is almost literally additive. Trace metals are the clearest case: the concentration of, say, copper or iron in the final litre is the copper or iron contributed by the dissolved powder *plus* the copper or iron already dissolved in the water. Endotoxin behaves the same way – pyrogen in the water adds to pyrogen from the powder. Nuclease activity and organic carbon, likewise, can enter from either side. The powder maker controls one input to that sum with great care. The other input – the water – is chosen later, by whoever reconstitutes the powder, and is usually not characterised at all.

The powder is the half you control. The water is the half your customer adds – and, as it turns out, the half nobody measures.

2. The half you measure, and the half you do not

Why is the water half invisible? Because the rules never asked for it. A pharmacopoeial Water for Injection has to meet its monograph – conductivity, organic carbon, endotoxin, microbial limits – but that monograph **does not require elemental impurities to be measured or reported** at all. ICH Q3D, the guideline that governs the 24 trace metals, is written for the *finished drug product*, not for the water feeding into it. So a water can be entirely legitimate Water for Injection and carry an elemental profile that no one has ever looked at.

The result is a genuine blind spot. A media-powder supplier can drive the powder's metal content down to parts per billion, ship it with a detailed Certificate of Analysis, and watch its customers dissolve it in whatever qualified water they happen to use – water whose own metal, endotoxin and nuclease contribution is unknown. The tighter the powder specification, the larger this unmeasured water contribution looms in relative terms, because the powder is no longer the dominant source it once was.

You cannot control what you do not measure.

That is the heart of it. This is not a criticism of anyone's water – most WFI is very good. It is that the water's contribution to the final medium is an **uncharacterised variable** sitting inside a specification everyone is working hard to hit. A recent conversation makes the point better than any argument: a major supplier of cell-culture media powder described being under real pressure to lower the impurity load of its powder, because the targets were making every sale harder. Asked whether its customers measured the impurities in the water they dissolved the powder in, the supplier had no answer. Nobody was measuring the water. The whole industry has been optimising one half of a two-part sum.

3. What it looks like to measure the water

Closing the gap is not conceptually hard – it means holding the water to the standard of the medicine, and reporting the result. That is precisely what PAN-Celltech does with WFI Beyond: it applies **ICH Q3D – a finished-drug elemental-impurity standard – to the water itself**, measuring all 24 elements by validated ICP-MS and reporting the actual values, not a pass/fail, on every Certificate of Analysis. Across two representative lots the picture is consistent: on one, all 24 come back below the limit of quantification; on the other, 23 of 24 do, with antimony the sole exception – 2.6 µg/L at the start of fill, back below the limit of quantification by the end, and even at that peak roughly 3,500-fold below its ICH Q3D parenteral limit.

One element deserves singling out, because it is the one that matters most to a protein and the one no rulebook lists. **Iron**, together with copper, catalyses oxidation and aggregation of biologics by Fenton chemistry – the same family of chemistry that rusts a nail, acting on your product. Copper is one of the 24 ICH Q3D elements, so it is measured as a matter of course. **Iron is not in ICH Q3D, and it is not in the water monograph either** – it is required by no standard anywhere. WFI Beyond measures it regardless, and reports it in a dedicated **oxidation-metals addendum**; in the addendum issued so far, iron too was below the limit of

quantification. The principle is simple: measure the thing no rulebook asks for, because the molecule cares even if the monograph does not.

The same CoA carries the other classes that cross from water into the final medium: **endotoxin more than 50 times below the compendial limit** (specified below 0.005 EU/mL), **nuclease-free** release (RNase and DNase not detected) and **animal-component-free** status by signed declaration. And the water is backed by a filed FDA Type IV (excipient) Drug Master File (MF044505); PAN-Celltech also holds a filed DPBS DMF (MF044371). In other words, the half of the impurity budget nobody was measuring can arrive fully quantified – ready to drop straight into a customer's own ICH Q3D risk assessment and filing.

4. What to do about it – for both sides of the powder

The unmeasured half is an opportunity, not just a risk, and it reads differently depending on which side of the powder you sit.

If you manufacture and sell media powder, the water is the lever that lets you make a hard specification both meetable and provable:

- **Specify the reconstitution water.** Recommend a characterised water to your customers, so the final-liquid impurity load is controlled and documented rather than left to chance – and your own specification conversation gets easier.
- **Hand over the whole budget on paper.** Your powder CoA plus a water CoA that already carries the 24 elements and iron give your customer the final medium's elemental dossier, half-built. A target that was hard to argue becomes a documented number.
- **Convert the powder to a documented liquid.** PAN-Celltech can reconstitute and formulate a powder into a ready-to-use GMP liquid on the WFI Beyond base, with the full elemental dossier – so a premium, documented liquid product can be offered without building the fill capability in-house. A water decision becomes a formulation partnership.

If you use media powder – reconstituting it for your own process – the message is shorter: the water you choose is the half of your medium's impurity budget you can still control after the powder is bought. Choosing a water that is characterised to a finished-drug standard turns an assumed number into a known one, and does so at the cheapest layer, before the powder is ever dissolved.

5. Said plainly

Two honest boundaries keep this argument exact. First, we are **not** claiming the water is always the largest source of impurity in a medium – that depends entirely on the powder, the water and the numbers involved. The claim is narrower and more durable: the water is the **unmeasured, uncontrolled variable** in a specification everyone is trying to hit, and an unmeasured variable cannot be managed. Second, how much the water matters depends on **which impurity classes** the targets are about. For elemental impurities, endotoxin and nucleases, the water contributes directly and the case is strong; for an impurity that originates only in the powder's own synthesis, the water is not the answer. The practical first step is therefore a single question – which impurities, specifically? – after which the water contribution can be scoped and, if it matters, measured.

The deeper point is one PAN-Celltech has made across this series about water, buffers and reagents: in biologics, the quality of a raw material is inseparable from the quality of its documentation. The water in the powder is simply the clearest example yet of a measurement that was always there to be made, and that almost no one was making.

Related reading: [Beyond Compendial – Applied to Buffers and Reagents](#) maps the full impurity dossier to downstream buffers; [In-Depth Industry Edition D02 – Water](#) is the full water story behind WFI Beyond.

Frequently asked questions

Isn't the powder the main source of impurities, not the water? —

It can be – but not always, and that is the point. The final medium's impurity load is the powder's plus the water's. As powder specifications tighten, the water's uncharacterised contribution becomes relatively more important. The honest position is that the water is the unmeasured variable; whether it dominates depends on the specific impurities and numbers.

Which impurities actually come from the water? —

Chiefly trace (elemental) metals, endotoxin, nuclease activity and organic carbon. For trace metals the water's contribution adds directly to the powder's in the final solution. Impurities that arise only in the powder's own synthesis are not addressed by the water.

Why measure iron if no guideline requires it? —

Because iron, with copper, catalyses oxidation and aggregation of biologics by Fenton chemistry – a direct threat to protein stability – yet iron sits in neither the water monograph nor the 24 elements of ICH Q3D. WFI Beyond measures it anyway and reports it in a dedicated oxidation–metals addendum, so the risk is quantified rather than assumed.

Can PAN turn our powder into a ready-to-use liquid? —

Yes. PAN-Celltech can reconstitute and formulate a media powder into a GMP liquid on the WFI Beyond water base, supplied with the full elemental dossier and a Certificate of Analysis per lot, in formats from small vials to 1000 L single-use bags.

How is the water's elemental profile documented? —

All 24 ICH Q3D elements are measured by validated ICP–MS and the actual values are reported on every Certificate of Analysis, with iron added in an oxidation–metals addendum. The water is also backed by a filed FDA Type IV (excipient) Drug Master File (MF044505).

Measure the other half

Ask for a WFI Beyond specification and elemental dossier, or talk to us about converting your powder to a documented GMP liquid.

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Manufactured to GMP in an EU Annex 1 facility within an ISO 9001 quality system (a capability, not a certification). WFI Beyond is an opt-in, beyond-compendial water grade available on request; elemental values are reported per lot on the Certificate of Analysis.