Beyond Compendial, Applied to Buffers and Reagents

By Sarah Gierl, Head of R&D, PAN-Celltech · Rev 1.5 · 25 Nov 2026 · for antibody, mRNA, cell & gene and vaccine downstream processing · Download the PDF

Key takeaways

- Compendial (Ph. Eur./USP) buffers meet the monograph - but a modern regulatory filing is judged against the ICH impurity dossier, not the monograph alone.
- The paper maps five impurity classes to buffers and reagents: elemental impurities (ICH Q3D), residual solvents (Q3C), nitrosamines (M7(R2)), extractables and leachables (Q3E, draft), and TSE/BSE safety (EMA/410/01 Rev. 3).
- It shows which of these matter most for monoclonal antibodies, mRNA/pDNA, cell & gene therapy and vaccines - the range covers all four.
- WFI Beyond and PAN's documentation close these gaps where a molecule needs it; nuclease-free water and animal-component-free status (TSE/BSE safety) where it counts, backed by a signed declaration.
- Buffer-specific numbers come from the per-lot Certificate of Analysis - published attributes are conservative and never fabricated.

The impurity control, ICH-grade documentation and single-use assurance behind WFI Beyond - extended across the downstream portfolio, and mapped to what each modality needs.

In brief. The WFI Beyond standard was never really about water. It was about a way of making and documenting a raw material - controlling the impurities a modern filing actually has to clear, measuring them, and reporting the values on the Certificate of Analysis. A buffer is water plus solutes: it inherits every water risk and adds the solutes' own. This paper carries the "Beyond" standard from the water to the whole downstream portfolio - DPBS, chromatography and formulation buffers. It walks the modern impurity dossier - endotoxin, nucleases, elemental impurities (ICH Q3D), residual solvents (ICH Q3C), nitrosamines and mutagenic impurities (ICH M7(R2) with the current EMA guidance), extractables & leachables (the emerging ICH Q3E), and TSE/BSE safety (EMA/410/01 Rev. 3) - and maps what matters most to each modality: monoclonal antibodies, mRNA, cell & gene therapy and vaccines. The short version: we have it all, and we put the numbers on the CoA.

1. "Beyond" was never really about water

WFI Beyond earned its name by going past the compendial monograph on the attributes that actually threaten a modern biologic - endotoxin more than fifty times below the limit, organic carbon ten times below, conductivity more than five times below, nuclease-free, animal-component-free, and elemental impurities characterised to a finished-drug standard - including copper and iron, the two metals that catalyse antibody oxidation by Fenton chemistry - all reported lot by lot. But none of that is a property of water. It is a way of making

and documenting a raw material: decide which impurities matter to today's molecules, control them, measure them, and hand the customer the data.

That way of working does not stop at the water. A buffer is water plus solutes - salts, acids, bases, sugars, surfactants. So it inherits every risk the water carried, and then adds the solutes' own: elemental impurities from the salts, residual solvents and potential nitrosamine precursors from synthesis, and leachables from the single-use container it ships in. If anything, the impurity question is larger for a buffer than for the water beneath it.

A buffer is water plus solutes - it inherits every water risk and adds the solutes' own. The "Beyond" standard belongs on the buffer at least as much as on the water.

This paper takes the WFI Beyond philosophy and applies it across the downstream portfolio - DPBS, chromatography and formulation buffers alike - so the same controlled, measured, documented standard runs under every step of the train.

2. The modern impurity dossier - what a filing must clear

The pharmacopoeial monographs were written for a simpler era of medicine. The first European Pharmacopoeia dates back to 1969, long before today's biologics - and its monographs remain the baseline a raw material must meet. By design, though, a monograph sets a defined floor - conductivity, total organic carbon, endotoxin - and does not cover the full ICH impurity dossier a modern biologics filing must clear: elemental impurities, residual solvents, nitrosamines, and extractables and leachables. A biologic reaching a patient today has to answer for impurity classes those monographs never named - and the questions arrive in the raw materials long before they arrive in the drug. Here is the dossier a modern filing actually has to clear, and the basis on which the portfolio is built to clear it:

Impurity class	Why it matters	The standard - and the basis we work to
Endotoxin	Pyrogenic; a direct patient-safety concern in any injectable	Controlled well below the compendial ceiling; reported on the CoA
Nucleases (RNase / DNase)	Degrade nucleic acids - variability for proteins, a direct potency hit for mRNA and gene therapy	Controlled through the WFI Beyond water base, which is released nuclease-free; for other buffers, lot-specific RNase/DNase testing with a separate certificate on request
Elemental impurities	Trace metals - copper and iron above all - catalyse oxidation and aggregation by Fenton chemistry; a finished-drug requirement, and iron sits outside ICH Q3D	ICH Q3D - the 24 elements by ICP-MS, measured values (not pass/fail) on the CoA; on the WFI Beyond base, copper and iron both below LOQ
Residual solvents	Process solvents that must be limited and declared	ICH Q3C - controlled and declared

Impurity class	Why it matters	The standard - and the basis we work to
Nitrosamines / mutagenic impurities	DNA-reactive carcinogens; the class that forced global recalls from 2018	ICH M7(R2) and the current EMA nitrosamines guidance - risk-assessed and controlled
Extractables & leachables	Migrate from single-use films and container-closure into the product	Screened against the emerging ICH Q3E framework; films tested - DEHP and other phthalates, Bisphenol A, dioxin, melamine not identified
TSE / BSE & animal origin	An animal-component question runs through every filing	TSE/BSE safety (animal-component-free), to EMA/410/01 Rev. 3 - by signed declaration
Organic carbon & conductivity	General markers of purity and ionic control	Held well within compendial limits; reported on the CoA

Note. *ICH Q3E (extractables & leachables) is an emerging guideline still at draft (Step 2) stage; we build to its framework now so the portfolio is ready as it finalises. Product-specific values - the actual numbers for a given buffer, grade and pack - are reported on that product's Certificate of Analysis.*

3. One standard, every modality - we have it all

What makes this powerful is the same thing that made WFI Beyond powerful: the controlled standard is not specific to one product. Antibodies, mRNA, cell and gene therapies and vaccines rest on profoundly different biology - but all of them run on buffers, and each simply leans on a different part of the same impurity dossier. The specification answers all of them; the emphasis shifts by modality:

Modality	What matters most in the buffers	How the portfolio covers it
Monoclonal antibodies	Low trace metals (copper & iron); ultra-low endotoxin	Built on the WFI Beyond water base, which removes trace copper and iron - the two Fenton catalysts of antibody oxidation (iron beyond what ICH Q3D even asks); ICH Q3D elemental control and low endotoxin for the injectable
mRNA & LNP products	Nuclease-free, above all else	WFI Beyond as the nuclease-free water base - the single most important attribute for payload potency; lot-specific RNase/DNase testing of the buffers on request
Cell & gene therapy	Endotoxin + nuclease control + sterility	Ultra-low endotoxin and single-use sterile; nuclease control through the WFI Beyond water base, with lot-specific buffer testing on request - no margin for pyrogens or contamination in patient-proximate products
Vaccines	Endotoxin control and sterility at scale	Pyrogen safety and batch-to-batch consistency held across large production volumes

Read down the table and the message is simple: whatever you are making, the same controlled standard sits beneath your buffers. You do not assemble it modality by modality from different suppliers - we have it all, under one standard and one Certificate of Analysis.

4. The documentation is the product

Under GMP, controlling an impurity is only half the job - proving and documenting it is the other half, and it is the half that lands on your QA team. The Beyond approach is built to hand that work over, not tip it over the fence.

- **Measured values, not pass/fail -** the elemental profile and the attribute panel arrive as actual numbers on the Certificate of Analysis, ready to drop into your own ICH Q3D risk assessment and your filing.
- **A signed BSE/TSE & ICH Q3 declaration -** non-animal origin (out of scope of EMA/410/01 Rev. 3), with residual solvents, nitrosamines and elemental impurities risk-assessed across every product-contact material.
- **Single-use where it touches the product -** pre-sterilised (e.g. gamma-irradiated), single-use product-contact paths remove a contamination and carry-over entry point, with the film screened for extractables and leachables.
- **Regulatory support scaled to your need -** the two most fundamental utilities already carry filed FDA Type IV Drug Master Files - WFI Beyond (MF044505) and DPBS (MF044371) - to reference directly through a letter of authorisation; where another product genuinely needs it, a custom DMF can be filed on request, and a validated stability study is available as an option.

The economics point the same way: the documentation is part of the product, and a raw material that arrives fully characterised is one your QA function does not have to re-create. Impurity control and total cost of ownership are the same story told twice.

5. Conclusion

“Meets the monograph” tells you a buffer cleared a floor written for an earlier era of medicine. It does not tell you whether it was made for your molecule. The Beyond standard starts from the other end - from the impurities a modern biologic actually has to answer for - and it applies to the whole downstream portfolio, not just the water: endotoxin controlled and measured, nuclease freedom specified on the WFI Beyond water base and available per lot on the buffers on request, elemental impurities measured to ICH Q3D, residual solvents to Q3C, nitrosamines assessed to M7(R2) and EMA guidance, extractables and leachables screened to the emerging Q3E, TSE/BSE safety closed to EMA/410/01 Rev. 3 - reported, lot by lot, on the Certificate of Analysis.

Because it is one standard rather than a modality-specific patchwork, it can sit beneath an entire pipeline - antibodies, mRNA, cell and gene therapies and vaccines alike. Whatever you are making, and wherever you are in its life, we have it all - controlled, measured and documented, under the buffers as much as in the water.

Go deeper: the water this standard began on is In-Depth Industry Edition D02 · Water; the full downstream toolkit it runs beneath is In-Depth Industry Edition D01 · Downstream.

Companion technical papers: TP-01 · The Open Downstream; TP-03 · From Bench to GMP; TP-04 · WFI Beyond – Beyond Compendial.

Frequently asked questions

What does "beyond compendial" mean? +

Which impurity guidances does a modern filing test against? +

Which impurities matter most for mRNA, cell & gene and vaccines versus antibodies? +

Is WFI Beyond animal-free and nuclease-free? +

Where do the buffer-specific numbers come from? +

Talk to us about the Beyond standard

Ask for a WFI Beyond specification, a Certificate of Analysis, or a beyond-compendial version of any downstream buffer.

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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 grade available on request.