PAN-BIOTECH · PAN-CELLTECH · DOWNSTREAM WHITEPAPER

Beyond Compendial, Applied to Buffers and Reagents

By PAN-Celltech R&D · Rev 1.0 · 4 Aug 2026 · for antibody, mRNA, cell & gene and vaccine downstream processing

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).
- 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 and animal-component-free where it counts.
- 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 (EMA/410/01) - 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 far below the limit, nuclease-free, animal-component-free, elemental impurities characterised to a finished-drug standard, 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. 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	Manufactured and tested to a nuclease-free basis
Elemental impurities	Trace metals catalyse oxidation and aggregation; a finished-drug requirement	ICH Q3D - the 24 elements by ICP-MS, with measured values (not pass/fail) available on the CoA
Residual solvents	Process solvents that must be limited and declared	ICH Q3C - controlled and declared
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	Animal-component-free; TSE/BSE statement to EMA/410/01
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; ultra-low endotoxin	ICH Q3D elemental control protects against oxidation and aggregation; low endotoxin for the injectable
mRNA & LNP products	Nuclease-free, above all else	RNase/DNase-free buffers and WFI - the single most important attribute for payload potency
Cell & gene therapy	Endotoxin + nuclease control + sterility	Ultra-low endotoxin, nuclease-free and single-use sterile - 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.
- **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 -** where a product genuinely needs it, a DMF listing can be filed on request for you to reference directly, and a validated stability study is available as an option - neither carried on every item, both there when your filing calls for it.

This is the same argument the companion paper, *Beyond the Unit Price*, makes on economics: 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 and nucleases controlled, 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, animal origin closed to EMA/410/01 - 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.

Talk to us about the Beyond standard

To request a product specification, a Certificate of Analysis or an ICH Q3D elemental data set for a downstream buffer or reagent - in any modality - or to discuss a DMF listing or stability study for a product you depend on, contact us at info@pan-celltech.com or visit www.pan-biotech.com.

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Frequently asked questions

What does "beyond compendial" mean?

It means going beyond the Ph. Eur./USP monograph on the attributes that actually matter for a sensitive molecule - for example endotoxin, nuclease activity and animal-origin risk - rather than only meeting the minimum the monograph requires.

Which impurity guidances does a modern filing test against?

Chiefly ICH Q3D (elemental impurities, 24 elements by ICP-MS), Q3C (residual solvents), M7(R2) with EMA guidance (nitrosamines), Q3E (extractables and leachables - currently draft/Step 2, cited as emerging) and EMA/410/01 (TSE/BSE safety).

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

Nuclease freedom and animal-component-free status are critical for mRNA/pDNA and cell & gene; elemental and leachable control matter across all

modalities; TSE/BSE safety applies wherever any animal-derived risk could enter. The paper maps each class per modality.

Is WFI Beyond animal-free and nuclease-free?

Yes - WFI Beyond is animal-component-free and nuclease-free, with endotoxin roughly fifty times below the compendial limit, and it is backed by a filed FDA Drug Master File.

Where do the buffer-specific numbers come from?

From the per-lot Certificate of Analysis, tested and released against a defined panel - not advertised as fixed marketing figures. Published product attributes are limited to fixed properties such as composition and, where defined, pH.

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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PAN-Biotech GmbH · PAN-Celltech GmbH (GMP arm / manufacturer of record) · www.pan-biotech.com
Manufactured to GMP in an EU Annex 1 facility within an ISO 9001 quality system. WFI Beyond is an opt-in, beyond-compendial grade available on request.