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In-House Research - Whitepaper - Q3 2026

GC-MS Analysis Of Bisphenols: A Validated Method For Simultaneous Multi-Analogue Detection In Complex Matrices



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About Medistri

Medistri, a Swiss company established in 2006, is a trusted partner to the Medical Device and Pharmaceutical industries. With a 13,193 m² facility and more than 92 employees, Medistri provides specialized services in Sterilization, Laboratory, Validation, Packaging, and Manufacturing.

Operating 24/7 from its facilities in Domdidier, Switzerland, and Székesfehérvár, Hungary, Medistri supports customers ranging from startups to global manufacturers.

Committed to advancing healthcare product development, Medistri combines specialized infrastructure with scientific expertise to support every stage of the product lifecycle. Its laboratory operates under GLP and ISO/IEC 17025 standards and holds STS 504 accreditation, delivering high-quality testing services for the Pharmaceutical, MedTech, and BioTech sectors.

To help manufacturers address increasing regulatory scrutiny surrounding bisphenols, Medistri has developed a Whitepaper presenting a validated GC-MS method for the simultaneous detection of 16 bisphenol analogues in complex matrices. It explores the regulatory context, analytical challenges, and method validation while demonstrating how robust chemical characterization supports compliance with ISO 10993-18 and other international requirements.

Medistri invites you to explore this Whitepaper as a practical resource for understanding the analytical challenges and regulatory considerations surrounding bisphenols. We hope it provides valuable insights for your chemical characterization studies. For further information or to discuss how Medistri can support your projects, please contact us at contact@medistri.com.

— The Medistri Team



Medistri's Sterilization Chamber



In-House Medistri's Laboratory

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GC-MS Analysis Of Bisphenols: A Validated Method For Simultaneous Multi-Analogue Detection In Complex Matrices

Scope Of Application: Medical Devices (ISO 10993-18) / Food Contact (EU 10/2011) / Toy Safety

Coverage: 16 Bisphenol Analogues Simultaneously (BPA, BPS, BPF, BPB, BPE, BPC, BPG, BPZ, BPTMC, BPAP, BPM, BPP, BPBP, BPAF, BPC, BADGE)

Accreditation: ISO/IEC 17025

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Version: 2, May 2025

List Of Abbreviations

Abbreviation	Definition
BPA	Bisphenol A (CAS 80-05-7)
BADGE	Bisphenol A bis(2,3-dihydroxypropyl) ether (CAS 5581-32-8)
BPAP	4,4'-(α -Methylbenzylidene)bisphenol, "Bisphenol AP" (CAS 1571-75-1)
BPAF	2,2-Bis(4-hydroxyphenyl)hexafluoropropane, "Bisphenol AF" (CAS 1478-61-1)
BPB	4,4'-(1-Methylpropylidene)bisphenol, "Bisphenol B" (CAS 77-40-7)
BPBP	4-[(4-Hydroxyphenyl)diphenylmethyl]phenol, "Bisphenol BP" (CAS 1844-01-5)
BPC	2,2-Bis(4-hydroxy-3-methylphenyl), "Bisphenol C" (CAS 79-97-0)
BPE	4,4'-Ethylidenebisphenol, "Bisphenol E" (CAS 2081-08-5)
BPG	4,4'-(Propane-2,2-diyl)bis(2-isopropylphenol), "Bisphenol G" (CAS 127-54-8)
BPF	Bis(4-hydroxyphenyl)methane, "Bisphenol F" (CAS 620-92-8)
BPP	α,α' -Bis(4-hydroxyphenyl)-1,4-diisopropylbenzene, "Bisphenol P" (CAS 2167-51-3)
BPS	4,4'-Sulfonyldiphenol, "Bisphenol S" (CAS 80-09-1)
BPTMC	4,4'-(3,3,5-Trimethylcyclohexane-1,1-diyl)diphenol, "Bisphenol TMC" (CAS 129188-99-4)
BPZ	1,1-Bis(4-hydroxyphenyl)cyclohexane, "Bisphenol Z" (CAS 843-55-0)
BPA-d16	2,2-Bis(4-hydroxyphenyl)propane-d16, "Bisphenol A D16" (CAS 96210-87-6)
BSTFA	N,O-Bis(trimethylsilyl)trifluoroacetamide (CAS 25561-30-2) — silylation reagent used for derivatization
TMCS	Trimethylchlorosilane
CAS	Chemical Abstracts Service
DCM	Dichloromethane (CAS 75-09-2)
TDI	Tolerable Daily Intake — acceptable exposure value set by EFSA
E&L	Extractables & Leachables

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Abbreviation	Definition
EFSA	European Food Safety Authority
EI+	Electron Impact (positive)
GC-MS	Gas Chromatography–Mass Spectrometry
GUM	Guide to the Expression of Uncertainty in Measurement
ISO	International Organization for Standardization
ISTD	Internal Standard — here BPA-d16
LC-MS/MS	Liquid Chromatography tandem Mass Spectrometry
SML	Specific Migration Limit
LOD	Limit of Detection
LOQ	Limit of Quantification
m/z	Mass-to-charge ratio
RT	Retention Time
RSD	Relative Standard Deviation
SIM	Selected Ion Monitoring
SPE	Solid Phase Extraction
U_{exp}	Expanded uncertainty (k=2, confidence level ≈ 95%) per the GUM approach
FOPH	Federal Office of Public Health (Switzerland)
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
TMS	Trimethylsilanol (CAS 1066-40-6)
S/N	Signal-to-noise ratio
DRRR	Deutsches Referenzbüro für Ringversuche und Referenzmaterialien
USP	United States Pharmacopeia
FDA	Food and Drug Administration

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1. Bisphenols: The Problem And The Regulatory Context

1.1. Evolving Toxicological Knowledge And Substitution Dynamics

Bisphenols are a family of industrial organic compounds whose use in technical polymers and epoxy resins goes back several decades. Their structural features (two phenolic rings linked by a central bridge) make them particularly effective for synthesizing high-strength plastics, internal coatings, and components intended for food contact or medical devices. This industrial ubiquity has, however, been accompanied by growing recognition of their ability to migrate out of polymer matrices and to interact with hormonal systems.

Bisphenol A (BPA, CAS 80-05-7) prompted the first scientific concerns in the early 2000s. Studies have documented its effects on reproduction, embryonic development, metabolism, and certain immune functions.

In the face of accumulating data, regulatory authorities progressively tightened the conditions of use for BPA, pushing manufacturers toward analogues, chiefly bisphenol S (BPS, CAS 80-09-1), bisphenol F (BPF, CAS 620-92-8), and bisphenol B (BPB, CAS 77-40-7). These substitutes share the same molecular backbone and exhibit similar biological mechanisms of action, which has shown that replacing one bisphenol with another does not solve the underlying problem.

This substitution has therefore broadened the analytical challenge: the goal is no longer to monitor BPA alone, but to identify and quantify the entire chemical family simultaneously. Bisphenols share certain physicochemical properties, but their analytical behavior and toxicity levels vary from one compound to another, which demands a rigorously validated method.

1.2. Migration And Real-World Exposure Routes

The risk associated with bisphenols lies not only in their toxicity, but above all in their capacity to migrate out of the materials that contain them. This release-by-diffusion phenomenon intensifies under several factors: prolonged contact with food, biological fluids, or organic solvents; thermal fluctuations; and aging or mechanical degradation of the material.

For food-contact materials, studies have shown that this migration can occur at room temperature, its magnitude depending on the nature of the polymer, the type of simulant, and the contact duration. For medical devices, the risk is even more critical: the materials are in direct or indirect contact with the human body, sometimes for extended periods, and the released compounds can reach sensitive biological fluids. In this context, extractables and leachables (E&L) studies represent an unavoidable regulatory and toxicological imperative.

1.3. Applicable Regulatory Framework

In response to the accumulation of toxicological data, authorities have progressively tightened requirements. EFSA lowered the tolerable daily intake (TDI) for BPA to 0.2 nanograms per kilogram of body weight per day – a value that places acceptable exposure levels at the detection limits of the most capable analytical methods.

Scope of application	Compound(s)	Limit / Status
EU – Plastic food contact (Reg. 10/2011)	BPA	SML 0.05 mg/kg food
Switzerland (FOPH) – Plastic food contact	BPA	0.05 mg/kg
Switzerland (FOPH) – Coatings for infant food	BPA	Zero migration
Switzerland (FOPH) – Toys	BPA	0.04 mg/L
Switzerland – Polycarbonate baby bottles	BPA	Banned
Switzerland – Thermal papers	BPA, BPS	< 0.02% w/w
EU REACH – Consumer articles	BPA	Restricted since March 2018
EU – Thermal papers	BPA	Restricted since January 2020
ISO 10993-18 – Medical devices	All bisphenols	Chemical characterization mandatory
ECHA – Restriction proposal 2022	BPA + analogues	Assessment ongoing

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2. Analytical Challenges Specific To Bisphenols

2.1. Constraining Physicochemical Properties

Bisphenols are phenolic compounds characterized by low volatility, moderate-to-high polarity, and a marked tendency to interact with polymer matrices. These properties directly govern their behavior at each analytical stage: extraction, derivatization, chromatographic separation, and detection.

Without prior chemical modification, direct gas-chromatographic analysis proves poorly suited: limited volatilization, broad or ill-defined chromatographic peaks, and a risk of partial thermal degradation during injection. Conversely, liquid-chromatography approaches take advantage of their polarity but run into substantial matrix effects when the matrices are complex, causing instability of the analytical signal.

2.2. Concentration Levels And Sensitivity Requirements

In current regulatory contexts (food migration, E&L studies per ISO 10993-18), the concentrations to be measured generally fall in the ng/g range, or below. At these levels the analytical method must not only be sensitive, but also stable and reproducible. A low limit of quantification is only meaningful when paired with good precision and an uncertainty compatible with the regulatory decisions to be made.

2.3. Matrix Complexity And Matrix Effects

Bisphenols are analyzed in highly diverse matrices: medical-device extracts, regulatory food simulants (Tenax®, ethanol, acetic acid, isooctane), and polymers subjected to accelerated extraction conditions. These matrices contain numerous compounds liable to interfere: plasticizers, stabilizers, antioxidants, oligomers, and thermal or oxidative degradation products considered co-extractives.

In LC-MS/MS, these co-extractives impair ionization efficiency (ion suppression), compromising signal stability and forcing heavy adaptations: solid-phase extraction (SPE) cleanup, systematic use of deuterated standards, and matrix-specific calibration strategies. In GC-MS, matrix effects are generally less pronounced but persist for certain bisphenols of low volatility or moderate thermal stability (notably BPS and BPF). Inter-matrix robustness is therefore a decisive criterion for any method intended for routine use on samples of varied nature.

2.4. State Of The Art: Strengths And Limitations Of Published Approaches

Liquid chromatography (LC-MS/MS)

Widely adopted for its sensitivity and its compatibility with polar compounds without prior derivatization, LC-MS/MS remains strongly dependent on matrix effects in complex polymer extracts. It often requires significant methodological adjustments for each matrix type, which limits its transferability in a routine multi-matrix context.

GC-MS without derivatization

Performance remains insufficient for reliable trace-level quantification: inadequate volatility, asymmetric peaks, reduced reproducibility, and the risk of degradation in the injector. This approach is now very rarely used for the determination of bisphenols in complex matrices.

GC-MS after silyl derivatization

Introducing a chemical derivatization step radically transforms performance. By converting the phenolic functions into trimethylsilyl (TMS) derivatives, analyte volatility increases, thermal behavior is stabilized, peak resolution sharpens, and the signal-to-noise ratio improves. Comparative solid-phase studies confirm recovery rates of 93–96% for GC-MS/BSTFA (Jurek & Leitner, 2015), with better inter-matrix reproducibility than LC-MS/MS approaches in polymer extracts rich in co-extractives.

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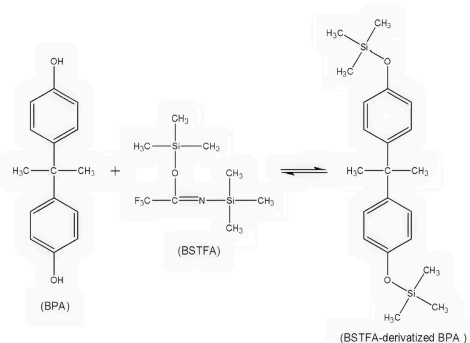


Figure 1 - Reaction scheme: BPA + BSTFA

3. The Medistri Method: Development, Choices, And Key Parameters

3.1. Positioning And Development Philosophy

The philosophy guiding the development of the Medistri method rests on a central principle: favor a robust, reproducible approach across a wide range of matrices rather than optimize performance on a single matrix. This positioning responds directly to the intended application contexts – E&L studies for medical devices (ISO 10993-18) and specific-migration testing for food-contact materials (EU 10/2011) – which impose high demands in terms of comparability, traceability, and transferability of results.

In practice, this methodological choice translates into a single operating sequence covering 16 bisphenols and derivatives in one analysis, with validation documented under ISO/IEC 17025 accreditation.

3.2. Rationale For The GC-MS / BSTFA Derivatization Choice

Compared with LC-MS/MS approaches, GC-MS after derivatization offers several decisive advantages in the intended context:

- Better chromatographic separation in matrices rich in co-extractives.
- Instrumental stability, favorable for multi-series studies spread over time.
- More uniform analytical response across matrices of differing nature.
- Lower sensitivity to ion-suppression effects.

The chosen silylating reagent, BSTFA (N,O-bis(trimethylsilyl)trifluoroacetamide) with 1% TMCS, offers the best compromise between reaction efficiency on phenolic functions, stability of the resulting derivatives, and compatibility with GC-MS detection in SIM mode. The derivatization conditions were validated experimentally (see §3.4), not adopted on a purely theoretical basis.

3.3. Instrumentation

All analyses are performed on a Perkin Elmer Clarus 690 gas chromatograph coupled to a Clarus SQ 8T mass spectrometer (positive EI source). Data acquisition and processing are handled by TurboMass software v6.1.

Parameter	Specification
Capillary column	Elite-5MS, 30 m × 0.25 mm I.D., 0.25 µm df (Perkin Elmer, Art. N9316282)
Carrier gas	Helium, constant flow
Injection volume	2 µL, autosampler
Liner	Topaz Split Precision with wool, 4 mm × 6.3 × 78.5 mm (Restek 23799)
Solvent delay	5.00 min
Ionization source	Electron impact (EI+), 70 eV
Acquisition mode	SIM (Selected Ion Monitoring)
Internal standard	BPA-d16 (deuterated bisphenol A), 100 µg/mL in methanol

3.4. Experimental Optimization Of The Derivatization Conditions

A systematic comparative study was conducted to identify the optimal derivatization conditions. Several parameters were evaluated (see Figures 2 and 3): BSTFA volume (25, 50, 100 µL), reaction temperature (room temperature, 30 °C, 40 °C), duration (5, 15, 30 min), and pyridine addition (0, 25, 50 µL). The selected conditions (25 µL BSTFA, 40 °C, 30 min) ensure complete derivatization of all 16 analytes with high inter-series reproducibility. The impact of each parameter was evaluated individually:

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(1) The 40 °C temperature represents the threshold above which silylation kinetics are complete for all 16 analytes, including bisphenols with more limited thermal stability such as BPS. A lower temperature (room temperature or 30 °C) leads to partial derivatization for certain analytes, producing an underestimation of the concentration.

(2) The 30-minute duration ensures that reaction equilibrium is reached: at 5 min the conversion rate remains incomplete; at 15 min the results are acceptable but vary by analyte.

(3) The 25 µL BSTFA volume corresponds to the stoichiometric excess sufficient to cover both phenolic functions of each bisphenol in a sample at 10 µg/mL, without excess reagent that would penalize chromatographic separation by saturating the source.

(4) Pyridine addition (a catalyst for the silylation reaction) proved to bring no measurable benefit and to be potentially disruptive for certain analytes; it was therefore excluded from the final protocol.

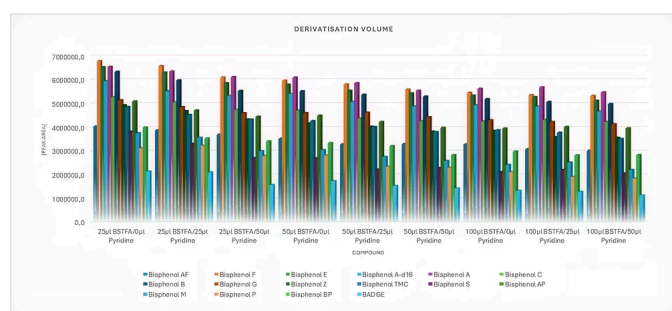


Figure 2 - Effect of BSTFA volume on the instrumental response (sum of relative peak areas, 16 bisphenols, 1 µg/mL standard). Three volumes were compared: 25, 50, and 100 µL (conditions: 40 °C / 30 min, n-hexane solvent). The 25 µL volume is the minimum stoichiometric excess ensuring complete silylation of both phenolic functions; higher volumes provide no significant gain and generate a reagent excess liable to disturb the chromatographic separation. Selected optimal condition: 25 µL BSTFA + 0 µL pyridine.

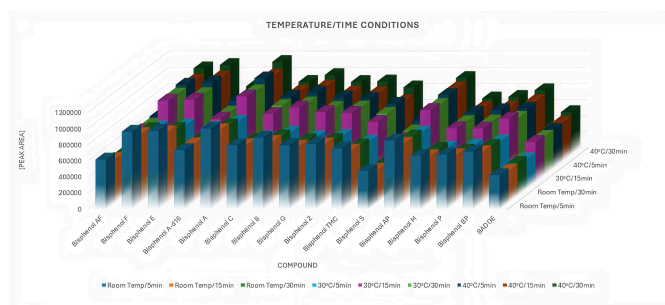


Figure 3 - Effect of reaction temperature (room temperature, 30 °C, 40 °C) and incubation time (5, 15, 30 min) on the BSTFA derivatization rate (sum of relative peak areas, 16 bisphenols, 25 µL BSTFA, n-hexane solvent). Room temperature and 30 °C lead to incomplete derivatization for several analytes (notably BPS). The 5-minute duration is insufficient at any temperature; 15 min gives analyte-dependent variable results. The 40 °C / 30 min combination ensures complete conversion and the best inter-series reproducibility for the 16 compounds. Selected optimal conditions: 40 °C, 30 min.

The effect of the reaction-medium solvent was also the subject of a quantitative study (see Figure 4) comparing n-hexane, chloroform, and ethyl acetate across the 16 target bisphenols. The choice of solvent directly affects the integrity of the TMS derivatives: a polar solvent promotes partial rehydrolysis of the silylated groups, whereas an aprotic, nonpolar solvent preserves their stability. The results obtained are presented below:

Solvent	CAS No.	Sum of areas (16 bisphenols)	Relative response (%)
n-Hexane	110-54-3	18,547,777.7	37.46
Chloroform	67-66-3	15,612,817.9	31.53
Ethyl acetate	141-78-6	15,477,224.0	31.26

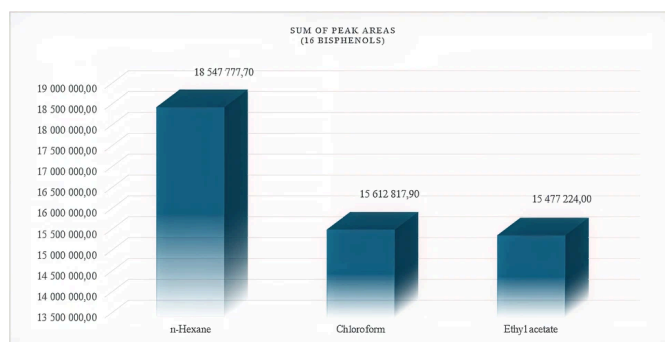


Figure 4 - Comparison of the instrumental response (sum of areas, 16 bisphenols) for three reconstitution solvents after BSTFA derivatization: n-hexane (CAS 110-54-3), chloroform (CAS 67-66-3), and ethyl acetate (CAS 141-78-6). Standard 1 µg/mL, conditions: 40 °C / 30 min / 25 µL BSTFA. n-Hexane shows the highest response (+19% vs chloroform, +20% vs ethyl acetate) and was selected.

n-Hexane produces the highest and most stable

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instrumental response for nearly all analytes (Figure 4). This superiority is explained by its low polarity, which preserves the integrity of the silylated derivatives and minimizes parasitic interactions: the sum of areas for the 16 bisphenols reaches 18,547,778 in n-hexane, versus 15,612,818 for chloroform and 15,477,224 for ethyl acetate — i.e., +19% and +20% additional response, respectively. It was selected as the official injection solvent for the method.

3.5. Experimental Optimization Of The Derivatization Conditions

The GC-MS method is built around targeted SIM acquisition. Monitoring characteristic ions specific to the TMS derivative of each bisphenol improves sensitivity, reduces background noise, and ensures effective discrimination against co-extracted compounds. The table below lists the 16 target compounds with their chromatographic and detection parameters:

No.	Compound	CAS No.	RT (min)	Quant. ion / Qual. ions [m/z]
1	Bisphenol AF	1478-61-1	11.48	73 / 480, 411, 225
2	Bisphenol F	620-92-8	12.81	73 / 344, 179
3	Bisphenol E	2081-08-5	13.05	73 / 358, 344, 343
4	ISTD BPA-d16	96210-87-6	13.26	368 / 369, 367, 73
5	Bisphenol A (BPA)	80-05-7	13.34	357 / 358, 79
6	Bisphenol C	79-97-0	13.93	385 / 386, 73
7	Bisphenol B	77-40-7	14.02	357 / 358, 73
8	Bisphenol G	127-54-8	14.16	73 / 442, 441
9	Bisphenol Z	843-55-0	16.38	73 / 412, 369
10	Bisphenol TMC	129188-99-4	16.62	73 / 454, 383, 179
11	Bisphenol S (BPS)	80-09-1	16.97	73 / 394, 379, 135
12	Bisphenol AP	1571-75-1	17.22	419 / 420, 73
13	Bisphenol M	13595-25-0	18.39	73 / 476, 475, 207
14	Bisphenol P	2167-51-3	19.56	475 / 476, 207, 73
15	Bisphenol BP	1844-01-5	20.09	73 / 420, 419, 331
16	BADGE	5581-32-8	21.84	73 / 207, 147, 103

3.6. Extraction Protocols

Liquid extraction (Procedure A)

100 mL of aqueous sample is spiked with 10 µL of BPA-d16 (100 µg/mL). Extraction in a separatory funnel (3 × 10 mL chloroform), evaporation to dryness on a rotary evaporator, reconstitution in 1 mL methanol, then evaporation to dryness at 80 °C before derivatization.

Solid extraction (Procedure B)

0.1 g of solid material is spiked with 10 µL of BPA-d16 (100 µg/mL), extracted in 10 mL chloroform (ultrasonic bath, 50 °C, 30 min), centrifuged (5 min / 1,200 rpm), then filtered and evaporated to dryness before derivatization. Mean recovery rates: 95.3% (dichloromethane) and 89.8% (chloroform); DCM was standardized for sample preparation.

Derivatization protocol (common)

- Complete evaporation to dryness at 80 °C.
- Add 25 µL BSTFA (with 1% TMCS).
- Incubate at 40 °C with orbital shaking (180 rpm), 30 min.
- Add 975 µL n-hexane, homogenize → sample ready for GC-MS injection.

3.7. Calibration Strategy And Quality Control

A 6-level external calibration curve (0.2 – 0.5 – 1.0 – 2.0 – 5.0 – 10.0 µg/mL) is prepared in duplicate over three independent series. Quantification is performed by normalization to the BPA-d16 internal standard. Linearity is required ($R^2 \geq 0.995$) before any acceptance of results.

Following analysis of the uncertainty profile, the 0.1 µg/mL level was excluded from the routine range (uncertainty $\geq 40\%$). The routine LOQ is set at 2 µg/mL; values between 0.2 and 2 µg/mL are reportable as an “estimated value” with no associated uncertainty.

Each analytical sequence includes: a control check at 2 µg/mL at the start and end of the sequence, an extraction blank per batch, an intermediate control check every 10 samples, and a leak check at the start of each day.

4. Analytical Validation Results

Validation conducted in accordance with internal Medistri procedures, the principles of ISO/IEC 17025, and the requirements of ISO 10993-18 – Report #2302572 Rev.2,

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4.1. Linearity

Linearity is verified over the 0.2–10 µg/mL range for the 16 compounds across three independent series. The acceptance criterion ($R^2 \geq 0.995$, no systematic curvature in the residuals) is met for all analytes in every series. Representative calibration curves and the associated residual plots are presented in Figures 5, 6, and 7 below.

Result $R^2 \geq 0.995$ for all 16 bisphenols (criterion met in all 3 validation series)

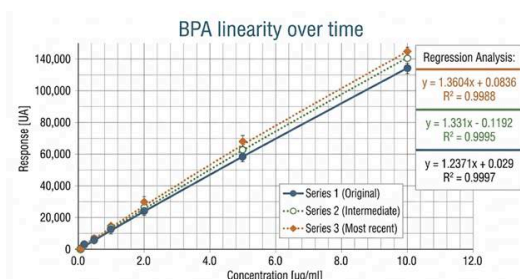


Figure 5 - Representative calibration curve (BPA, Series 1) over the range of 0.2–10 µg/mL, with regression line and equation ($R^2 \geq 0.995$).

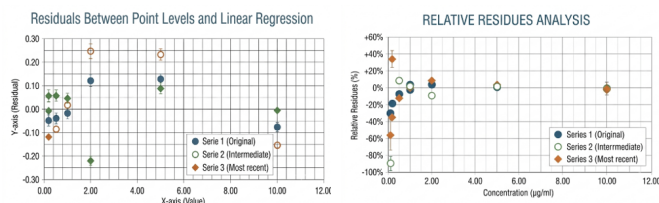


Figure 6 & 7 - Residual plots (BPA-d16, Series 2 and 3) illustrating the absence of systematic curvature and the random distribution of deviations around zero, in accordance with the acceptance criterion. The three calibration series were performed by two different operators, confirming inter-series reproducibility.

4.2. Limits Of Detection And Quantification

Parameter	Value / Criterion	Comment
LOD	0.01 – 0.03 µg/mL	Determined experimentally (S/N, repeatability)
Routine LOQ	2 µg/mL	Defined by uncertainty profile ($U < 25\%$)
Measurement range	0.2 – 10 µg/mL	$R^2 \geq 0.995$
LOQ solid matrix (BPA)	< 10 ng/g	Compatible with ISO 10993-18 thresholds

4.3. Repeatability And Intermediate Precision

Level	Concentration (µg/mL)	RSDr repeatability (S)	RSDR intermediate precision (S)
STD2	0.2	11%	22%
STD3	0.5	11%	22%
STD5	2.0	8%	16%
STD6	5.0	8%	16%

All acceptance criteria were met for all 16 compounds at the four concentration levels. No systematic inter-operator bias was observed, confirming the transferability of the method within the laboratory.

4.4. Accuracy And Recovery

Accuracy tests were performed on samples spiked at the STD2, STD3, STD5, and STD6 levels, over three days and two operators. Analytical recovery ranges from 92.0% to 100.1% for all bisphenols studied. These values are consistent with those reported in the literature for comparable GC-MS/BSTFA methods (Jurek & Leitner, 2015: 93–96%).

4.5. Expanded Measurement Uncertainty

The expanded uncertainty (U , $k=2$, confidence level $\approx 95\%$) was calculated using the GUM approach, incorporating the main sources of variability: sample preparation, instrumental calibration, weighing, and analytical repeatability. The acceptance threshold $U < 25\%$ is reached from 2 µg/mL onward for all compounds.

Compound	U at 2 µg/mL
Bisphenol AF	$\leq 22.9\%$
Bisphenol F	$\leq 23.3\%$
Bisphenol E	$\leq 21.0\%$
Bisphenol A (BPA)	$\leq 24.3\%$
Bisphenol S (BPS)	$\leq 23.1\%$
BADGE	$\leq 23.3\%$
All other analogues	$\leq 24.7\%$

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5. External Assessment: Interlaboratory Proficiency Testing

5.1. DRRR Program – Plastic Matrix (Sample 2)

Medistri took part in the DRRR proficiency-testing program covering BPA quantification in a polymer matrix (assigned value: 1048.20 µg/kg ± 166.78 µg/kg). This program makes it possible to observe inter-laboratory dispersion across different analytical platforms:

Laboratory	Technique	Result (µg/kg)	z'-score
Lab 1	LC-MS/MS	1237.38	1.05
Lab 2	UPLC-FLR	1019.22	-0.16
Lab 3 (Medistri)	GC-MS derivatization	1257.04	1.16
Lab 4	LC-MS/MS	1178.40	0.72
Lab 5	LC-MS/MS	954.47	-0.52
Lab 7	LC-MS/MS	587.23	-2.56
Lab 8	LC-MS/MS	1100.00	0.29
Lab 10	LC-MS/MS	1166.35	0.66

The strong inter-laboratory dispersion (587 to 1257 µg/kg for the same material) confirms that the extraction step remains the principal source of bias, regardless of the instrumental technology. The Medistri result ($z' = 1.16$) falls within the satisfactory performance zone ($|z| \leq 2$), demonstrating the reliability of the derivatized GC-MS method in a real interlaboratory context.

5.2. TOYTEST TY109 Program – Childcare Articles (LGC Axio, 2024)

The TOYTEST Round 109 program (LGC Axio Proficiency Testing, Bury, UK) targeted the determination of total BPA in a plastic representative of a childcare article (assigned value: 18.73 mg/kg). This scheme explicitly compares several analytical technologies:

Laboratory	Technique	Result (mg/kg)	z-score
TY1011	LC-MS/MS	17.70	-0.09
TY1067 (Medistri)	GC-MS (WI-165)	18.73	0.00
Other participants	Various (LC-MS, GC, FLR)	11.72 – 34.10	-0.59 to 1.29

z' -score = 0.00 — Perfect concordance between the Medistri result and the value assigned by LGC. Best score among the 6 participating laboratories. This result constitutes an independent external validation of the WI-165 method under the real conditions of an international comparison program.

6. Applications Of The Method

6.1. Extractables & Leachables (E&L) Studies — ISO 10993-18

Within E&L studies for medical devices, the derivatized GC-MS method integrates naturally into the analytical strategy: it provides targeted quantification of the bisphenols identified during the prior non-targeted screening, with analytical traceability consistent with the requirements of ISO 10993-18. Its track record on complex polymer extracts confirms the stability of its performance despite the presence of numerous co-extractives.

6.2. Specific Migration — Regulation (EU) No 10/2011 And Swiss DFI 817.023.21

For specific-migration testing, the method has been adapted to the regulatory simulants, notably Tenax® (simulant E for dry foods) and the liquid simulants (ethanol, acetic acid, isooctane). The solid-matrix LOQ (< 10 ng/g) is compatible with the imposed migration thresholds. The method covers BPA and its substitution analogues (BPS, BPF, BPB) in a single analysis.

6.3. Toy Safety

Participation in the TOYTEST TY109 program directly confirms the method's ability to meet regulatory requirements for toy safety. The Swiss limit of 0.04 mg/L for BPA in toys is quantifiable with the method's LOQ after unit conversion based on the standardized extraction conditions.

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6.4. Identified Limitations And Complementarity With LC-MS/MS

Because the method is optimized for targeted analysis, it complements (but does not replace) the non-targeted screening approaches that are indispensable in complete E&L studies on unknown materials. Certain bisphenols of high polarity or limited thermal stability (BPS, some sulfonated derivatives) may exhibit more variable silylation efficiency. In these specific cases, a complementary LC-MS/MS analysis remains relevant.

7. Critical Discussion And Outlook

7.1. Summary Of The Method's Contributions

The main lesson of this work is that derivatized GC-MS constitutes a well-suited response to the current analytical constraints associated with bisphenols, provided the derivatization step is mastered rigorously. The Medistri method stands out for its transversality: designed from the outset as a multi-matrix tool, it demonstrates consistent performance across E&L extracts, food simulants, and solid plastic matrices.

The comparison with LC-MS/MS approaches during the DRRR and TOYTEST programs confirms that derivatized GC-MS offers at least equivalent accuracy and robustness, with better response stability in complex polymer matrices. This robustness translates directly into greater confidence in results intended for regulatory decisions or toxicological risk assessments.

7.2. Operational Points Of Vigilance

- Quality and freshness of the BSTFA reagent: incomplete or unstable derivatization is the principal source of analytical variability, which calls for rigorous control of the reaction conditions (temperature, duration) that can affect reproducibility.

- Stability of low-concentration standard solutions (< 10 µg/mL): freshness recommended, storage at 2–8 °C.

7.3. Future Developments

The regulatory environment for bisphenols continues to evolve: ECHA is currently assessing a broadened restriction covering BPA and its analogues with endocrine-disrupting activity. This evolution could require expanding the analytical panel and lowering the LOQ for certain compounds. The methodological platform developed is adaptable to these changes through reassessment of uncertainty profiles and updating of the SIM conditions for newly integrated compounds in the panel.

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8. Conclusion

Bisphenols today represent an analytical challenge at the intersection of materials chemistry, public health, and constantly evolving regulatory frameworks. Their widespread use in technical polymers and epoxy resins, combined with their endocrine-disrupting potential, demands rigorous and reliable analytical surveillance in the fields of medical devices and food-contact materials.

The GC-MS method developed and validated by Medistri under document WI-165 and validation report #2302572 Rev.2 meets this requirement with a pragmatic and documented approach.

It simultaneously covers 16 bisphenols and derivatives in varied solid and liquid matrices, relying on a validated BSTFA derivatization and a selective SIM acquisition.

Its performance — linearity ($R^2 \geq 0.995$), LOQ of 2 $\mu\text{g/mL}$ (< 10 ng/g in solid matrix), accuracy 92–100%, uncertainty < 25% — is consistent with the requirements of ISO 10993-18 and ISO/IEC 17025.

Participation in the DRRR ($z' = 1.16$, satisfactory) and TOYTEST TY109 ($z' = 0.00$, perfect concordance) proficiency-testing programs provides independent external confirmation of the reliability of the results produced. Applying the same method to E&L studies and specific-migration testing illustrates its transversality as a major operational asset in a context where the boundaries between regulatory domains are progressively tightening.

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- Validation Report #2302572 Rev.2 – Quantitative Analysis of Bisphenols by GC-MS (10 January 2025)
- Report F258 – Inter-Laboratory report for bisphenols analysis by GC-MS “Small-ILC” (14 January 2025)
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Standards and regulations

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- ISO 10993-12 – Sample preparation and reference materials (current version)
- ISO/IEC 17025 – General requirements for the competence of testing and calibration laboratories
- ISO 13528 (2022) – Statistical methods for use in proficiency testing
- Regulation (EU) No 10/2011 – Plastic materials in contact with food
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About the Author

With over 12 years of dedicated experience in analytical chemistry, Daniel Avella joined Medistri as Head of the Chemistry Laboratory. In his role, he leads the development of new analytical methods and serves as the primary officer ensuring the compliance and validity of testing procedures face to the Swiss Accreditation Service (SAS). He plays a key role in maintaining the scientific accuracy and regulatory excellence of Medistri's laboratory operations.

At Medistri, he brings a deep, hands-on expertise in chemical characterization and validation protocols, providing strategic guidance to the pharmaceutical and medical device industries. Driven by a passion for scientific precision and data integrity, Daniel applies a highly practical and solution-oriented approach to method validation.

The Medistri Lab team's expertise spans across biocompatibility testing, microbiology, chemical characterization, and method validation, ensuring compliance with international standards such as ISO 10993 and ISO 17025. Medistri Lab and its team of experts support manufacturers and regulatory professionals in navigating the evolving landscape of biocompatibility assessments with confidence, clarity and regulatory compliance.

The team's commitment to precision, reliability, and continuous improvement reflects Medistri's broader mission to deliver integrated solutions that meet the highest standards of safety and quality in pharmaceutical and medical device testing.



Daniel Avella
Head of Chemistry, Medistri

Daniel is a highly specialized professional in advanced chromatography, with extensive expertise in Liquid and Gas Chromatography-Tandem Mass Spectrometry and FID detectors. Prior to leading Medistri's chemistry division, he spent 12 years in a leading laboratory environment specializing in environmental analysis. During this tenure, he spearheaded research and testing for trace organic contaminants, micropollutants, and pharmaceutical residues in complex environmental and drinking water matrices. His qualification in chemical laboratory technology, combined with over a decade of high-level industrial experience and strict adherence to Swiss accreditation standards, makes him a leading expert in robust method validation and state-of-the-art chemical analysis.



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