

Biocompatibility in Dental Photopolymer Additive Manufacturing: A Material–Process–Workflow Perspective

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Paper	Function	Main contribution
I	Framework	Material–Process–Workflow architecture for dental photopolymer biocompatibility
II	Industrial implementation	Production-scale case studies in hearing-device and dental photopolymer manufacturing
III	Audit methodology	Wavelength-matched post-cure audit for the post-TPO chemistry transition

Companion paper note

This article is the first paper in a three-part perspective trilogy on engineering-led photopolymer additive manufacturing biocompatibility. Paper II is “Industrial Implementation of a Material–Process–Workflow Framework in Dental and Hearing-Device Photopolymer Additive Manufacturing” (DOI 10.5281/zenodo.21973422). Paper III is “Wavelength-Matched Process Control as a Prerequisite for the Post-TPO Photopolymer Transition” (DOI 10.5281/zenodo.21973554).

Abstract

Direct-printed orthodontic aligners, denture bases and dental prostheses are scaling in clinical use, but the published dental literature has predominantly approached photopolymer biocompatibility from a chemistry-centred perspective. The 2023 REACH SVHC listing of TPO and the subsequent harmonised Repr. Cat. 1B classification under Delegated Regulation (EU) 2024/197 are driving substitution to TPO-free formulations across the European dental segment; chemistry substitution alone does not, by itself, ensure a compliant device-level biological evaluation.

This perspective proposes a Material–Process–Workflow framework in which device-level biological performance depends on three interacting engineering variables: material chemistry, cure kinetics governed by the Jacobs working curve, and the post-processing workflow (drain, clean, dry, post-cure), integrated through a formal validation and release step. The three-variable architecture is methodologically related to Quality-by-Design frameworks established in pharmaceutical and medical device manufacturing under the ICH Q8/Q9/Q10 guidance documents; the specific contribution of this perspective is the systematic integration of photopolymer cure kinetics as the central process variable connecting material chemistry to the post-processing workflow and to the device-level validation hierarchy, a connection that has not been developed in the dental photopolymer literature to date. The framework is examined against the peer-reviewed evidence base on dental photopolymer cytotoxicity, post-cure dependence and denture base hydrolytic stability against ISO 20795-1 thresholds. Standardised extractables methodologies and longer-term in vivo clinical follow-up emerge as the principal research priorities for the field through 2030.

Keywords: dental 3D printing · dental photopolymer biological evaluation · system-level framework · TPO post-SVHC · Jacobs working curve · ISO 10993 · ISO 20795-1 · post-processing chain · degree of cure · cytotoxicity · Quality-by-Design

Scope and methodology. This article is a system-level perspective written from an industrial-academic position by the founder of one of the manufacturers active in this segment (3Dresyns by Resyner Technologies S.L.); the manufacturer's portfolio is used only as an illustrative case and not as the primary evidentiary basis of the review, and the companion papers of this trilogy develop the industrial portfolio, clinical case studies and audit methodology separately. Methodological limitations of the single-author perspective are made explicit in §6. The perspective draws on peer-reviewed dental, orthodontic and biomedical adjacency publications from 2014 through May 2026, identified through Scopus, PubMed and

Web of Science searches. Pre-2014 literature is excluded because directly-printed orthodontic aligners were not commercially available before that date. Evidence is coded as P (peer-reviewed independent measurement), M (manufacturer technical data sheet) or I (internal production-environment characterisation), with code symbols appearing where the distinction informs interpretation. Internal characterisation data are cited as indicative of framework support and not as peer-reviewed quantitative measurement; this limitation is restated in §6.

1. Introduction

1.1 Why dental photopolymer biocompatibility is a system question

Dental and orthodontic photopolymer devices differ from general industrial photopolymer parts along three engineering axes that modulate the cytotoxicity risk of residual reactive species. First, prolonged mucosal contact: direct-printed clear aligners are worn 20–22 hours per day across 6–24 month treatments [P1]; night guards 6–8 hours per night across years; denture bases 12–16 hours per day across the prosthetic service life. Industrial parts have minimal human contact and finite service life. Second, thin-wall geometries: direct-printed aligners are 0.5–0.9 mm wall thickness; surgical guide inserts operate at sub-millimetre tolerances. The high surface-to-volume ratio increases the leaching surface relative to bulk volume. Third, high-throughput laboratory workflows: dental laboratories typically produce on the order of tens to hundreds of devices per day per operator across aligners, models, splints and crown-and-bridge components (typical production-environment range). Variability in post-processing — bath dilution, drying time, post-cure dose, wavelength matching — can dominate outcome variability when print parameters are held constant.

A photopolymer resin is a chemical formulation; a compliant medical device is the outcome of the full manufacturing chain from formulation through validation. The device-level biocompatibility therefore depends on the integrated chemistry–process–workflow combination rather than on the chemistry alone.

1.2 The TPO regulatory transition

The European regulatory trajectory for diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO) — historically the dominant photoinitiator in commercial dental photopolymer systems — unfolded over 2021–2023. In September 2021 the ECHA Risk Assessment Committee adopted an opinion proposing harmonised classification of TPO as Repr. Cat. 1B. On 14 June 2023 ECHA added TPO (CAS 75980-60-8) to the REACH SVHC candidate list (29th batch). On 19 October 2023 the European Commission adopted Delegated Regulation (EU) 2024/197, formalising the harmonised classification of TPO as Reproductive Toxicant 1B and Skin Sensitiser 1B (H360Fd) under the CLP Regulation Annex VI [S8,S9]. The EU classification has created a clear substitution driver in the European market and may influence formulation strategies in other jurisdictions; regulatory timelines and requirements differ by region and a direct extrapolation to non-EU markets is outside the scope of this perspective.

The substitution requires more than a single replacement. The photoinitiator governs polymerisation kinetics, cure depth profile, colour stability and the residual photoinitiator content of the printed part. Several substitution directions have been explored in the photoinitiator chemistry literature [P2], each presenting distinct trade-offs across absorption window, cure kinetics, post-cure residual content under ISO 10993-12 extraction, and long-term clinical validation status; comparative photochemistry across candidate systems is outside the scope of this perspective. Residual TPO has been measured in additively manufactured dental splint materials after curing, with values strongly dependent on material formulation and post-curing protocol [P3], confirming that photoinitiator residues remain a measurable post-cure outcome rather than a theoretical concern. The TPO substitution is therefore not a single chemistry step but a redesign that propagates through cure kinetics and the post-processing chain.

1.3 The Material × Process × Workflow framework

This perspective develops a framework for dental photopolymer biocompatibility based on three interdependent engineering variables (Figure 1). The three-variable architecture is methodologically related to Quality-by-Design (QbD) frameworks formalised in pharmaceutical and medical device manufacturing under the ICH Q8, Q9 and Q10 guidance documents, in which product quality is engineered into the process rather than tested into the product through end-point inspection. The specific contribution of the present perspective is the systematic integration of photopolymer cure kinetics — governed by the Jacobs working curve — as the central process

variable connecting material chemistry to the post-processing workflow and to the device-level validation hierarchy, a connection that has not been developed in the dental photopolymer literature to date.

Material chemistry covers photoinitiator selection, monomer architecture and additive selection, determining the upstream extractables potential of the formulation. Cure kinetics is governed by the Jacobs working curve $C_d = D_p \cdot \ln(E/E_c)$ [P4], where C_d is the cure depth, D_p the resin penetration depth at the curing wavelength, E_c the critical exposure dose and E the applied dose; cure kinetics determines the residual reactive species fraction at the end of post-cure. The post-processing workflow is the four-step sequence — drain, clean, dry, post-cure — where each step is linked to the next by physical-chemistry dependencies that make the sequence

order-dependent; a formal validation and release step follows, integrated through ISO 13485 quality management traceability.

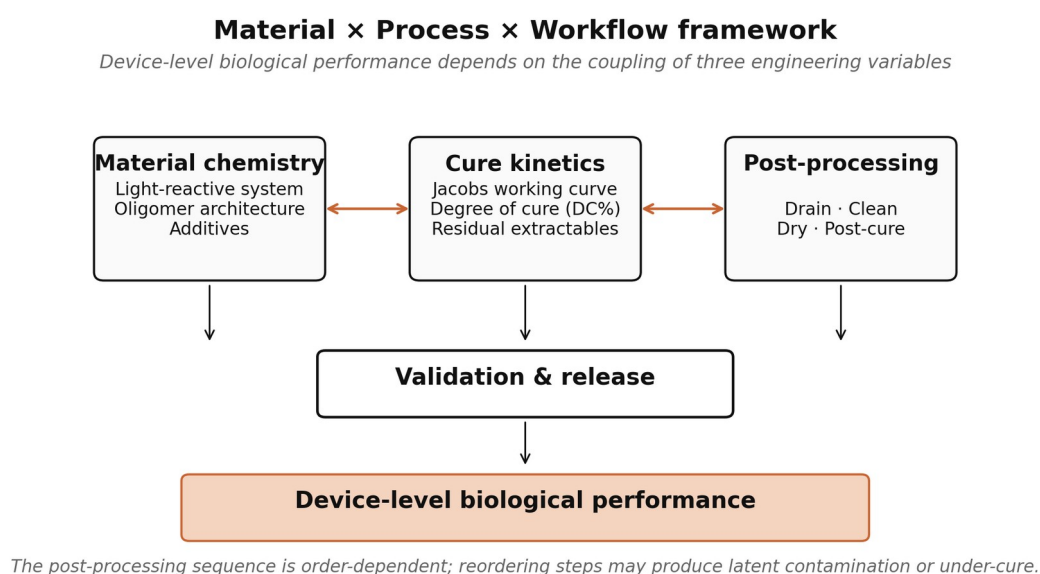


Figure 1. Material × Process × Workflow framework. Three interacting engineering variables — material chemistry, cure kinetics and post-processing workflow — jointly determine device-level biological performance through a validation and release step. The post-processing sequence is order-dependent; reordering or omitting steps may produce latent contamination or under-cure that does not surface until downstream validation.

1.4 What is specifically novel in the proposed framework

The Material–Process–Workflow architecture is methodologically related to QbD frameworks under ICH Q8/Q9/Q10 and to ISO 13485:2016 process validation logic; the genuine novelty of the present perspective is therefore bounded by three specific contributions rather than by a wholesale reconceptualisation. First, the systematic integration of the Jacobs working curve as the central cure-kinetics variable connecting material chemistry to the post-processing workflow and to the device-level validation hierarchy — a connection that has not been developed in the dental photopolymer literature to date. Second, the explicit consolidation of the published peer-reviewed evidence on cure-kinetics × cytotoxicity coupling [P10,P11,P12] and on ISO 20795-1 hydrolytic stability [P16,P17] into a coherent system-level architecture, rather than as a collection of isolated process or chemistry studies. Third, the operational coupling of the post-processing four-step workflow (drain, clean, dry, post-cure) to the validation hierarchy through ISO 13485 traceability, addressing the latent-failure-mode structure that dominates production deviation in dental laboratories. The present perspective therefore reframes existing peer-reviewed evidence and standards-based methodology into a

dental-photopolymer-specific engineering architecture; it does not propose a new physical-chemistry model and does not report new kinetic measurements.

The remainder of the perspective is organised as follows. Section 2 develops the photoinitiator chemistry layer in the context of the TPO regulatory transition. Section 3 develops the monomer-free chemistry concept and its definitional boundaries. Section 4 develops the Jacobs working curve × biocompatibility coupling. Section 5

details the post-processing chain and the validation hierarchy. Section 6 discusses the peer-reviewed evidence base, framework limitations and the research directions identified for the field through 2030.

2. Photoinitiator chemistry post-TPO SVHC

2.1 Photoinitiator substitution as a system constraint

Beyond the cytotoxicity considerations introduced in §1.2, the photoinitiator selection determines four coupled performance parameters of the cured part: polymerisation kinetics, cure depth profile, colour stability and residual photoinitiator content under ISO 10993-12 extraction. Each candidate substitution direction in the photoinitiator chemistry literature [P2] presents a distinct profile across these four parameters. The selection of a

specific photoinitiator system for a given dental application is therefore an integrated

chemistry–process–workflow decision rather than a chemistry-only step: a substitution that performs favourably on one parameter (e.g. in vitro cytotoxicity) may underperform on another (e.g. cure kinetics under the installed post-cure cabinet base, §2.2), and the validation of the substituted system as a whole requires the full Material × Process × Workflow assessment developed in this perspective. Comparative photochemistry across candidate systems and the engineering of specific photoinitiator formulations are outside the scope of this review.

The cure kinetics, absorption window and residual content of the chosen photoinitiator system propagate forward through the Jacobs working curve (§4) and the post-processing chain (§5) into the final extractables profile of the device.

2.2 Wavelength match in the post-cure cabinet

Spectral compatibility cannot be inferred from the labels TPO-containing or TPO-free alone. Cure response depends on the absorption characteristics and concentration of the photoactive system, the spectral irradiance and dose delivered by the printer or post-cure unit, formulation optical properties, specimen geometry and the required cured-state endpoint. A change in formulation chemistry therefore requires verification of the actual chemistry–equipment pairing and confirmation of degree of cure or another application-relevant endpoint under defined conditions.

3. Monomer chemistry — definitional clarification

3.1 The conventional dimethacrylate architecture

Conventional dental photopolymer formulations are dimethacrylate networks built from three classes of reactive component: a high molecular weight oligomer backbone (UDMA, 470 g/mol; Bis-EMA, 540 g/mol) providing the mechanical envelope; reactive diluent monomers (TEGDMA 286 g/mol; HEMA 130 g/mol; Bis-GMA 512 g/mol) reducing formulation viscosity to the processable range; and a photoinitiator system.

The reactive diluent monomers are the critical biocompatibility variable: their low molecular weight and high diffusion coefficient in the cured polymer network combine with typical 1–5% wt unreacted fraction at end of post-cure to produce ready diffusion through the cured matrix into the contact medium [P5]. Cytotoxic, allergenic and estrogenic effects of unreacted dental dimethacrylate monomers are documented across decades of dental materials research, with HEMA, TEGDMA and Bis-GMA all implicated in oral mucosal toxicity under prolonged contact [P5,P6]. The reactive diluent monomer architecture therefore represents a persistent chemistry-side biocompatibility constraint that cannot be eliminated by post-cure optimisation alone.

3.2 "Monomer-free" as a category label

The dental photopolymer literature is inconsistent in the use of "monomer-free", "monomer-reduced" and "biocompatible". The present perspective uses these terms operationally as defined here. Strictly, no UV-curable photopolymer system is chemically devoid of reactive species capable of polymerisation; the term "monomer-free" (MF) as used by some commercial dental photopolymer manufacturers [P7] denotes formulations free of intentionally added low-molecular-weight reactive diluent monomers (typically <500 g/mol dimethacrylate species such as TEGDMA, HEMA or Bis-GMA), with the low-viscosity function delivered instead by reactive oligomers and reactive functional groups bound to higher molecular weight scaffolds. The MF label

is therefore a category designation — referring to the absence of the intentionally added low-molecular-weight reactive diluent fraction historically associated with leachable cytotoxicity in conventional dental photopolymers — and not a literal absence of all reactive species. This industrial-commercial usage diverges from the strict polymer-chemistry interpretation, which would require absence of any polymerisable species, and is outside the formal scope of ISO 4049 and ISO 20795-1, which characterise dental polymeric materials by physical-mechanical and extractables thresholds rather than by reactive-component molecular-weight criteria.

Three operational categories follow (Table 1): (i) monomer-containing formulations retain reactive diluents as the low-viscosity component, with typical 1–5% wt unreacted at end of post-cure; (ii) low-residual-monomer formulations retain dimethacrylate chemistry but optimise post-cure to reduce unreacted fraction to 0.5–1% wt—a process-side mitigation of a chemistry-side liability; (iii) monomer-free formulations remove the intentionally added low-molecular-weight reactive diluent monomer fraction at the formulation level. The third approach removes the diluent-monomer liability at chemistry design; the second mitigates it at post-cure. The term 'monomer-free' is therefore used here in its established industrial-commercial sense rather than as a strict polymer-chemistry descriptor.

Category	Diluent monomer	Typical residual unreacted (post-cure)	Mitigation locus
Monomer-containing	Yes (TEGDMA, HEMA, Bis-GMA)	1–5% wt	None
Low-residual-monomer	Yes	0.5–1% wt	Process (extended post-cure)
Monomer-free (MF)	No (oligomeric / scaffold-bound reactive groups)	<0.1% wt (M-data) reported by some manufacturers [P7]	Chemistry (formulation design)

Table 1. Operational categorisation of dental photopolymer chemistries used in this perspective.

3.3 Bio-derived content

A parallel chemistry direction is the substitution of petroleum-derived oligomers with bio-derived alternatives — lignin-based, soy-based and castor-oil-based reactive intermediates [P8]. The research-to-commercial transition is a continuing development boundary; bio-derived content claims should be read alongside quantitative bio-content reporting per ASTM D6866 carbon-14 methodology rather than as marketing categories. Certain commercial monomer-free dental photopolymer families report combining the monomer-free architecture with bio-derived reactive content (M-data, manufacturer documentation; specific bio-content varies by grade) [P7].

3.4 Sectorial context — generalisation of the framework

The framework presented here is intended to apply across the commercial dental photopolymer segment rather than to a single manufacturer's portfolio. Current TPO-free or low-TPO direct-printed aligner chemistries from several established commercial suppliers — Graphy (Tera Harz TC-85 DAC, TA-28); Senertek (Clear-A); LuxCreo (Luxprint); Keystone; SprintRay; Formlabs Dental; NextDent; Detax; Ackuretta; and others — face the same coupled chemistry–kinetics–workflow constraints discussed here, even where the specific oligomer backbones, photoinitiator selections and post-cure protocols differ across suppliers. Independent peer-reviewed cytotoxicity characterisation across this segment is consolidated in the Goracci et al. (2025) PRISMA systematic review [P13] and reviewed in §6.1. The Material × Process × Workflow framework is intended as a structural map of the constraints the segment shares, not as a competitive claim about one supplier's position within it; the specific quantitative outcomes per supplier portfolio remain to be characterised under standardised extractables protocols (§6.4). Specific industrial implementations of the framework — including the application portfolio of one manufacturer in this segment — are developed in Paper II, “Industrial Implementation of a Material–Process–Workflow Framework in Dental and Hearing-Device Photopolymer Additive Manufacturing” (DOI 10.5281/zenodo.21973422).

4. The Jacobs working curve × biocompatibility coupling

4.1 Jacobs working curve fundamentals

The exposure-dose dependence of cure depth in vat photopolymerisation is described by the Jacobs working curve [P4]: $C_d = D_p \cdot \ln(E/E_c)$, where C_d is the cure depth from the build surface ($\propto m$), D_p the penetration depth of the resin at the curing wavelength (the depth at which the absorbed dose decreases by a factor of e), E_c the critical exposure dose (the threshold below which no measurable cure occurs), and E the applied exposure dose at the build surface. D_p depends on the resin absorption coefficient at the curing wavelength, dominated by photoinitiator concentration and any pigment or filler optical density; E_c depends on photoinitiator efficiency, radical scavenger content and the gel-point conversion of the network. Working curve calibration is specific to the printer-resin pairing; the values do not transfer directly across printers because irradiance spectrum and intensity profile differ [P9]. Site-level working curve validation is therefore required for each dental laboratory

operating environment.

4.2 Coupling cure kinetics to biological performance

The biological consequence of incomplete cure is not visible at the dimensional level. A part printed at C_d just above the nominal layer thickness achieves inter-layer bond and exits the printer with specified geometry, but the cure profile beneath the surface layer is heterogeneous. Regions of incomplete network formation contain unreacted reactive species — diluent monomers in conventional formulations, oligomeric reactive groups in MF chemistries — that diffuse through the cured matrix into the contact medium during prolonged wear.

The peer-reviewed evidence linking post-cure protocol to cytotoxicity outcome is consistent across multiple studies. Iodice et al. (2024) [P10] demonstrate post-printing curing time effects on cytotoxicity of direct-printed orthodontic aligners, with cell viability rising toward the ISO 10993-5 threshold as post-cure dose increases beyond manufacturer minimum specifications. Kim et al. (2024) [P11] characterise washing temperature and centrifugation time effects on uncured-resin elimination, demonstrating that washing parameters determine the residual uncured surface layer that subsequently contaminates the post-cured part. Hwangbo et al. (2021) [P12] document washing time and solution effects on biocompatibility and mechanical properties. The Jacobs working curve is therefore not solely a dimensional control parameter; in the dental application context it is part of the biocompatibility-determining chain. The same printed geometry can yield a device within the operational compliance position or outside it depending on matched cure conditions, without visible dimensional difference.

4.3 Degree of cure as the release metric

The degree of cure (DC) measures the fraction of reactive groups consumed during polymerisation. As-printed DC in vat photopolymerisation typically falls in the 50–70% range [P9]; post-cure under matched wavelength and dose drives DC into the >90% range. The release threshold depends on application class and resin-workflow combination. Three DC measurement methods are recognised: FTIR monitoring of the methacrylate C=C absorbance band at 1635–1640 cm^{-1} (gold-standard quantitative); DSC measurement of the residual cure exotherm (rapid screening); and ISO 4049 indirect measurement applying the standard's flexural strength threshold as a proxy.

Release thresholds are application-specific. Degree-of-conversion acceptance criteria should be defined for the specific formulation, measurement method, geometry, workflow and intended application. No universal release threshold is proposed in this paper. Optimised post-cure protocols for dental photopolymer applications have been reported to drive DC into the >90% range under matched wavelength and dose conditions [P10,P11,P12], with the specific operational release threshold depending on both the structural requirement of the device and the biological-risk implication of the residual reactive fraction; release-grade DC values in this regime are therefore product- and workflow-specific rather than universal sector values. DC% metrology requires FTIR or DSC equipment not typically present in dental laboratory environments; laboratory-level validation operates primarily at the visual and geometric tiers, with DC% verification at the resin manufacturer side (TDS-level) or at academic laboratories.

5. Post-processing workflow and validation

5.1 The four-step workflow

After printing, the dental photopolymer part passes through a four-step post-processing workflow — drain, clean, dry, post-cure — linked by physical-chemistry dependencies that make the sequence order-dependent,

followed by a formal validation and release step (§5.4). Reordering or omitting workflow steps produces non-recoverable contamination or under-cure that does not surface until downstream validation. The dental literature has historically focused on the print step; production experience suggests post-processing deserves comparable attention. Print failures are typically obvious and recoverable; post-processing failures tend to be latent and frequently non-recoverable — dimensional drift is not detected until customer measurement; biocompatibility non-conformance is not detected until ISO 10993 testing or until clinical complications emerge.

5.2 Drain and cleaning chemistry

After print completion the part remains in the vat covered by a film of uncured resin (typically 50–500 μm depending on resin viscosity and platform orientation; typical production-environment range). Drain protocol depends on viscosity: low-viscosity resins (<2000 mPa·s) require 30–60 s inversion; high-viscosity systems (>2000 mPa·s) require ≥ 300 s. Heating to 30–40 °C during drain reduces resin viscosity by approximately

30–50% (typical production-environment observation) and proportionally accelerates drainage.

Cleaning chemistry is matrix-driven: hydrophobic dental MF resins require organic solvents that dissolve uncured monomer or oligomer without attacking the cured polymer; water-soluble sacrificial resins require aqueous fluids. Cross-application between hydrophobic and water-soluble systems produces non-functional cleaning. Two systematic failure modes account for most production rejects in this step: cross-application of cleaning fluid, and bath contamination. A two-bath cascade protocol with periodic primary-bath replacement and secondary-bath promotion extends cleaning fluid service life while preventing the deposition-instead-of-cleaning mode that produces latent process deviation at low production volumes.

5.3 Drying and post-cure

After cleaning, the part surface carries residual cleaning fluid at the level of microlitres per square centimetre. If post-cure begins before complete evaporation, the residual solvent is photo-trapped in the cured matrix surface layer, producing two non-recoverable consequences: a permanent extractable load detectable in ISO 10993-12 polar-medium extraction (the trapped solvent migrates back through the cured matrix under aqueous contact); and localised under-cure beneath the solvent film (the solvent scavenges radicals and dilutes monomer concentration). The post-cure step closes the gap between as-printed DC (50–70%) and operational release threshold (typically >90%, §4.3). The post-cure equipment must match the photoinitiator absorption spectrum; a laboratory transitioning resin chemistry without verifying cabinet wavelength produces parts at sub-threshold DC despite formally following the manufacturer's cure protocol — the central operational issue developed in Paper III, “Wavelength-Matched Process Control as a Prerequisite for the Post-TPO Photopolymer Transition” (DOI 10.5281/zenodo.21973554).

Table 2 consolidates the order-dependent workflow failure modes discussed across §5.2–5.3, distinguishing immediate effect from downstream risk at device validation.

Workflow deviation	Immediate effect	Downstream risk at validation
Insufficient drain time	Uncured resin film retained on part surface	Cleaning bath contamination accelerates; latent surface non-conformance at next batch
Cross-application of cleaning fluid (hydrophobic / water-soluble mismatch)	Non-functional cleaning; deposition rather than removal	Elevated extractables under ISO 10993-12; surface defects at visual inspection
Cleaning bath contamination beyond service threshold	Deposition-instead-of-cleaning; residual layer on part surface	Cytotoxicity risk under prolonged contact; batch-to-batch variability
Incomplete drying before post-cure	Cleaning solvent photo-trapped in cured matrix surface layer	Permanent extractables load (ISO 10993-12); localised under-cure beneath solvent film
Post-cure cabinet wavelength mismatch with photoinitiator absorption	Sub-threshold degree of cure at dimensional release point	Elevated unreacted reactive species; cytotoxicity concerns at Tier 5 evaluation
Post-cure dose below manufacturer specification	Heterogeneous cure profile beneath part surface	Failure of Tier 4 DC verification and/or Tier 5 biocompatibility

		evaluation
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Table 2. Order-dependent post-processing workflow deviations — immediate effect at the deviation step and downstream risk at device validation. Each deviation is non-recoverable once it propagates beyond the next workflow step.

5.4 The validation hierarchy

Validation is the formal release of the part as fit for service. A six-tier hierarchy of increasing rigour, each necessary but not sufficient, is widely used (Figure 2). The hierarchy is integrated through ISO 13485:2016 quality management system traceability. A part may pass Tier 1 visual inspection but fail Tier 4 degree of cure verification; a part may pass Tier 4 but fail Tier 5 biocompatibility due to upstream cleaning-fluid contamination. The necessity of all six tiers reflects the integrated character of the biocompatibility outcome.

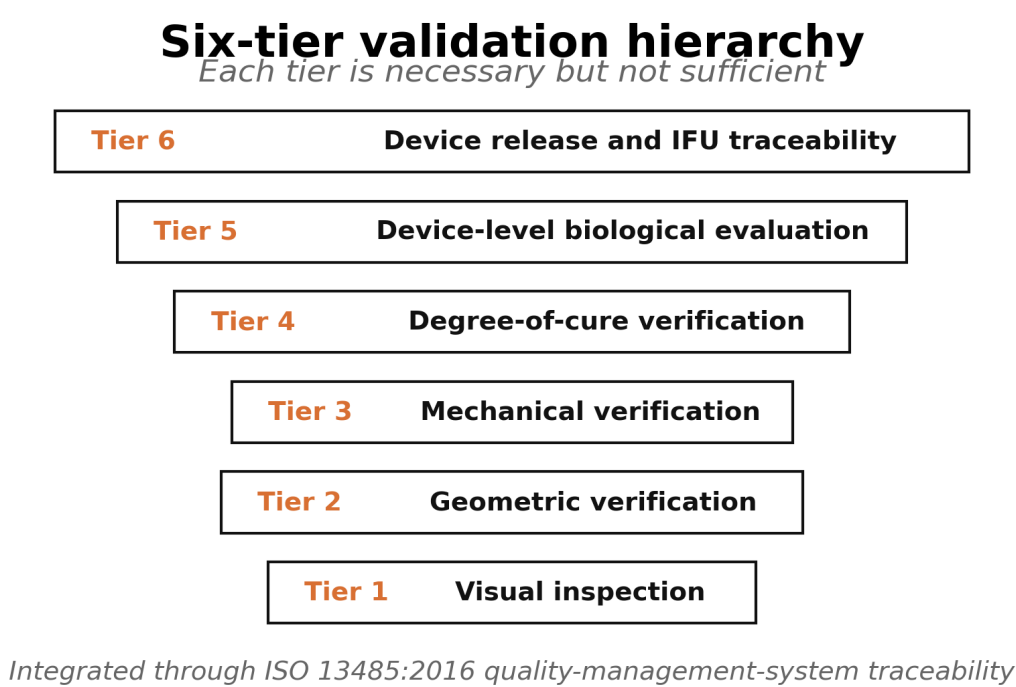


Figure 2. Six-tier validation hierarchy for dental photopolymer devices. Tier 1: visual inspection (macroscopic surface defects, post-cure colour, tackiness, contamination). Tier 2: geometric verification (coordinate measurement, comparator gauging, optical scanning against CAD). Tier 3: mechanical verification (ISO 178 flexural, ISO 527 tensile, ISO 868 Shore hardness; application-specific standards apply, e.g. ISO 20795-1 for denture bases or ISO 20795-2 for orthodontic appliances). Tier 4: degree of cure verification (FTIR C=C absorbance at 1635–1640 cm⁻¹; DSC residual exotherm; ISO 4049 indirect conversion assessment). Tier 5: biocompatibility evaluation (cytotoxicity acceptance per ISO 10993-5, ≥ 70% cell viability; ISO 10993-10 and ISO 10993-23 irritation and sensitisation; panel composition per device class and contact duration). Tier 6: device release and IFU traceability (formal compliance documentation linking cured part to resin batch certificate, cleaning fluid lot, post-cure equipment calibration record, validation test results). The hierarchy is integrated through ISO 13485:2016 quality management system traceability.

6. Peer-reviewed evidence base, limitations and future directions

6.1 The peer-reviewed evidence base supporting the framework

The Material × Process × Workflow framework is supported by independent peer-reviewed evidence across several dental and adjacent biomedical indications. The Goracci et al. (2025) [P13] PRISMA-compliant systematic review of cytotoxicity, estrogenicity, biofilm-formation and oral-soft-tissue evidence on marketed direct-printed orthodontic aligner resins reports non-cytotoxic behaviour as a consistent observation across the chemistries for which independent peer-reviewed cytotoxicity data were available at the time of the review (Graphy Tera Harz TC-85 DAC, with additional studies on TA-28 and Senertek Clear-A [P14,P15] also reporting outcomes that met their study-specific biological acceptance criteria under recommended post-curing

protocols). The systematic review separately catalogues additional marketed shape-memory direct aligner resins — including LuxCreo grades and other commercial implementations — for which independent peer-reviewed cytotoxicity characterisation in direct head-to-head comparison with the chemistries reviewed above was not yet available at the time of the systematic review; head-to-head peer-reviewed characterisation of these catalogued grades represents the immediate external validation step for the field.

The peer-reviewed evidence on cure kinetics × cytotoxicity coupling is consistent: Iodice et al. (2024) [P10] demonstrate post-cure dose dependence; Kim et al. (2024) [P11] characterise washing protocol effects; Hwangbo et al. (2021) [P12] document washing time and washing solution effects. The peer-reviewed evidence on denture base water sorption and solubility against ISO 20795-1 thresholds is provided by Lee et al. (2023) [P16], who measured NextDent Denture 3D+ water sorption at $31.51 \pm 0.92 \text{ } \mu\text{g/mm}^3$ (marginal relative to the 32 threshold) and solubility at $5.32 \pm 0.61 \text{ } \mu\text{g/mm}^3$ (failing the 1.6 threshold by more than threefold under independent DLP testing). The comprehensive Greil et al. (2023) [P17] evaluation across four commercial

3D-printed denture base resins reported water sorption in the 25.31–37.94 $\mu\text{g/mm}^3$ range and solubility in 0.08–8.27 $\mu\text{g/mm}^3$ across the tested set. ISO 20795-1 compliance is therefore not a universal property of 3D-printed denture base resins; it depends on the integrated chemistry–process–workflow combination.

Peer-reviewed validation of specific framework elements applied to commercial dental photopolymer portfolios is documented in Lee et al. (2023) [P1] for mechanical hydrolytic stability under simulated oral exposure; Sabatini et al. (2024) [P18] for ceramic composite concentrate reinforcement of interim dental resin in a multicentre study across Bern, Biruni, São Paulo and Geneva; Biun et al. (2023, 2024) [P19,P20] for CBCT-registration maxillary phantom methodology; Berretta et al. (2023) [P21] for orthodontic space maintainer application; and Bleilöb et al. (2025) [P14] for direct-printed aligner biocompatibility under variable wall thicknesses.

Study	Application	Framework element	Scope limitation
Goracci 2025 [P13]	Direct aligner systematic review	Cytotoxicity evidence consolidated across segment	Several marketed grades not yet independently tested
Iodice 2024 [P10]	Direct aligner cytotoxicity	Post-cure dose effect on in vitro cytotoxicity	Single chemistry tested
Kim 2024 [P11]	Direct aligner post-processing	Washing protocol effect on residual cure profile	In vitro testing only
Hwangbo 2021 [P12]	Dental resin mechanical and biological	Washing time and solvent on biocompatibility	Limited sample size
Lee 2023 [P16]	NextDent DLP denture base	ISO 20795-1 solubility failure documented	Single product tested
Greil 2023 [P17]	4-resin denture base benchmark	Cross-vendor variability range quantified	Different supplier set
Lee 2023 [P1]	Direct aligner mechanical hydrolytic	Hydrolytic stability under simulated oral exposure	Mechanical scope only
Sabatini 2024 [P18]	Multicentre crown trueness study	Ceramic composite reinforcement	Indirect crowns only

Table 3. Summary of peer-reviewed studies anchoring the framework (code P).

6.2 Internal characterisation — illustrative example

Some commercial dental photopolymer manufacturers maintain internal production-environment

The following observation is manufacturer-generated evidence obtained under the stated specimen preparation, extraction and analytical conditions. It is not an independent comparative study and does not, by itself, establish the biological safety or regulatory suitability of a finished medical device. Internal characterisation indicated a lower measured extractables response than the selected internal comparator under the specific test conditions. Cross-vendor and device-level conclusions require independently defined comparative testing. The absolute

magnitude is strongly dependent on extraction protocol (medium, time, temperature, agitation, surface-to-volume ratio) and on the upstream chemistry-process-workflow chain, so cross-vendor and cross-study quantitative comparison remains limited; this perspective therefore uses internal characterisation data as indicative of framework support rather than as peer-reviewed quantitative measurement. The standardised extractables protocol direction (§6.4) addresses this limitation.

6.3 Methodological and framework limitations

The framework is single-author and industrial-academic in origin, written by the founder of one of the dental photopolymer manufacturers active in this segment (3Dresyns by Resyner Technologies S.L.). The methodological transparency this implies is the necessary counterpart of the perspective's reliance on the manufacturer's portfolio as the principal source of illustrative product examples and internal characterisation data; every peer-reviewed citation is independently verifiable, and every internal data point is coded explicitly with the I designator.

The cytotoxicity evidence base in the published dental literature is dominated by methodological heterogeneity—specific extraction conditions, cell lines, exposure protocols and viability assays differ across studies in ways

that limit precise cross-study quantitative comparison. The Goracci et al. (2025) [P13] PRISMA review provides the most consolidated synthesis available at the time of this perspective; the binary ISO 10993-5 $\geq 70\%$ cell viability threshold used as compliance criterion under-represents the underlying quantitative variability across studies.

The Jacobs working curve $\times$ biocompatibility coupling (§4) is demonstrated qualitatively here with reference to the underlying physical chemistry and to peer-reviewed observations of post-cure dose effect on cytotoxicity [P10,P11,P12]; specific quantitative DC% values per resin-printer-application combination are

manufacturer-published for several commercial portfolios but vary across suppliers and workflows. The DC% measurement metrology requires FTIR or DSC equipment not typically present in dental laboratory environments; in practice laboratory-level validation operates at Tiers 1-2 (visual, geometric), with mechanical and DC% verification at the manufacturer (TDS) or academic level. The metrology gap is addressed in practice through TDS-anchored release specifications and validated post-processing chain documentation rather than per-device DC% measurement.

The framework is intended to generalise in its three-variable structure across the dental photopolymer segment (§3.4); the specific quantitative outcomes apply to the particular resin-process-workflow combinations that have been characterised, and other portfolios applying the framework structure would generate their own quantitative outcomes.

6.4 Research directions for the field through 2030

Four research directions are identified for the dental photopolymer field through 2030.

First, standardised extractables protocols. The current state of dental photopolymer extractables quantification suffers from methodological heterogeneity. ISO 10993-12:2021 defines the sample preparation protocol but the downstream quantification methodology varies across studies. The field would benefit from a standardised extractables protocol — specified extraction medium, defined chromatographic separation (LC-MS or GC-MS as appropriate), defined quantification by reference to certified analytical standards — that would enable cross-vendor comparison.

Second, longer-term in vivo clinical follow-up. The cytotoxicity evidence base is dominated by in vitro short-term testing (7–14 days). Real clinical exposure spans months to years for aligners and years for denture bases. Longitudinal in vivo clinical follow-up beyond two years tracking device retention, oral mucosal response, patient-reported outcomes and hypersensitivity events is the research gap that will refine the framework as direct-printed dental applications mature.

Third, bio-derived dental photopolymers at higher bio content. Manufacturer roadmaps in the segment target progressively higher bio content through replacement of petroleum-derived oligomers with lignin-based, soy-based and castor-oil-based reactive intermediates [P8]. The research-to-commercial transition of these

alternatives requires coordinated chemistry-process-workflow characterisation rather than chemistry substitution alone.

Fourth, 4D shape-memory polymer architecture. Thermo-responsive shape-memory photopolymer chemistries have entered the direct-printed aligner and flexible denture base segments, supporting sustained force expression and elastic insertion-recovery cycles respectively. The development trajectory extends the 4D architecture to adaptive prosthetic-fit components, dynamic-load occlusal devices and controlled-degradation orthodontic appliances over the 2025–2030 horizon.

7. Conclusions

The biocompatibility of a dental photopolymer device is shaped by the coordinated manufacturing chain — chemistry, cure kinetics, post-processing — rather than fixed at the liquid resin stage. The Material × Process × Workflow framework proposed here is intended as a structural map of this coupling, organising the dispersed dental photopolymer literature into a coherent system-level view. The framework is methodologically related to QbD frameworks established in pharmaceutical and medical device manufacturing under ICH Q8/Q9/Q10; its specific contribution is the systematic integration of the Jacobs working curve as the central cure-kinetics variable connecting chemistry to validation. The framework is supported by independent peer-reviewed evidence: the Goracci et al. (2025) systematic review of direct-printed aligner cytotoxicity; the cure-kinetics ×

cytotoxicity coupling documented in Iodice (2024), Kim (2024) and Hwangbo (2021); the denture base water sorption and solubility comparison against ISO 20795-1 thresholds in Lee (2023) and Greil (2023). Absolute quantitative outcomes of specific resin-process-workflow combinations remain subject to the methodological heterogeneity of the current literature.

Standardised extractables protocols, longer-term in vivo clinical follow-up beyond two years, and the 4D shape-memory architecture already deployed in direct printed aligners define the dental photopolymer development trajectory through 2030. The framework is intended to inform the field as it transitions through the TPO regulatory substitution and the scale-up of direct-printed dental device production; the second paper of this trilogy applies it to a documented commercial portfolio and to a peer-reviewed industrial-scale production case, and the third paper develops a wavelength-matched audit methodology for the post-TPO chemistry transition.

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Disclosure. The author is the founder and Scientific Director of 3Dresyns by Resyner Technologies S.L., a manufacturer of photopolymer resin systems for dental, orthodontic and biomedical additive manufacturing applications. This perspective is written from an industrial-academic perspective; the manufacturer's product portfolio is used as illustrative example of framework application rather than as the principal subject of review. All peer-reviewed citations are independently verifiable; all internal production-environment characterisation data are coded explicitly with the I evidence designator and subject to the limitations declared in §6. Device-level regulatory classification of any finished medical device remains with the legal manufacturer of that device under the applicable jurisdictional framework.

Source-use map for the shared trilogy bibliography. [P6] provides general polymer-additive-manufacturing context; [P15] complements the direct-aligner post-processing and cytotoxicity evidence; [P19–P20] support the adjacent digital-registration workflow context; and [I1] is manufacturer documentation used only to describe the disclosed cleaning-workflow framework. These sources do not establish final-device biological acceptance.

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