



# Clinical translation of injectable hydrogels: from bioactive polymers to long-acting drug delivery systems

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## Abstract

Injectable hydrogels (IHs) have emerged as versatile biomaterials that enable localized therapy through minimally invasive delivery. Their in situ sol–gel transition supports sustained and targeted release of therapeutics, enhancing patient comfort and reducing dosing frequency. However, clinical translation remains limited due to challenges in achieving controlled degradation, ensuring long-term biocompatibility, scaling production, and meeting regulatory standards. Despite these hurdles, several IH-based formulations are progressing through clinical trials or have reached the market, underscoring their therapeutic potential. This review examines the major translational barriers and highlights recent advances that are accelerating the adoption of IHs in precision and personalized medicine.

**Keywords** Biomaterials · Injectable hydrogels · Drug delivery systems · Clinical translation · Personalized medicine

## Introduction

Injectable hydrogels (IHs) are three-dimensional networks of hydrophilic polymers capable of retaining large amounts of water, designed to undergo in situ gelation upon injection and to support controlled delivery of therapeutics. IHs are gaining attention in a wide range of biomedical applications due to their feasibility for localised and minimally invasive treatments, thereby improving patient compliance [1]. Beyond essential biocompatibility, these polymeric networks may be engineered to exhibit controlled degradation

and stimuli-responsive behaviour tailored to their target application [1]. Moreover, their ability to transition from sol to gel in situ allows for injection in liquid form and subsequent solidification at the target site, adapting to the tissue environment. Coupled with their capacity to encapsulate drugs or cells, IHs are well-suited for local drug delivery and tissue engineering in the context of various clinical applications [2].

The biomedical significance of hydrogels lies in their potential to bridge synthetic materials with biological systems. These systems mimic the extracellular matrix (ECM), providing an environment prone to cell adhesion, proliferation, and differentiation [3] and making them promising candidates for regenerative medicine. Clinically, IHs have been deployed in oncology, spinal function, and ophthalmic treatments, reflecting their versatility and therapeutic relevance.

Despite their potential, several challenges hinder the clinical translation of IHs. Although extensive research has enhanced the understanding of their properties, ensuring consistent performance and scalability remains difficult [1]. Material design must balance mechanical robustness, biodegradability, and biocompatibility, ensuring structural integrity under physiological conditions while degrading at a predictable rate without triggering immune responses [4]. Manufacturing processes must meet regulatory standards, emphasising the need for standardised protocols and early incorporation of critical quality attributes [5].

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Bridging the gap from laboratory to innovation and large-scale production also presents some complexity. Preclinical studies frequently expose limitations in material performance, not evident in early-stage experiments [6]. Moreover, choosing appropriate animal models for preclinical studies is crucial to ensure reliability and translatability of research findings [7].

One recent success involves ionic fluid-based hydrogels, which undergo gelation upon injection and form localised depots for controlled drug release. Several variants of this strategy have shown efficiency in preclinical animal models and are advancing towards clinical trials [8].

This review explores hydrogel design considerations, identifies critical factors for clinical translation, and examines successful case studies to elucidate the elements required to bring these innovative technologies from bench to market.

A comprehensive literature search was conducted in PubMed, the FDA and EMA webpages and clinicalTrials.gov to identify publications, clinical trials and marketed products reporting on IHs with translational or clinical relevance. Search strings combined terms related to injectable hydrogels, drug delivery, biomaterials, and clinical translation using the following operators: (“injectable hydrogel” OR “ionogel”) AND (“clinical” OR “biomedical application” OR “drug delivery”).

Publications were included if they reported in vivo, preclinical, or clinical use of IHs for therapeutic. They were

also included if described clinical translation, regulatory approval, or commercialisation of IH-based systems.

## Design and engineering of IHs

### The variety of biomaterials and resulting hydrogels

IHs are composed of either natural or synthetic polymers, each offering unique advantages for biomedical applications (Fig. 1). Natural polymers such as alginate, chitosan, collagen, and hyaluronic acid (HA) have been widely attracted considerable attention due to their intrinsic biocompatibility and bioactivity. Since the 1980s, efforts have been made to bring these systems into clinical use, with early examples including collagen-based hydrogels for aesthetic applications such as Zyplast® and Fibrel®. Collagen, a primary component of the ECM, has been widely recognised for its ability to promote cell adhesion and proliferation [9]. Its early adoption was also motivated by its feasibility of extraction and excellent biocompatibility.

During the 1990s, HA- and cellulose-based hydrogels were introduced for the treatment of osteoarthritis and genitourinary disorders. These polymers offered enhanced versatility due to their functional groups, which allowed for chemical modifications to tailor hydrogel properties to specific therapeutic needs [9, 10]. More recently, in the early 2010s, focus shifted towards alginate- and chitosan-based hydrogels, further broadening the range of biopolymers used for

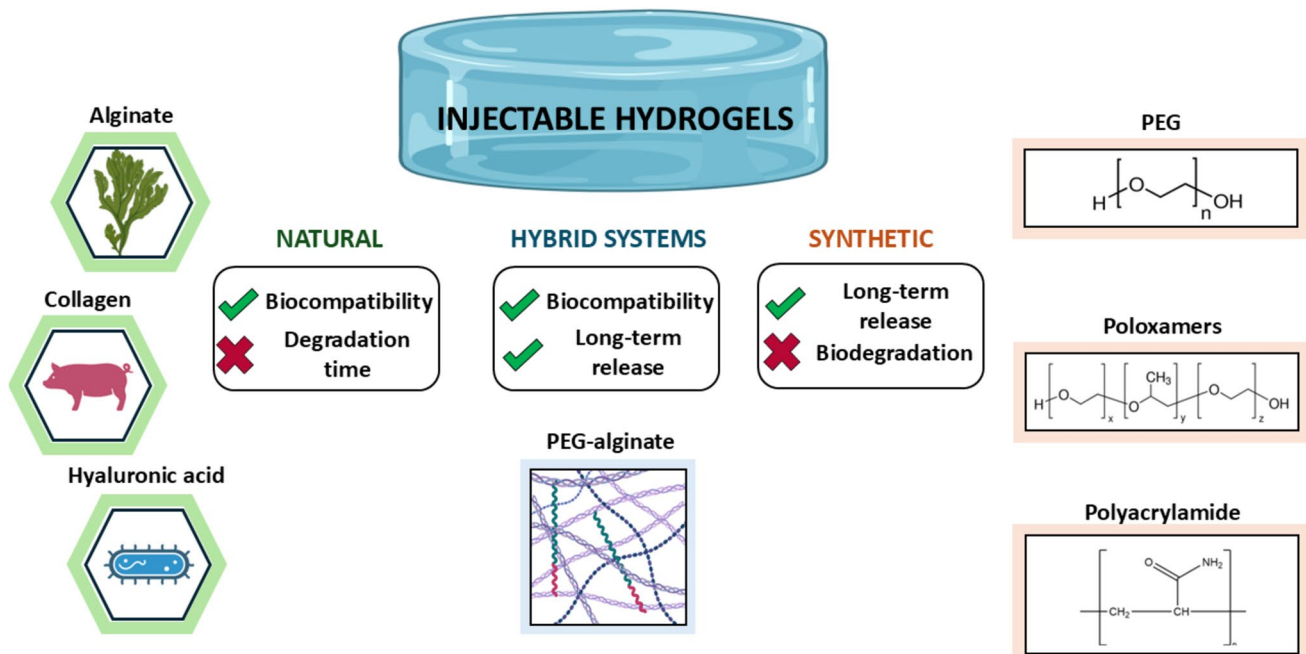


Fig. 1 Schematic classification of IHs by polymer sources

clinical applications. Alginate is prized for its gentle gelation behaviour and capacity to encapsulate cells or drugs, making it highly suitable for tissue engineering and wound healing [11, 12]. One commercial example is Algisyl®, an alginate-based hydrogel used to treat heart failure by reinforcing the left ventricular wall.

Chitosan, on the other hand, stands out for its inherent antimicrobial properties, which make it a strong candidate for wound dressings and drug delivery systems [13, 14]. As in the case of BST-CarGel®, a chitosan-based hydrogel used since 2012 for osteoarthritis treatment. It supports cartilage repair when combined with bone marrow stimulation techniques, exemplifying the clinical value of biopolymer-based scaffolds.

Among synthetic polymers, PEG-based ones are the most extensively used for developing IHS. This polymer has led to marketed hydrogels in the early 2000s as PerioGlas®, an intraosseous gel designed to induce dental bone regeneration. PEG-based hydrogels are highly amenable to chemical modification, allowing control over crosslinking density. This tunability enhances their mechanical integrity and enables precise regulation of drug release profiles. An example is Jelmyto®, a PEG-based formulation used for intravesical delivery of Mitomycin in the treatment of urothelial cancer [15, 16].

Additionally, PEG derivatives such as Pluronic® block copolymers are widely employed due to their thermoresponsive behaviour, particularly useful in applications requiring sol–gel phase transitions under physiological conditions [17, 18]. However, the broader clinical application of PEG-based hydrogels has been limited by their poor *in vivo* degradability. Despite this, several devices are currently marketed for intra-articular use as bone fillers, including Dynagraft® and Actifuse®.

Polyacrylamide-based hydrogels also offer significant advantages, notably in their highly tunable mechanical properties. Their stiffness and elasticity can be precisely adjusted, making them suitable for a range of biomedical applications. The polymer's chemical structure supports functionalization and integration of bioactive agents. In clinical practice, polyacrylamide hydrogels such as NOLTREX® and Arthroamid® have been used to treat osteoarthritis by providing mechanical support and pain relief [19, 20].

In recent years, hybrid and composite systems have emerged as a promising choice that combines the strengths of both natural and synthetic polymers. These hybrid hydrogels capitalise on the biological functionality of natural polymers while leveraging the mechanical robustness and tuneability of synthetic polymers [21–23]. Composites incorporating alginate and PEG, like Emdogain®, have demonstrated improved tissue regeneration when applied periodontally. PEG-fibrinogen hybrids are another example, employed to relieve joint pain in the treatment of early

cartilage defects. Moreover, the integration of nanoparticles [24] or bioactive ceramics [25] into PEG-based matrices has further expanded their applicability in regenerative medicine and cancer treatment.

As medical devices, hydrogels used for genitourinary or osteoarthritic diseases are primarily evaluated for biocompatibility and physical performance. However, once they are engineered for drug delivery purposes, they fall under more complex regulatory pathways associated with pharmaceutical or combination products. This shift requires detailed pharmacokinetic data, stability evaluation, and rigorous clinical trials to ensure the safety and efficacy of the drug component. These regulatory demands highlight the importance of early-stage planning and interdisciplinary collaboration in the development of hydrogel-based drug delivery systems. Encouragingly, several systems currently in clinical trials are showing promising data for the controlled release of peptides and other bioactives.

Interestingly, ionic liquid-based hydrogels or ionogels represent an innovative class of *in situ* forming materials for localised drug delivery. These hydrogels incorporate organic salts with low melting points (ionic liquids, ILs) into polymeric networks, yielding materials with dual ionic and polymeric properties. Their unique features, including high thermal stability, ionic conductivity, low volatility, and exceptional solvation capability, make them advantageous for biomedical applications [8]. In injectable formulations, ILs promote rapid *in situ* gelation at the site of administration, forming structured drug depots that enhance the solubility of a broad range of bioactive agents (proteins, peptides, and small molecules). Additionally, ILs can exert multifunctional biological effects, such as antimicrobial activity, anti-inflammatory effects, and tissue repair [26].

Structurally, ionogels are composed of ILs either physically embedded in or covalently bonded to hydrogel matrices, typically based on natural polymers like oxidised hyaluronic acid, chitosan, or gelatin [27]. Their injectability is enhanced by their tuneable viscosity and intrinsic self-healing properties. Moreover, their electrical conductivity and responsiveness to magnetic stimuli open the door to integration with bioelectronic devices and advanced wound healing technologies [28].

### The behaviour of hydrogels as a function of the administration route

Various administration routes, such as subcutaneous, intramuscular, intratumoral, intra-articular and intraocular, have been explored to address specific clinical needs [29]. Below, we discuss the advantages, limitations and current perspectives associated with the most used routes for IHS administration.

## Hydrogels administered by the subcutaneous route

Subcutaneous (SC) delivery is one of the most common methods for IHs, favoured for its minimally invasive nature and capacity to provide localised and sustained release of therapeutic agents. This route is particularly suitable for managing chronic disease, as it allows extended drug release, reducing dosing frequency and improving patient adherence [30]. A key advantage of SC-administered IHs is their ability to form depots at the injection site, which facilitates gradual drug diffusion into systemic circulation. This enhances the drug's half-life and minimises systemic side effects. Additionally, SC injections are typically easier to administer compared to other routes, making them suitable for outpatient care or even self-administration [31].

However, SC administration does present challenges. The local environment, including enzymatic activity and immune responses, can influence hydrogel degradation and drug release kinetics. Variables such as injection volume, viscosity, and mechanical properties must be optimised to avoid patient discomfort and inflammation. Achieving predictable biodegradation without triggering adverse immune reactions remains a major obstacle in these approaches [32]. Recent innovations include enzyme-responsive IHs, as those developed by Coulter et al. [33]. Based on a peptoid-peptide formulation covalently conjugated with zidovudine, this system showed sustained antiviral release over 35 days in an *in vivo* rat model by leveraging local phosphatase activity to trigger gelation [33].

Ionogels have been promising for SC delivery due to their structural adaptability and multifunctional nature. These systems integrate the ionic conductivity and stability of ILs with the robustness of polymer frameworks, offering precise control over drug release. Notable studies include IHs formed by PBAimBF<sub>4</sub> and oxidised hyaluronic acid with antibacterial and fast-gelling properties, incorporating antibacterial imidazolium ILs for diabetic wound healing in a mouse model [34].

Talking about clinical translation, most of the hydrogels designed for subcutaneous use serve aesthetic purposes such as filling facial wrinkles or treating cutaneous scars (Table 6). It's noteworthy to point out Vantas® and Supprelin LA®, marketed as drug delivery systems in the early 2000s for the treatment of prostate cancer and precocious puberty, respectively.

## Hydrogels administered by the intramuscular route

Intramuscular (IM) injection is gaining attention in drug delivery, regenerative medicine, and vaccine development. The well-vascularized muscle tissue offers a suitable environment for drug absorption while maintaining drug reservoirs at the injection site [35].

Challenges associated with IM delivery include site discomfort, tissue irritation, and patient-specific variability, which can impact hydrogel behaviour. Since IHs are typically optimised for soft-tissue environments, the strong mechanical forces acting within muscles preclude depot stability and reproducible drug release profiles [35]. Furthermore, the IM route was targeted over the years for systemic absorption, reducing the clinical advantage of a bulky hydrogel system compared with simpler depot technologies (e.g. liposomes, microspheres).

Innovations such as needle-free jet injection systems, studied by Lawal et al., have shown promise in enhancing hydrogel penetration while minimising pain and tissue damage [36]. There remains a considerable way to go before an IM-targeted hydrogel can progress into clinical trials and ultimately reach the market. The last attempt was done in 2020 with GADinLADA®, an intrainguinal vaccine for the delivery of recombinant human glutamic acid dehydrogenase from an aluminium hydrogel (NCT04262479). The study was discontinued mostly due to administration site disorders, including muscle rupture.

## Hydrogels administered by the intra-articular route

Intra-articular (IA) injection is an effective method for treating joint disorders, such as osteoarthritis (OA) and cartilage defects. This localised delivery targets the synovial cavity, offering sustained therapeutic presence with minimal systemic side effects [37–40].

One primary advantage of these systems is the ability to form a drug depot within the joint space, mitigating the rapid clearance typically seen with small-molecule drugs in synovial fluid. Furthermore, hydrogels can be engineered to mimic the viscoelasticity of the synovial environment, reducing joint friction and enhancing cushioning. These properties make IA hydrogels an outstanding alternative to surgical interventions [41, 42].

Similar to the IM route, the harsh mechanical environment within the joint can accelerate hydrogel degradation and compromise drug retention. Thereby, achieving long-term mechanical resilience and biocompatibility is a technical challenge. Disease progression heterogeneity among patients also requires tailored hydrogel formulations [43].

Recent advances have tackled these challenges. García-Couce et al. developed a thermosensitive chitosan/Pluronic® F127 hydrogel for IA delivery of etanercept [44] and dexamethasone [45], reducing inflammation and promoting cartilage regeneration in murine models. While Liu et al. evaluated a hydroxypropyl chitin/HA hydrogel that showed bio-lubricating and chondroprotective properties, suggesting dual functionality in joint lubrication and cartilage protection [39].

It is important to highlight that a wide range of IA-administered hydrogels are already commercialised for the treatment of articular defects, representing around 50% of all hydrogel-based systems on the market and nearly 40% of those currently in clinical trials. These include pain-relief products such as EUFLEXXA® and Orthovisc®, as well as bone fillers like PerioGlas® and Dynagraft®.

### Hydrogels administered by the intratumoral route

Intratumoral (IT) administration of IHs represents an innovative strategy for localised cancer treatment. This approach allows direct injection into solid tumours, forming a localised drug depot that enhances retention and minimises undesired cytotoxic effects. IT hydrogels are under development for chemotherapeutics, immunotherapies and photothermal agents, enabling sustained and targeted drug exposure on the tumour site while reducing off-target effects [46].

Smart hydrogels can also respond to tumour-specific stimuli such as pH or enzymatic activity, enabling controlled drug release. Furthermore, for tumours that cannot be fully resected, IT hydrogels offer a minimally invasive therapeutic option [47–52].

However, the variability towards tumour environment, including variations in vascularisation and interstitial pressure, can hinder uniform hydrogel dispersion and drug penetration. Additionally, the immunosuppressive microenvironment and mechanical stress from injection can influence their therapeutic performance [53, 54].

Recent studies suggest that IL-based hydrogels could offer enhanced performance in this context. Certain ILs, particularly those with guanidinium cations and long alkyl chains, have demonstrated strong cytotoxic effects against various cancer cell lines, in some cases outperforming traditional chemotherapeutics like mitomycin C [55]. In this regard, it is noteworthy that a hydrogel formulation for mitomycin C release called Jelmyto® has already been commercialised. This system, based on a blend of Pluronic, PEG and HPMC, illustrates the feasibility of hydrogel-based chemotherapeutic delivery.

While IT hydrogels show strong potential, further research is needed to optimise their intratumoral diffusion. The development of stimuli-responsive hydrogels and combination therapies holds the potential to revolutionise cancer treatment through more precise therapeutic solutions.

### Hydrogels administered by the intravitreal route

Intravitreal (IVT) delivery of IHs is an emerging strategy for treating retinal diseases, including age-related macular degeneration (AMD), diabetic retinopathy, and glaucoma. This approach enables direct drug delivery to the posterior

segment of the eye, bypassing systemic circulation and ensuring localised, prolonged therapeutic action.

One key benefit of IVT hydrogel systems is their ability to extend drug residence time within the vitreous humour, reducing dose frequency and improving treatment adherence [56–61]. Hydrogels can encapsulate anti-angiogenic drugs, corticosteroids, or neuroprotective agents for controlled release over weeks or months. Additionally, IHs can support retinal tissue engineering by acting as scaffolds that support cell transplantation and modulate degenerative eye diseases [62–65].

Despite these advantages, the unique physicochemical environment of the vitreous humour poses challenges. Maintaining optical clarity is essential to avoid impairing vision, while ensuring controlled biodegradation without inflammation or toxicity remains a major hurdle. The small volume of the vitreous cavity further restricts the injectable volume, necessitating precise formulation adjustments to adapt the therapeutics [66]. Among all the cases reviewed, only one IVT hydrogel has been identified, which is derived from a decellularized human membrane for the treatment of retinal defects. The clinical trial is currently ongoing, with conclusive results expected over the course of the next year.

As shown in Table 1, each administration route should be selected based on therapeutic goals and drug features, always aiming to improve patient comfort and compliance [67].

## Challenges in clinical translation

### Biocompatibility and safety concerns

Biocompatibility encompasses both short-term and long-term host responses, addressing the possible adverse biological responses triggered by a drug or medical device [68]. Ideally, materials should degrade in a controlled manner, producing non-toxic, metabolizable by-products [69]. Achieving this is challenging due to the diversity of hydrogel formulations, crosslinking mechanisms, and bioactive additives [70]. As discussed above, natural polymers typically excel in this regard due to their innate compatibility with biological pathways [71].

In vitro assessments, such as MTT assays, live/dead staining and transcriptomic profiling, provide insights into cytotoxicity and cellular stress responses [72]. However, in vivo evaluations using animal models are essential for understanding tissue integration, fibrosis and immune reactions. These are typically supported by imaging techniques like fluorescence microscopy or MRI, along with histological analyses [73].

Toxicity can arise from several sources, including the base polymer, crosslinking agents, degradation byproducts,

**Table 1** Comparison of administration routes for hydrogel delivery systems

Administration route	Injection site	Advantages	Challenges	Typical applications
Subcutaneous (SC)	Fatty layer under the skin	<ul style="list-style-type: none"> <li>- Minimally invasive</li> <li>- Suitable for self-administration</li> </ul>	<ul style="list-style-type: none"> <li>- Limited volume (~ 1–2 mL)</li> <li>- Variable degradation rates</li> </ul>	Chronic disease therapies (e.g. diabetes, hormonal therapy), monoclonal antibodies
Intramuscular (IM)	Muscle tissue	<ul style="list-style-type: none"> <li>- Higher vascularisation leading to rapid systemic uptake</li> <li>- Larger volumes (~ up to 5 mL)</li> </ul>	<ul style="list-style-type: none"> <li>- More painful</li> <li>- Risk of nerve or blood vessel damage</li> </ul>	Long acting injectables (e.g. vaccines)
Intra-articular (IA)	Joint space	<ul style="list-style-type: none"> <li>- Reduces systemic toxicity</li> <li>- Hydrogels improve residence time in synovial fluid</li> </ul>	<ul style="list-style-type: none"> <li>- Technically demanding</li> <li>- Risk of infection or joint damage</li> </ul>	Osteoarthritis, rheumatoid arthritis, and local anti-inflammatory therapies
Intratumoral (IT)	Tumoral tissue	<ul style="list-style-type: none"> <li>- Maximises local drug concentration</li> <li>- Reduces systemic toxicity</li> <li>- Immune stimulation in situ</li> </ul>	<ul style="list-style-type: none"> <li>- Tumour accessibility hurdles</li> <li>- Heterogeneous distribution</li> </ul>	Cancer immunotherapy, chemotherapeutic delivery, and localised gene therapy
Intravitreal (IVT)	Vitreous humour of the eye	<ul style="list-style-type: none"> <li>- Direct delivery to the posterior eye</li> <li>- Minimises systemic exposure</li> <li>- Prolongs drug residence time</li> </ul>	<ul style="list-style-type: none"> <li>- Highly sensitive injection site</li> <li>- Risk of retinal detachment</li> </ul>	Age-related macular degeneration, diabetic retinopathy, and ocular inflammation

Abbreviations: SC, subcutaneous; IM, intramuscular; IA, intra-articular; IT, intratumoral; ITV, intravitreal.

and additives such as drugs or growth factors [74]. Traditional crosslinkers like glutaraldehyde are known for their cytotoxicity, prompting the development of safer alternatives like click chemistry and enzymatic or UV-activated methods [75].

Accumulation of acid by-products from PLGA degradation can lead to localised tissue irritation, inflammation and immune cell activation [76]. Designing mixed hydrogels with natural polymers often helps mitigate these risks [77].

Concerns also extend to other non-degradable polymers such as PEG with regard to its capacity to induce mild immune responses over time [78]. Indeed, multiple clinical reports and post-marketing studies have documented pre-existing anti-PEG IgG and IgM antibodies in 20–70% of human sera. These antibodies are thought to arise from prior environmental or pharmaceutical exposure (e.g., to PEGylated drugs, cosmetics, or food additives) [79]. For hydrogel systems employing PEG as a crosslinker or coating material, the immunologic risk depends on molecular weight, branching, and presentation. Covalently crosslinked PEG networks that do not release soluble PEG chains are generally less immunogenic than degradable or surface-exposed architectures that shed PEG fragments into circulation [80]. Regulatory guidance increasingly expects developers to evaluate anti-PEG antibody incidence and cross-reactivity when PEG is a major component of long-acting or systemic hydrogels. Preclinical screening can

include in-vitro complement activation assays, binding ELISAs for anti-PEG IgG/IgM, and in-vivo monitoring for infusion-related reactions [81].

Conversely, while natural polymers (e.g., collagen, gelatin, alginate, chitosan, fibrin, hyaluronic acid) generally degrade into bioactive or easily cleared fragments, batch-to-batch variability can lead to inconsistent by-product profiles. Indeed, natural polymer hydrogels present a different immunogenicity profile, dominated by source-derived variability and residual contaminants. Because these materials are often harvested from animal or microbial origins, batch-to-batch differences in purity, molecular weight distribution, acetylation/deacetylation degree, and endotoxin burden can markedly influence local and systemic immune responses [78]. For instance, partially deacetylated chitosan has been reported to activate macrophages through Toll-like receptor pathways, however, this is not the case when chitosan is used in a highly purified form (medical grade). Similarly, alginates contaminated with polyphenols or endotoxins have been shown to elicit foreign body inflammation [82] and xenogeneic collagens containing residual telopeptides are known to trigger humoral immune recognition [83]. Even ostensibly “pure” hyaluronic acid preparations can induce transient inflammation if residual crosslinkers (e.g., BDDE) or protein impurities persist above specification limits [84]. Consequently, rigorous source control, depyrogenation, and

chemical characterization are indispensable parts of a risk-based ISO 10993 program.

In this way, whereas for synthetic polymers, anti-PEG responses emphasize the need for immunological monitoring even for previously “inert” excipients, for natural polymers, biologic variability and residual contaminants highlight the importance of process validation and compositional analytics to assure reproducible host tolerance. In both cases, comprehensive ISO 10993-driven assessments (cytotoxicity, sensitization, systemic toxicity, and degradation product profiling) provide the empirical foundation to de-risk immune complications before first-in-human use.

For its part, hybrid materials provide tuneable properties but may generate unpredictable degradation profiles, especially when combined with inorganic additives like nanoparticles. These hybrids can raise long-term safety concerns related to bioaccumulation or interference with cellular signalling. As such, elucidating the metabolic and excretory pathways of all degradation products is imperative for clinical translation [4].

To aid risk-based planning of preclinical safety evaluations, Table 2 summarizes the biological evaluations for different types of hydrogels according to ISO 10993 standards, depending on their composition and route of administration.

### Assessment methods for biodegradation profiles

Biomaterial degradation is an inherently complex and multifactorial process involving physical, chemical, and mechanical changes that are often interdependent. Accurate evaluation of these processes is essential, particularly in biomedical applications where degradation profiles influence not only the functional lifespan of a material but also its biocompatibility and therapeutic performance [85]. Functional groups such as esters, ethers, amides, and anhydrides contribute to the degradation behaviour, leading to surface erosion, molecular weight changes, mass loss, and altered mechanical properties like tensile strength and viscosity [4].

Current methodologies for assessing degradation profiles can be broadly categorised into physical, mechanical, and chemical approaches. Among these, physical methods such as gravimetric analyses are widely used due to their simplicity. However, they often led to misinterpretation, as mass changes might be due to material solubility or water loss rather than real degradation [84]. Mechanical testing evaluates performance changes over time, offering insights into the structural integrity of the material. Still, they do not account for chemical breakdowns of biomaterials or by-products formed [79]. Chemical characterisation techniques, while more technically demanding, offer the most robust and regulatory-relevant assessment, as they allow for direct quantification of degradation products' compositional shifts.

Despite this, most hydrogel degradation studies still rely heavily on gravimetric analysis to report mass loss over time. While this offers a useful overview, it falls short of the stringent regulatory requirements, especially those defined by ISO 10993 standards, which emphasise comprehensive chemical profiling and toxicological risk assessment. Advanced analytical techniques such as Fourier-transform infrared spectroscopy (FTIR), high-performance liquid chromatography (HPLC), and mass spectrometry (MS) are thus essential for a rigorous understanding of hydrogels' biodegradation and for translation into clinical use.

### Biodegradation pathways

The chemical degradation of biomaterials used in IHs proceeds via distinct mechanisms, influenced by polymer structure, formulation, and surrounding physiological conditions. These degradation pathways, summarised in Fig. 2, are critical to the rational design of materials for specific biomedical applications.

#### Hydrolytic degradation

Synthetic polyesters such as poly (lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL) undergo hydrolysis through cleavage of ester bonds. The resulting by-products, typically lactic and glycolic acid, are metabolised via natural pathways. Remarkably, PLGA degradation kinetics can be tuned by varying the lactic-to-glycolic acid ratio, with higher glycolic acid content accelerating hydrolysis [86–89].

Hydrolytic degradation, driven under physiological conditions, offers uniformity and reproducibility since it is not dependent on the enzymatic or metabolic activity of the patient. However, the resulting acidic microenvironment may trigger inflammatory responses, potentially leading to tissue irritation or immune reactions. This also accelerates localised breakdown, compromising mechanical integrity in load-bearing contexts. Therefore, strategies to buffer or neutralise acidic by-products are often considered to mitigate these potential drawbacks.

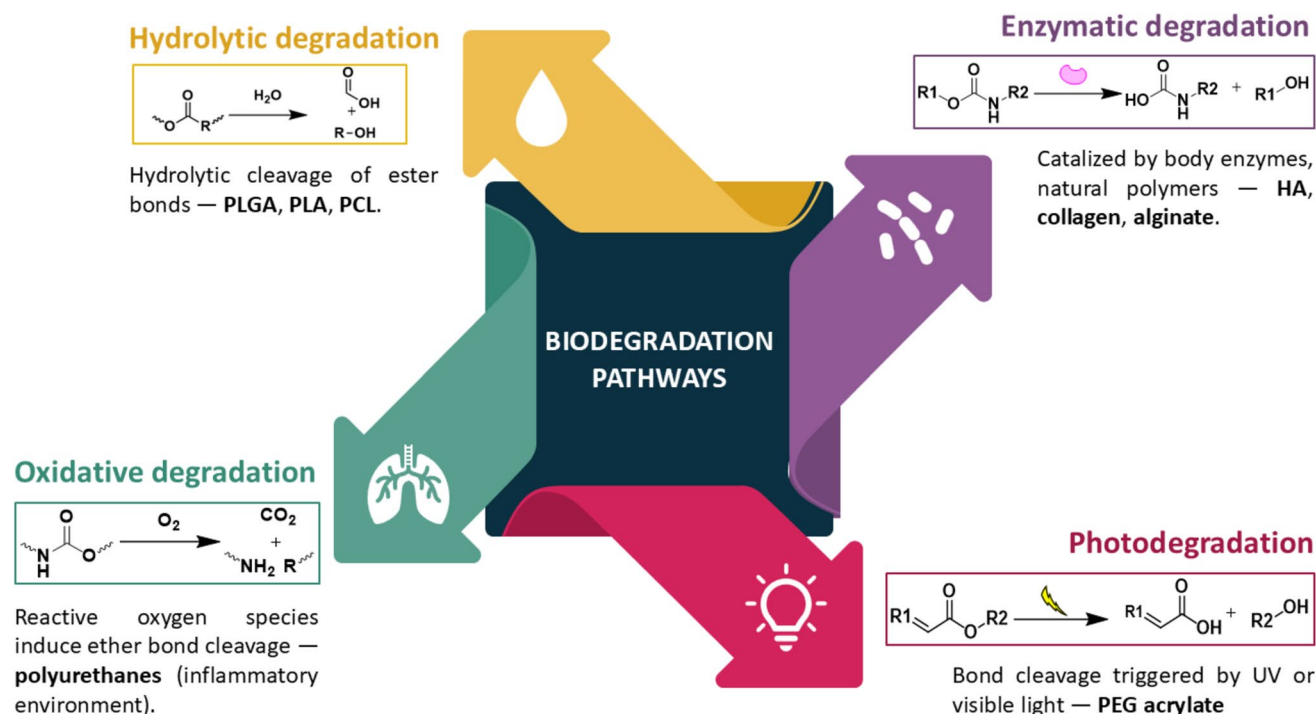
For its part, most ionogels are often designed with polycarbonate polymers, which can also degrade through hydrolysis under physiological conditions. However, IL components tend to persist longer, as many of them are not easily broken down within the body [90, 91]. Safe degradation of ionogels in the body requires careful design to ensure non-toxic and compatible with human metabolism byproducts [92, 93].

Because local depots of ionogels can result in prolonged tissue exposure and potential systemic distribution, developers should quantify parent and metabolite concentrations in plasma and organs using radiolabelled or LC–MS/MS

**Table 2** ISO 10993 biological evaluation matrix for IHs

Hydrogel — Route	Cytotoxic (10,993–5)	Irritative/ Sensitive (10,993–10)	Systemic toxicity (10,993–11)	Genotoxic (10,993–3)	Implants (10,993–6)	Hemocompati- bility (10,993–4)	Chronic toxicity (10,993–11/3)	By-products (10,993–18)	Pyrogen/ Endotoxin
Alginate/ chitosan in situ forming hydro- gels — SC/ IM/IA	Yes	Conditional (SC route)	Yes	Conditional (if residual crosslinkers)	Conditional (IM/IA implants)	Conditional (if blood contact)	Conditional (if long-term implant > 30 days)	Yes (quantify enzymatic frag- ments)	Yes (critical for natural poly- mers)
Collagen/ fibrin hydrogels — SC/ IM	Yes	Yes	Yes	Conditional (if residual crosslinker)	Yes	Conditional (if blood contact)	Yes	Yes (quantify peptide frag- ments)	Yes (critical for natural polymer)
HA pre-formed gels — SC/IA	Yes	Yes	Yes	Conditional (if residual crosslinkers)	Conditional (IA implants)	Conditional (if blood contact)	Conditional (if long-term implant > 30 days)	Yes (quantify HA fragments or residual crosslinkers)	Yes (critical for natural polymer)
PEG-based hydrogels — IT	Yes	Yes	Yes	Yes (if acrylates)	Yes	Conditional (if blood contact)	Yes	Yes (quantify PEG frag- ments)	Yes
Thermorespon- sive Pluronic gels — IT	Yes	Yes	Yes	No	Yes	Conditional (if blood contact)	Conditional (if long-term implant > 30 days)	Yes (residual solvents)	Yes
Acrylamide gels — IM	Yes	Yes	Yes	Yes (risk induced by acrylamide monomers)	Yes	Conditional (if blood contact)	Yes (long-term carcino- gen)	Yes (quantify acrylamide monomers)	Yes
Bioceramics in hydrogel — IA/ bone filler	Yes (particle cytotoxicity conditional)	Yes	Yes	Conditional (if chemical addi- tives)	Yes	Conditional (if blood contact)	Yes	Yes	Yes
Drug-loaded hydrogels — all routes	Yes (must include drug and matrix)	Yes	Yes	Yes	Conditional (IM/IA/IT implants)	Conditional (if blood contact or IV route)	Conditional (if long-term implant > 30 days)	Yes (quantify polymer and drug metabo- lite)	Yes
Ionogels — IT/SC	Yes	Yes	Yes	Yes (risk induced by ILs)	Conditional (IT implants)	Conditional (if blood con- tact)	Yes	Yes (quantify ILs metabolite)	Yes

Abbreviations: IT, intratumoral; SC, subcutaneous; IA, intra-articular; IM, intramuscular; IV, intravenous; HA, hyaluronic acid. The testing flow begins with the cytotoxicity assay (ISO 10993–5), which is the mandatory starting point, only after passing this test further evaluations are conducted in the following order: irritation and sensitization (10,993–10) → systemic toxicity (acute or subchronic, 10,993–11) → genotoxicity (10,993–3) → implantation and hemocompatibility (10,993–6 / 10,993–4) → chronic toxicity and degradation by-products (10,993–11 / 10,993–18) → pyrogenicity or endotoxin testing. “Conditional” label indicates that the test is required only in depicted cases.



**Fig. 2** Representative biodegradation pathways for natural and synthetic polymers composing IHS

approaches to define clearance pathways and margins of safety [94, 95]. Local effects such as inflammation, fibrosis, or delayed healing can occur even when *in vitro* cytotoxicity appears low, underscoring the need for subchronic implantation and histopathological evaluation consistent with ISO 10993–6/11. ILs may also modulate immune and complement pathways and can perturb blood components through surfactant-like mechanisms, warranting immunotoxicity and hemocompatibility testing [96]. Given the chemical diversity of ILs, genotoxicity assays are generally required, and long-term studies may be necessary for persistent formulations. Currently, no ionogel-specific regulatory guideline exists; agencies apply conventional ISO 10993 and ICH frameworks, emphasizing degradation profiling, ADME studies, and risk-based justification of the chosen ionic chemistry. Consequently, claims of “superior cytocompatibility” should be treated cautiously, as *in vitro* assays may underestimate chronic or systemic toxicity [97]. Comprehensive chemical characterization, metabolite identification, and *in vivo* distribution studies remain essential prerequisites for regulatory acceptance and clinical translation of ionogel systems.

### Enzymatic degradation

Natural polymers such as collagen, alginate, and HA degrade through enzymatic cleavage catalysed by enzymes such as collagenase and hyaluronidase [98]. Notably, the degradation products can themselves be bioactive agents.

For instance, HA oligosaccharides released during degradation have been proven to enhance tissue regeneration [99, 100]. Another example could be chitosan hydrogels, which are enzymatically cleaved by lysozymes and other enzymes, presenting antimicrobial activity [101].

However, enzymatic degradation is highly variable across patient populations, influenced by genetics, immune response, disease state and metabolic conditions. This makes standardisation and reproducibility particularly challenging, so most natural-based hydrogels are marketed as fillers instead of drug release systems.

### Oxidative degradation

Synthetic polymers like polyurethanes are susceptible to oxidative degradation in the presence of reactive oxygen species (ROS), especially under inflammatory environments. This mechanism is particularly attractive for stimuli-responsive systems, as ROS levels are often elevated in cardiovascular pathologies such as atherosclerosis, hypertension, and ischemia–reperfusion injury [102]. By developing materials designed to degrade specifically in response to ROS, we can leverage this biological signal to trigger precise, localised material breakdown and subsequent drug release, ensuring targeted therapeutic effects. Materials designed to respond to oxidative cues offer spatial and temporal control over degradation. However, the

unpredictability of oxidative stress levels and the potential toxicity of by-products remain important concerns [103].

### Photodegradation

Photosensitive polymers offer another layer of control, undergoing degradation upon exposure to specific light wavelengths. For example, PEG-based hydrogels, such as PEG-acrylate, degrade upon UV or visible light exposure [104]. This precision is ideal for localised therapies, such as intratumoral delivery and ophthalmic treatments. However, photodegradable systems are limited by light penetration in tissues and potential instability under ambient light, restricting their broader clinical applicability [104].

### Manufacturing and scalability

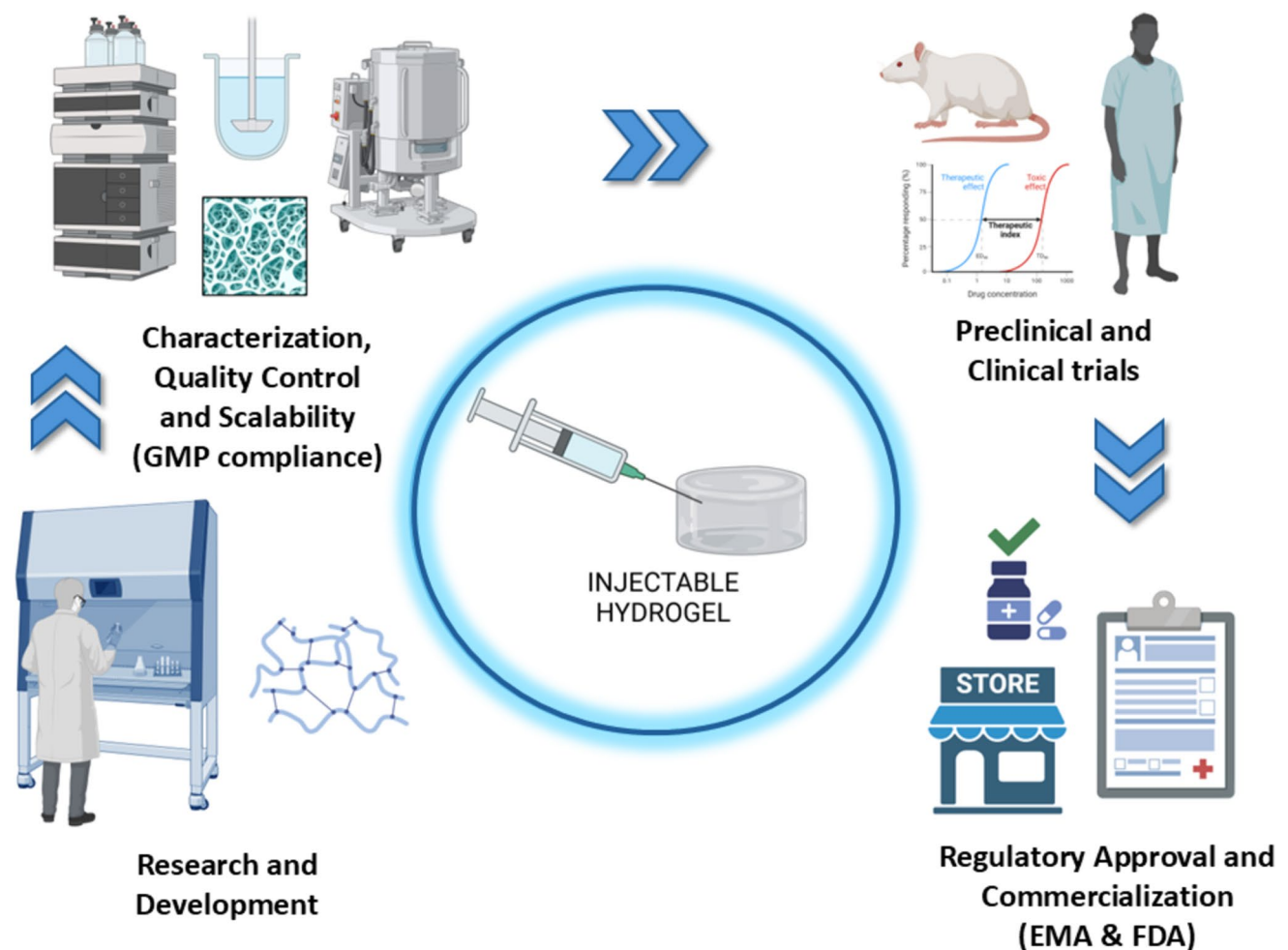
Scalability and reproducibility are fundamental cornerstones in transitioning IHs from lab to clinic [1, 105]. This is particularly relevant in applications such as drug delivery,

regenerative medicine, and tissue engineering, where batch consistency directly influences therapeutic efficacy and safety.

Reproducibility is often compromised by variability in raw materials, sensitivity to environmental conditions, and differences in manufacturing protocols [106]. A robust process must not only standardise formulation and crosslinking conditions but also ensure that degradation kinetics and biocompatibility remain within validated specifications. Figure 3 illustrates the stepwise approach required to transition from bench-scale development to clinically approved hydrogel products.

### Raw materials and their standardisation

The core reproducibility in IHs systems is the consistent quality of raw materials. Most IHs are synthesised from polymers such as PEG, HA, or chitosan, typically functionalized with reactive groups to enable gelation. However, subtle variations in their molecular weight, functionalization



**Fig. 3** Representative scheme of the developing process from laboratory research to the commercialisation of an IH product

degree, or purity can impact key hydrogel properties, including mechanical strength, gelation kinetics, and biocompatibility [107].

To address this, raw material sourcing and characterization must be tightly standardised. Suppliers should provide detailed certificates of analysis, and materials should undergo rigorous in-house testing for critical parameters [108]. Without this level of control, downstream variability becomes almost inevitable, precluding reproducibility and regulatory compliance.

### Manufacturing process control

Hydrogel production involves several independent steps, from polymer sterilisation to mixing it with crosslinkers or bioactives. Each stage introduces potential variability, underscoring the importance of rigorous process control [109].

Sterilisation is especially critical for clinical applications, yet it poses significant challenges. Techniques such as autoclaving, gamma irradiation, or filtration must be validated carefully, as they can alter polymer structure. For example, gamma irradiation, while effective, may induce

chain scission in some polymers, affecting the mechanical properties of the final hydrogel [110]. Thus, formulation, sterilization and delivery device must be co-designed to preserve hydrogel performance while meeting sterility and usability requirements. Table 3 summarizes common polymer classes and their compatibility risks with standard sterilization modalities (chain scission, yellowing, residual toxicants), likely rheology drift and practical mitigations such as radical scavengers, lyophilized precursor kits and on-device mixing.

In parallel, successful clinical translation of IHs requires concurrent design of the formulation and its delivery device to ensure sterility, dose accuracy, usability, and regulatory compliance. Common configurations include pre-filled syringes, lyophilized reconstitution kits, and dual-barrel or on-mix cartridge systems, each offering distinct trade-offs in stability, user steps, and mixing efficiency [111]. Device materials must be compatible with the hydrogel formulation and chosen sterilization method, while extractables, leachables, and dead volume are carefully validated. Injection performance—expressed as peak plunger force versus injection rate for the intended syringe and needle—should

**Table 3** Sterilization methods used for IHs

Polymer class	Sterilization methods	Compatibility risks	Rheology drift	Practical mitigations
Crosslinked HA or PEG hydrogels	Sterile filtration (common) EtO (common) Gamma radiation (rare)	Gamma radiation: chain scission	↓ viscosity / ↓ G' after ionizing radiation	Sterile filtration: when possible EtO cycle: long aeration Low radiation with antioxidants
Alginate-Ca <sup>2+</sup> hydrogels	Sterile filtration (common) EtO (common) Gamma radiation (rare) Autoclave (for solutions)	Gamma radiation: chain scission Autoclave: alter hydrogels structure	↓ viscosity and altered gelation kinetics (weaker Ca <sup>2+</sup> crosslinks)	Sterile filtration when possible EtO cycle: long aeration
Protein hydrogels (collagen, gelatine, fibrin)	Sterile filtration (common) EtO (common)	EtO accelerate proteolytic degradation	Denaturation, ↓ elasticity	Sterile filtration when possible EtO cycle: long aeration Minimize harsh heat
Acrylate hydrogels (PEG, PEGDA)	Sterile filtration (common) EtO (common) Gamma radiation (rare)	Photoinitiators may form reactive residues Gamma radiation: chain scission	↓ viscosity and altered gelation kinetics (reactive residues)	Sterile filtration when possible Use high-purity monomers Low radiation with antioxidants
Pluronic-based hydrogels	Sterile filtration (common) EtO (packaging)	EtO residues if not aerated	Rheology properties preserved	Sterile filtration when possible Minimize heat and cold cycles
Ionogels	Sterile filtration (common) EtO (packaging) Gamma radiation (rare)	EtO residues are problematic for lipophilic ILs Gamma radiation: chain scission	Not described	Sterile filtration at end point when possible
Polyurethane-based hydrogels	EtO (common) Gamma radiation (rare)	Gamma radiation: chain scission EtO residues Hydrolytic sensitivity	↓ G' after ionizing radiation	EtO cycle: long aeration Low radiation with antioxidants

Abbreviations: EtO, ethylene oxide; PEO, polyethylene oxide; PEG, poly(ethylene glycol); PEGDA, poly(ethylene glycol) diacrylate.

be quantified early, as viscosity and gauge strongly influence human factors such as comfort and controllability. Designs should enable single-hand operation and minimize user error through tactile or visual cues. For high-viscosity gels, motorized or mechanically assisted applicators may be required [112]. Product stability strategy should be defined in parallel with device design: lyophilization, separated-component cartridges, or antioxidant-stabilized formulations can enable ambient storage, while cold-chain logistics remain necessary for protein- or cell-containing hydrogels. Packaging materials, barrier properties, and temperature excursion tolerances must be established through validated studies [113, 114]. Integrating formulation, sterilization, and usability considerations from the outset facilitates manufacturability, regulatory acceptance, and consistent clinical performance.

Likewise, the mixing and crosslinking processes require strict regulation. Whether the crosslinking is physical, chemical, or enzymatic, it must occur under controlled conditions to ensure uniformity in hydrogel properties. Factors such as pH, temperature, and crosslinker concentration significantly influence the final product. Emerging technologies, like microfluidics and automated mixing systems, are increasingly being used to enhance process control, minimize operator errors, and improve reproducibility [115, 116].

### Challenges in scaling up production

While laboratory-scale production allows for close control of conditions, scaling up introduces new challenges. Parameters that are easily managed in small volumes can become problematic at an industrial scale. Pilot-scale studies are essential to identify them early and adapt protocols accordingly [117]. Fortunately, advances in scalable microfluidic manufacturing maintain homogeneity during scale-up, making them attractive tools for translational research [118].

### Quality control and regulatory compliance in scale-up processes

A robust quality control (QC) framework is indispensable when moving toward clinical or commercial application. QC must span the entire production chain, from raw materials to the final product, ensuring all the points discussed above, from batch-to-batch consistency to regulatory compliance.

Key QC parameters include gelation time, mechanical properties, swelling behaviour, degradation kinetics, and sterility [119]. A combination of analytical tools is typically employed, such as rheometry for viscoelastic profiling [120, 121], FTIR and NMR for chemical composition, and scanning electron microscopy (SEM) for microstructural analysis [122]. These assessments are especially relevant for applications such as tissue engineering, where mechanical cues influence cell behaviour and integration (Table 4).

Swelling behaviour is also interesting since it influences drug release rates and structural stability. Standardised testing for swelling ratios and equilibrium water content is strongly recommended for consistent product performance [123].

Furthermore, sterility and microbiological testing are indispensable. Traditional culture-based sterility assessments may be complemented by more sensitive techniques such as PCR. Likewise, residual crosslinker levels should be evaluated using mass spectrometry or similar high-sensitivity methods to ensure long-term biocompatibility [124].

In conclusion, the successful scale-up of IHs requires meticulous attention to material consistency, process reliability, and rigorous QC protocols. Every step must align with regulatory expectations to ensure safety, efficacy, and functional integrity. The incorporation of advanced analytical tools and automation technologies offers a promising path forward, enhancing reproducibility and facilitating the clinical and commercial translation of these biomaterials.

## Clinical trials and approved products

A total of 81 injectable hydrogel-based systems were identified across clinical trials (30) and marketed products (51). These were classified by administration route, polymer family, product type and therapeutic indication. The IA route represented the largest fraction (45%), followed by SC (20%), IT (15%), IVT (10%), and others (e.g., intravesical). Natural polymers (e.g., HA, collagen, chitosan, alginate) accounted for 55% of systems, synthetic polymers (e.g., PEG, PVA, Pluronic®, polyacrylamide) for 35%, and composite systems for 10%. Among all products and trials, 87% were categorized as medical devices, 12% as pharmaceutical products, and 1% as cell-based therapies.

Approvals and new trial initiations increased steadily after 2010, with notable peaks in 2014–2016 (orthopedic fillers) and 2020–2023 (drug delivery systems, e.g., Jelmyto® and CartiLife®).

### Overview of ongoing clinical trials

The clinical trials summarised in Tables 5 and 6 provide an outline of the current progress and challenges in the translation of IH technologies from the laboratory to clinical application. These trials reflect a growing interest in exploiting the unique properties of hydrogels to address a wide range of medical needs, from tissue regeneration and drug delivery to innovative approaches in contraception.

A distinction was made between Table 5 and Table 6 to reflect the different regulatory frameworks relevant to clinical translation. Hydrogels described in Table 5 are intended for drug delivery or cell therapy applications and therefore

**Table 4** Quality parameters evaluated to assess the performance of IHs

CQA / CPP	Performance link	Measure method
Gelation time (37 °C)	Ensures in situ set within clinical window	Tube inversion, vial-in-cup rheology (temperature ramp) Gelation time: 30 s–5 min
Syringeability	Usability, determines required applicator	Dynamic injection test. Measure plunger force for the intended needle gauge Peak force < 200 N for single hand
Modulus window by route (G')	Too soft → dispersion Too stiff → injection failure or tissue damage	Measure frequency sweep (1 Hz G') at 37 °C. Use in vitro mechanical mimic (tissues) SC – 1 to 500 Pa IA – 100 to 2000 Pa IVT—< 50 Pa
Degradation half-life	Sets residence time, release duration and safety	In vitro mass loss In vivo implantation histology (ISO 10993–6) Quantify degradation by-products by LC–MS
Burst limit (initial release)	Prevents toxicity	In vitro release measure at 24 h (< 10–20% depending on the target)
Endotoxin and pyrogen	Safety for natural polymers	Raw natural polymers pyrogenation. Endotoxin quantification by batch (< 100 EU/mL)
Stability	Shelf-life and dosing accuracy	Measure viscosity and G' modulus over time and after storage points
Residual solvent	Avoid toxicity risks	GC–MS / LC–MS
In vitro release mechanism	Translate to pharmacokinetic models (Korsmeyer–Peppas, Peppas–Sahlin or Hopfenberg)	Quantify drug release under multiple media conditions and relate it to rheological measures for storage modulus (G') and swelling ratio Fit data into predictive modelling (report R <sup>2</sup> )

Abbreviations: IT, intratumoral; SC, subcutaneous; IA, intra-articular; IV, intravenous; IVT, intravitreal.

classified under pharmaceutical regulations as conventional drugs. By contrast, the hydrogels listed in Table 5 fall under the category of medical devices, for which pharmacokinetic evaluation is not required; instead, regulatory approval primarily depends on evidence of biocompatibility and therapeutic performance.

Methodological quality appraisal was evaluated within the following standards: low (exploratory, Phase 1, single-arm, non-randomised, small sample size > 20 patients), moderate (randomised, single-arm studies with adequate sample size 20–50 patients) and high (randomised, controlled, multicentre, adequate sample size > 50 patients).

### Hydrogel design tendencies observed in clinical trials

IHs are currently being explored across a broad range of therapeutic areas, including cartilage repair (CartReve®, NCT05186935) and cancer treatment (Life Pearl®, NCT04595266). Thanks to their biomimetic properties and ability to deliver therapeutic agents in a localized and sustained manner, IHs have emerged as strong candidates not only in regenerative medicine but also in oncology.

As shown in Tables 5 and 6, ongoing clinical trials feature hydrogels derived from both natural (e.g., alginate, HA) and synthetic polymers (e.g., polyacrylamide, PEG). This

diversity allows for tailored control over critical characteristics, such as mechanical strength and degradation rates, making it possible to adapt formulations for different clinical needs. That said, despite the growing interest in hybrid systems, no current trials include mixed composite formulations. This absence underscores the persistent challenges in translating more complex hydrogel systems from preclinical research into clinical studies.

A recurring focus across many trials is site-specific drug delivery, aimed at maximizing treatment efficacy while minimizing systemic side effects. For instance, intratumoral hydrogels like *Gut Guarding Gel* (NCT03321396) provide localized drug delivery directly at tumour sites from an alginate matrix, thereby reducing the adverse effects associated with systemic administration.

### The most significant factors to discontinue trials

The range of clinical trials currently underway (Fig. 4) highlights the transformative potential of IHs across diverse fields of medicine. However, the gap between what is observed in clinical trials and what ultimately reaches the market remains significant. According to FDA regulations, clinical results from Phase I or II studies are not required to be reported if they are inconclusive, making it

**Table 5** A non-exclusive list of IHs intended for drug delivery or cell therapy applications, ordered by year of the study start

Name	Composition	Therapeutic agent	Clinical purpose	Administration route	Clinical Trial ID/year	State	Withdrawal reason	Quality
RMCL-CL001	Gelatin	Renal cells	Type II diabetes and chronic kidney disease	Kidney	NCT02525263/2016	Phase II	Therapy failed to improve renal function	Low
CLN-0046	PEG	Tyrosine kinase inhibitor	AMD	Intraocular	NCT03630315/2019	Phase I	Probable Phase II/III evaluation, no results report	Low
FX322	Pluronic	FX-332	Sensorineural hearing loss	Intratympanic	NCT04120116/2019	Phase II	Exploratory efficacy signals but limited clinical effect	High
Carti Life®	Fibrin	Autologous chondrocytes	Cartilage defects treatment	Intraarticular, knee	NCT05051332/2020	Phase III	No results report	Moderate
GADinLADA	Aluminium hydrogel	rhGAD65	Vaccination	Intrainguinal	NCT04262479/2020	Phase II	Safety proved but limited efficacy on C-peptide preservation	Low
Life Pearl®	PEG based microgel	Irinotecan	Colorectal cancer	Intraarterial	NCT04595266/2021	Phase II	No results report	High
Cart Revive®	Dextran-HA derivatives	-	Cartilage defects treatment	Intraarticular, knee	NCT05186935/2022	Phase II	No results report	Moderate
Re Space™	PEG	-	Post radiotherapy, spacer	Transperineal	NCT05369221/2022	Phase I	Probable Phase II/III evaluation, no results report	Low
UGN-102	PEG-PPO triblock copolymer	Mitomycin	Bladder cancer	Intravesicular	NCT05243550/2022	Phase III	Clinical efficacy proved, would require further confirmation	High
TumoCure®	Bulk polymer	Cisplatin	Head and neck cancer	Intratumoral	NCT05200650/2023	Phase I	No results report/ Recruiting	Low
Colorectal cancer treatment	Pluronic® F68 and F127	Fluorouracil	Colorectal cancer	Intrarectal	NCT06385418/2024	Phase II	No results report/ Recruiting	Moderate

Abbreviations: AMD, age-related macular degeneration; ECM, extracellular matrix; HA, hyaluronic acid; MI, myocardial infarction; PEG, polyethylene glycol; PPO, poly (p-phenylene oxide); PVA, polyvinyl alcohol; rhGAD65: recombinant human glutamic acid dehydrogenase; NCT, ClinicalTrials.gov identifier. The status of all clinical trials is Completed, unless otherwise specified in the column Withdrawal reason (active, recruiting).

difficult to ascertain the reason behind the withdrawal of many drug prototypes.

Based on the data compiled from these processes and clinical trials, summarised in Tables 5 and 6, we

hypothesize that the primary reasons for failure can be categorized into three key factors.

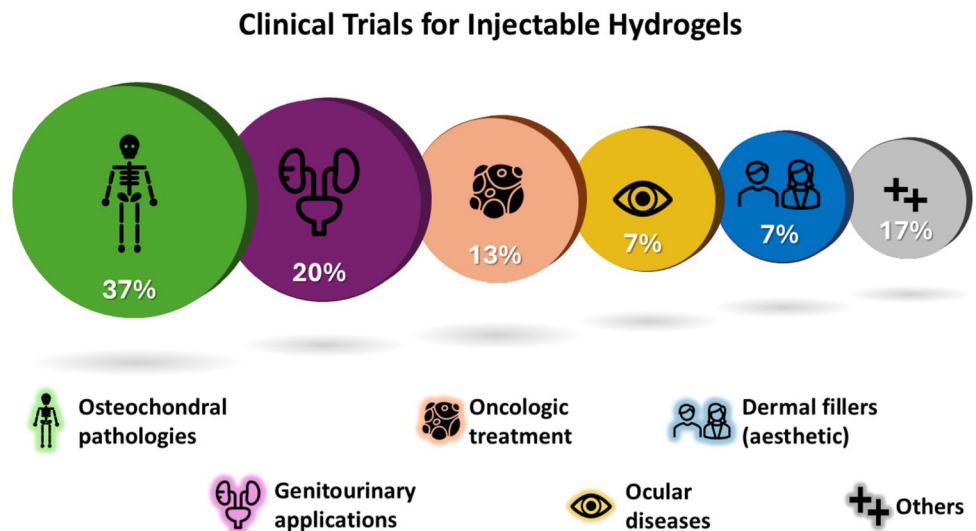
The most significant factor reported include the lack of efficacy. Even when preclinical results are promising, some hydrogels simply do not show meaningful clinical

**Table 6** A non-exclusive list of IHs undergoing clinical trials as medical devices, ordered by year of the study start

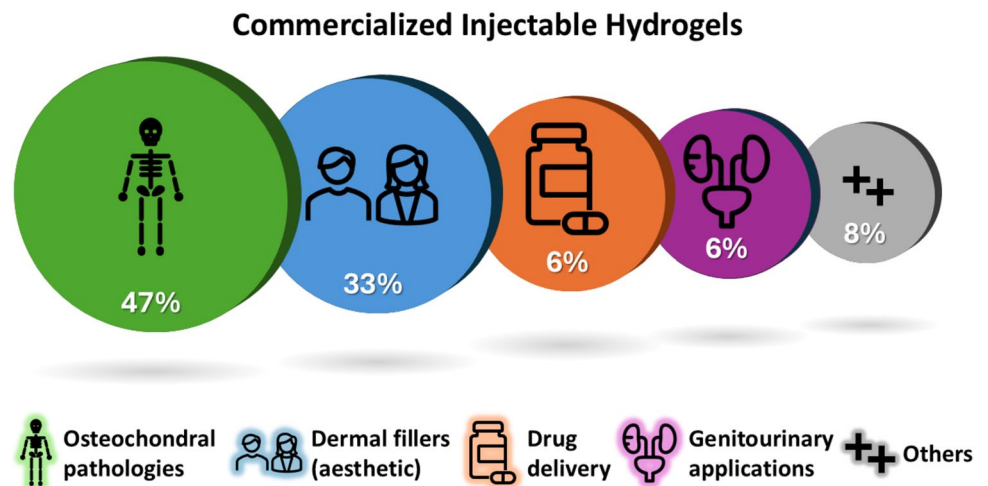
Name	Composition	Clinical purpose	Administration route	Clinical Trial ID/year	State	Withdrawal reason	Quality
Bulkamid®	Collagen	Female stress urinary incontinence	Transurethral	NCT00629083/2008	NA	Comparison to Contigen showed no significant efficacy differences	High
ESS505	Polyethylene terephthalate	Contraception	Intravasal	NCT01664052/2021	NA	Removed from the market on 2018 due to declining sales	High
Gut Guarding Gel	Alginate – calcium salt	Gastrointestinal tumour	Intratumoral	NCT03321396/2017	NA	Safety proved, no Phase II/III studies performed	Low
PAAG-OA	Polyacrylamide	Treatment of pain in osteoarthritis	Intraarticular, knee	NCT04179552/2019	NA	No results report	High
PROMGEL-OA	HPMC	Treatment of pain in osteoarthritis	Intraarticular, knee	NCT04061733/2019	NA	No results report	Low
PVA Hydrogel	PVA	Treatment of pain in osteoarthritis	Intraarticular, knee	NCT04693104/2019	NA	No results report	Moderate
BP-009	Unknown polymeric hydrogel	Post radiotherapy, spacer	Transperineal	NCT05423431/2020	NA	No results report	Low
Controtide®	Polynucleotide	Meniscus lesion	Intraarticular	NCT05322005/2020	NA	Comparison to Hyalubrix showed no significant efficacy differences	Moderate
Embozene®	Polyzene F-microspheres	Treatment of pain in osteoarthritis	Intraarticular, knee	NCT04379700/2020	NA	Safety proved, probable Phase II/III evaluation	Moderate
NOLTREX™	Polyacrylamide with silver ions	Arthrosis pain relief	Intraarticular, knee	NCT06429319/2020	NA	Therapeutic efficacy was not enough consistent	Moderate
SMI-01	Silk particles in hydrogel carrier	Tissue filler	Subcutaneous	NCT04534660/2020	NA	No results report	Moderate
JointRep®	Chitosan	Cartilage defects treatment	Intraarticular, knee	NCT04840147/2021	NA	No results report/ Recruiting	High
OptiSphere®	Microspheres	Treatment of pain in osteoarthritis	Intraarticular, knee	NCT04951479/2021	NA	Therapeutic efficacy was not enough consistent	Low
ADAM™	Styrene maleic acid	Contraception	Intravasal	NCT05134428/2022	NA	No result report/ Active	Moderate
Plenhyage®	Polynucleotide	Scars treatment	Intradermal	NCT05239117/2022	NA	No result report	Moderate
ArToFILL	HA hydrogel	Treatment of pain in osteoarthritis	Intra-articular	NCT06422169/2024	NA	No result report/ Recruiting	Moderate
Human membrane hydrogel	Decellularized human membrane	Retinal defect treatment	Intraocular	NCT06433284/2025	NA	No result report/ Active	Moderate
Hydrafil™	Unknown hydrogel	Degenerative disc disease	Intradiscal	NCT06011551/2025	NA	No result report/ Recruiting	High

Abbreviations: AMD, age-related macular degeneration; ECM, extracellular matrix; HA, hyaluronic acid; MI, myocardial infarction; NA, Not Applicable is used to describe trials without FDA-defined phases, including trials of devices or behavioural interventions; HPMC, hydroxypropyl methylcellulose; NCT, ClinicalTrials.gov identifier. The status of all clinical trials is Completed, unless otherwise specified in the column *Withdrawal reason* (active, recruiting).

**Fig. 4** Overview of IHs products classified by their clinical purposes



**Fig. 4** (continued)



benefits in human trials. For example, Noltrex™, a polyacrylamide hydrogel designed for osteoarthritis pain relief (NCT06429319), was ultimately discontinued due to insufficient efficacy consistency. In some cases, market comparison becomes a decisive factor, as seen with Controtide® (NCT05322005) and Bulkamid® (NCT00629083), which demonstrated clinical efficacy but did not show any significant advantages over existing marketed alternatives.

Inadequate study designs also plays a critical role. Trials with poorly defined endpoints, small sample sizes, and a lack of randomization can lead to inconclusive or misleading results as for ReSpace™ (NCT05369221) or Gut Guarding Gel (NCT03321396) which completed safety assessment but faced challenges to move further into efficacy evaluation.

Lastly, financial and logistical constraints are difficult to overcome. For example, the development of ESS505, a polyethylene-based hydrogel intended for contraceptive use (NCT01664052), was discontinued due to declining

commercial performance and the emergence of competitive long-acting reversible contraceptive options.

As discussed above, another key hurdle is regulatory, while inert hydrogels used in applications such as joint or dermal fillers are typically classified as medical devices, drug-loaded hydrogels fall under pharmaceutical regulations. This distinction subjects them to far more rigorous approval pathways under agencies such as the FDA or EMA. Thus, even though the safety and usability of hydrogels have been well-established in biomedical applications, the added complexity of drug delivery requirements significantly narrows the field of viable candidates for commercial translation. Table 7 presents a comparative overview of the FDA (U.S.) and EMA (Europe) approval pathways, highlighting the principal regulatory requirements for the transition from clinical research to market access.

Borderline cases, such as cell-laden hydrogels, often raise regulatory ambiguity regarding their classification

**Table 7** Comparison between FDA and EMA regulatory pathways

Aspect	FDA (U.S.)	EMA (Europe)
Application Pathways	NDA (New Drug Application) BLA (Biologic License Application) PMA (Premarket Approval)	MAA (Marketing Authorization Application)
Clinical phases	Phase 1: 20–100 healthy volunteers (1 year) Phase 2: 100–300 patients (2 years) Phase 3: 1,000–3,000 patients (3–5 years)	
Review process	Single agency review (FDA)	Centralized via EMA National competent authorities may review
Advisory committee review	Required for complex applications	Committee for Medicinal Products for Human Use
Approval Scope	U.S. market only	All EU member states (via centralized procedure)
Post-Approval Monitoring	Phase IV studies Pharmacovigilance report	Risk management plans Post-marketing studies Environmental impact reports
Emergency Use Authorization (EUA)	Granted during public health emergencies for unapproved products or unapproved uses of commercialized products	Conditional Marketing Authorization (CMA) can be granted during public health emergencies (e.g., COVID-19 vaccines)
Orphan Drug Designation	For rare diseases (<200,000 patients) Incentives: 7-year market exclusivity, tax credits, FDA fee waivers	For rare diseases (<5 in 10,000 people) Incentives: 10-year market exclusivity, research grants, protocol assistance
Drugs and Medical Devices classification	Drugs: Prescription vs OTC Medical Devices: Class I (low risk) Class II (moderate risk, often requires 510(k)) Class III (high risk, requires PMA)	Drugs: risk considered in approval type Medical Devices: Class I (low risk) Class IIa/IIb (medium risk) Class III (high risk, requires conformity assessment)

Abbreviations: 510 (k), FDA regulatory process used for medical devices to demonstrate a substantially equivalency to another device already legally marketed; OTC, drugs without prescription required; PMA, pre-market approval.

as Advanced Therapy Medicinal Products (ATMPs). ATMPs, as defined by the EMA, encompass gene therapy, somatic-cell therapy, and tissue-engineered products that use cells, genes, or engineered tissues to achieve a therapeutic effect. Cell-laden hydrogels such as RMCL-CL001 (NCT02525263) or CartiLife® (NCT05051332) combine living cells with biomaterial scaffolds, bridging between medical devices and biological medicines. Their classification depends on factors as the primary mode of action, the degree of cell manipulation, and whether the therapeutic outcome is driven mainly by the biological activity of the cells or by the physical properties of the scaffold.

### Approved hydrogel-based drug delivery systems

Tables 8, 9, 10 offer a detailed overview of IHs that have been brought for both medical and aesthetic use. These products support a variety of clinical applications, from tissue regeneration to dermal fillers or cancer treatments. Together, they provide a comprehensive insight into the diverse technological advancements in biomaterials, helping to understand their applications and potential benefits in everyday clinical practice. These tables also include a classification in terms of hydrogel type, within three categories, depending

on whether they are already-formed hydrogels injected as a ready-made viscoelastic implant (pre-formed viscoelastic gel), materials delivered in a liquid or precursor form and polymerizes/sets at the site (in situ gelation), or hydrogels used primarily as a temporary carrier or vehicle for particles / biologics (composite/carrier).

### Technological advancements and material innovations

Advances in biomaterials such as HA, collagen, PLA, and demineralized bone matrix (DBM) have significantly improved the biocompatibility, safety, and overall effectiveness of IHs. Innovations in crosslinking methods, controlled-release systems, and bioactive polymer design have extended product lifespan and enhanced therapeutic performance. These improvements have made IHs increasingly appealing across both medical and aesthetic fields, supporting broader clinical adoption.

### Clinical efficacy and safety

Products that demonstrate clear therapeutic benefits with minimal adverse effects tend to see the most success in clinical settings. For example, orthopaedic and regenerative

**Table 8** Non-exclusive list of commercialised IH products for aesthetic use, following intradermal administration ordered by year of approval

Product name	Composition	Year/Authority of approval	Clinical purpose	Hydrogel type
Zyplast(R)® Zyderm(R)®	Collagen from animal source	1981/FDA (USA)	Correction of contour deficiencies	Pre-formed viscoelastic gel
Fibrel®	Collagen	1988/EMA (EU)	Cutaneous scars	In situ gelation
Sculptra®	PLA	2004/FDA (USA)	Facial wrinkles	Composite (carrier)
Hylaform®	Modified HA from avian source	2004/FDA (USA)	Facial wrinkles	Pre-formed viscoelastic gel
Eleevess®	HA/ Lidocaine	2007/FDA (USA)	Moderate to severe facial wrinkles and folds	Pre-formed viscoelastic gel
Evolence® CollagenFiller	Collagen	2008/FDA (USA)	Facial wrinkles	Pre-formed viscoelastic gel
Ellansé®	HPMC/ PCL microspheres	2009/EMA (EU)	Facial wrinkles	Composite (carrier)
Juvéderm® XC	HA/ Lidocaine	2010/FDA (USA)	Facial wrinkles	Pre-formed viscoelastic gel
Belotero balance®	HA	2011/FDA (USA)	Facial wrinkles	Pre-formed viscoelastic gel
Bellafill	Collagen with PMMA microspheres/ Lidocaine	2015/FDA (USA)	Long-lasting dermal filler for acne scars	Composite (carrier)
Radiesse®	Hydroxyapatite and HPMC/ Lidocaine	2015/FDA (USA)	Correction of wrinkles, stimulation of natural collagen production	Composite (carrier)
Restylane® Lyft, Restylane® Refyne, Restylane® Defyne	HA/ Lidocaine	2016/FDA (USA)	Facial wrinkles	Pre-formed viscoelastic gel
Teosyal® RHA	HA	2017/FDA (USA)	Facial wrinkles and folds	Pre-formed viscoelastic gel
Revanesse® Versa +	HA/Lidocaine	2018/FDA (USA)	Facial wrinkles and folds	Pre-formed viscoelastic gel
Revanesse® Lips +	HA	2020/FDA (USA)	Filler-looking lip	Pre-formed viscoelastic gel
RHA® 2, 3, 4, Redensity	HA and BDDE/ Lidocaine	2021/FDA (USA)	Perioral rhytids	Pre-formed viscoelastic gel
Skinvive by Juvéderm	HA	2023/FDA (USA)	Facial wrinkles	Pre-formed viscoelastic gel

Abbreviations: BDDE, 1,4-butanediol diglycidylether; HA, hyaluronic acid; HPMC, hydroxypropyl methylcellulose; PCL, polycaprolactone; PLA, polylactic acid; PMMA, polymethylmethacrylate; FDA, U.S. Food and Drug Administration; PMA – Premarket Approval; 510(k) – Premarket Notification (U.S. device clearance pathway); SSED, Summary of Safety and Effectiveness Data.

therapies like OP-1®, Infuse® Bone Graft, and Cingal® have shown effective tissue regeneration and osteoarthritis pain management, supporting their continued use in clinical practice.

Similarly, drug delivery hydrogels such as Vantas®, Supprelin LA®, and Jelmyto® have proven effective in treating a range of pathological conditions. These systems enhance drug stability, reduce dosing frequency, and improve patient compliance, all while maintaining well-established safety profiles.

### Patient acceptance and minimally invasive procedures

Minimally invasive, non-surgical options have become increasingly popular among both patients and healthcare providers, primarily due to reduced recovery times and lower procedural risks. IH-based treatments for osteoarthritis, such as Synvisc®, Durolane®, SpaceOAR®, and Orthovisc®, offer effective symptom relief without the need for a surgical intervention, contributing to treatment adherence.

In the realm of drug delivery, products like Vantas® and Supprelin LA® provide long-acting effects via simple

subcutaneous injection, reducing dose frequency. Meanwhile, Jelmyto® enables targeted chemotherapy *through* catheter instillation, increasing local drug retention while minimizing systemic exposure and side effects. These features not only improve therapeutic outcomes but also make such treatments more acceptable and practical for patients in routine care.

In summary, the success of the products outlined in the table is the result of a combination of scientific advancements, regulatory compliance, patient preferences, and market dynamics.

### Future directions and innovations

It has been made clear that the main limitations of IHS in clinical translation stem from biocompatibility, mechanical stability, and regulatory challenges. Many hydrogels face issues in balancing their residence time on the body, as rapid degradation can compromise their therapeutic effect, while a slower one may lead to bioaccumulation and toxicity.

**Table 9** Commercialised IH products for orthopaedic use ordered by year of approval

Product name	Composition	Year/Authority of approval	Administration route	Clinical purpose	Hydrogel type
Emdogain®	Porcine decellularized matrix and PEG-alginate	1996/FDA (PMA, USA)	Flapless injection	Regenerates periodontal tissue	Composite (carrier)
Synvisc Hyalan G-F 20	HA derivatives	1997/FDA (PMA, USA)	Intraarticular, knee	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
Osteogenic protein 1(OP-1®) implant, OP-1® Putty	Collagen and HPMC/ Recombinant OP-1	2001/FDA (HDE, USA)	Spinal	Posterolateral lumbar spinal fusion	Composite (carrier)
Infuse® bone graft	Collagen/ BMP2	2002/FDA (PMA, USA)	Spinal	Spinal fusion and orthopaedic trauma surgeries	Composite (carrier)
EUFLEXXA®	HA	2004/FDA (PMA, USA)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
Orthovisc®	HA	2004/FDA (PMA/ USA)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
Coaptite®	HPMC salt and hydroxyapatite	2005/FDA (PMA, USA)	Submucosal	Female stress urinary incontinence	Composite (carrier)
PerioGlas®	PEG and glycerine/ Calcium phosphosilicate particles	2005/FDA (510(k), USA)	Intraosseous	Dental bone regeneration	Composite (carrier)
Dynagraft II®	DBM in Pluronic	2005/FDA (510(k), USA)	Intraosseous	Bone void filler	Composite (carrier)
Optium DBM Gel®	DBM in glycerol	2005/FDA (510(k), USA)	Spinal	Bone graft extender and void filler	Composite (carrier)
Grafton DBM gel®	DBM in glycerol	2005/FDA (510(k), USA)	Spinal	Bone graft extender and void filler	Composite (carrier)
AlloFuse Plus Paste®, AlloFuse Plus Putty®	Allographic DBM in PEG-PPO	2011/FDA (510(k), USA)	Spinal	Void filler, graft extender	Composite (carrier)
Gel-One®	Cinnamic acid functionalized HA	2011/FDA (PMA, USA)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
Solesta®	HA/ Dextranomer	2011/FDA (PMA, USA)	Rectal	Fecal incontinence	Composite (carrier)
BST-CarGel®	Chitosan	2012/EMA (EU), Canada	Intraarticular	Cartilage repair	In situ gelation
Kinex Bioactive Gel®	Collagen and HA	2013/FDA (USA)	Intraosseous	Bone void filler	Composite (carrier)
TraceIT® Hydrogel Tissue Marker	PEG	2013/FDA (USA)	Percutaneous	Improved soft tissue alignment for image-guided therapy	In situ gelation
Arthrosamid®	Polyacrylamide	2014/EMA (EU)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
Algisyl-LVR® Hydrogel Implant	Alginate	2014/EMA (EU)	Percutaneous	Advanced heart failure	In situ gelation
Monovisc®	High molecular weight HA crosslinked with biscarbodiimide	2014/FDA (USA)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
SINOVIAL®	HA	2014/EMA (EU)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
SpaceOAR®	PEG	2015/FDA (USA)	Transperineal, percutaneous	Prostate cancer radiotherapy	In situ gelation
Hymovis®	HA 500–730 kDa, functionalized with hexadecylamine	2015/FDA (USA)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel

**Table 9** (continued)

Product name	Composition	Year/Authority of approval	Administration route	Clinical purpose	Hydrogel type
Cingal®	High molecular weight HA crosslinked with biscarbodiimide/Triamcinolone hex-acetonide	2016/EMA (EU)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
GelrinC®	PEG diacrylate and denatured fibrinogen	2017/EMA (EU)	Intraarticular	Treatment of focal cartilage lesions	In situ gelation
TRIVISC®	HA	2017/EMA (EU)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
Durolane	HA	2017/FDA (USA)	Intraarticular, knee	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
SYNOJOYNT®	HA salt	2018/FDA (USA)	Intraarticular	Treatment of pain in osteoarthritis	Pre-formed viscoelastic gel
Actifuse®	Pluronic® F127 and silica phosphate salt	2018/EMA (EU)	Intraosseous	Bone void filler in spinal and orthopaedic application	Composite (carrier)
Tactoset®	HA and calcium phosphate	2019/FDA (USA)	Intraosseous	Bone void filler for orthopaedic application	In situ gelation
Bulkamid®	Polyacrylamide	2020/FDA (USA)	Transurethral	Female stress urinary incontinence	Pre-formed viscoelastic gel

Abbreviations: BMP2, bone morphogenetic protein-2; DMB, demineralized bone matrix; HA, hyaluronic acid; HPMC, hydroxypropyl methylcellulose; PEG, polyethylene glycol; PPO: poly (p-phenylene oxide); HDE, Humanitarian Device Exemptin; FDA, U.S. Food and Drug Administration; PMA – Premarket Approval; 510(k) – Premarket Notification (U.S. device clearance pathway); SSED, Summary of Safety and Effectiveness Data.

**Table 10** Commercialised IH products for drug delivery ordered by year of approval

Product name	Composition	Year/Authority of approval	Administration route	Clinical purpose	Hydrogel type
Vantas®	pHEMA and HPMA/Histrelin acetate and Gonadotropin hormone	2005/FDA (USA)	Subcutaneous	Palliative treatment of prostate cancer	Composite (carrier)
Supprelin LA®	pHEMA/Histrelin acetate	2007/FDA (USA)	Subcutaneous	Central precocious puberty	Composite (carrier)
Jelmyto®	Pluronic® F127, PEG 400, HPMC/Mitomycin	2020/FDA (USA)	Catheter instillation	Upper tract urothelial cancer	In situ gelation

Abbreviations: HPMA, poly (2-hydroxypropyl methacrylate); HPMC, hydroxypropyl methylcellulose; PEG, polyethylene glycol; pHEMA, poly (2-hydroxyethyl methacrylate); FDA, U.S. Food and Drug Administration.

Sterilization and reproducibility are also major concerns, as most polymers may degrade or lose functionality when exposed to common sterilization techniques. Furthermore, regulatory approval requires extensive preclinical and clinical studies to ensure safety and efficacy, which can be time and cost-consuming. Hence, overcoming these limitations is crucial for the successful clinical application of IHs.

There are several aspects that prove the study of IHs to be a truly promising field with a bright future. For instance, advances in 3D printing and biofabrication are revolutionizing the design of IHs, enabling precise customization of their structure and composition for specific applications. 3D

printing allows for the creation of intricate hydrogel networks that mimic native tissue architectures, enhancing their applicability in regenerative medicine and drug delivery [114]. Moreover, the development of smart hydrogels with stimuli-responsive release mechanisms holds great promise for targeted and controlled therapeutic delivery, minimizing side effects and improving efficacy [115].

Likewise, personalized medicine is driving the demand for patient-specific hydrogel systems, where biomaterials can be tailored based on individual clinical conditions, genetic profiles, and therapeutic goals. By incorporating patient-derived cells or biomolecules into hydrogels, these

systems can be fine-tuned to address unique physiological environments, enhancing therapeutic outcomes [116].

Additionally, the future of IHs lies in their integration as advanced diagnostic tools, such as biosensors and imaging technologies. Hydrogels embedded with diagnostic markers or sensors can provide real-time feedback on therapeutic efficacy, disease progression, or biomarker levels. This combination of therapy and diagnostics could enable more dynamic and responsive treatment regimens, paving the way for precision medicine applications [117].

Therefore, the progress of IH technology relies heavily on interdisciplinary collaboration between materials science, biology, and clinical medicine. Materials scientists contribute innovative polymer designs, biologists offer insights into cellular interactions, and clinicians ensure these systems meet practical therapeutic needs. These advancements have the potential to reshape drug delivery, regenerative medicine, and patient care in unprecedented ways.

## Conclusion

IHs have emerged as versatile biomaterials, with expanding applications in drug delivery, tissue engineering, and regenerative medicine. Their unique properties, such as biocompatibility, tuneable degradation, and stimuli-responsive behaviour, position them as transformative tools in modern healthcare.

Despite these advancements, bringing IHs from the lab to the clinic remains a challenge. Issues like scalability, reproducibility, regulatory compliance, and the need to manage immune responses and potential toxicity continue to pose significant barriers to translational research.

Looking ahead, the field is moving towards next-generation technologies, including 3D printing, smart hydrogels, and patient-oriented designs. When combined with advanced diagnostic methods, these approaches could significantly transform the landscape of hydrogel-based therapies. By addressing current limitations and encouraging cross-disciplinary collaboration, IHs are well-positioned to make a huge impact on personalized medicine, enhancing patient outcomes and redefining therapeutic strategies across a wide range of clinical applications.

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## Declarations

**Competing interests** The authors have no relevant financial or non-financial interests to disclose.

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