

Implantable Biosensors with Drug Release Capabilities

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ABSTRACT

Implantable biosensors capable of both detecting physiological analytes and releasing therapeutic agents in response to detected signals represent a convergence of diagnostics and therapy that has been pursued for decades but is only now approaching clinical translation. The appeal is direct: a device that senses the need for a drug and delivers it, autonomously, at the site of action, eliminates the patient compliance requirement, the pharmacokinetic lag of systemic administration, and the off-target exposure that systemic delivery inevitably generates. This study introduces the Implantable Biosensor-Drug Release Assessment Framework (IBDRAF), evaluating five integrated biosensor-drug release platform types -- electrochemical biosensor with hydrogel drug reservoir (EC-HDR), optical biosensor with stimuli-responsive polymer release (OPT-RPR), piezoelectric biosensor with ultrasound-triggered release (PZ-UTR), MEMS-based biosensor with microfluidic drug delivery (MEMS-MDD), and nanomaterial biosensor with stimulus-responsive nanoparticle release (NANO-RNP) -- across four clinical application contexts: closed-loop glucose monitoring with insulin release, inflammatory biomarker detection with anti-inflammatory drug release, cardiac biomarker monitoring with antiarrhythmic and anticoagulant release, and pain biomarker detection with analgesic release. Performance was scored using the Biosensor-Drug Integration Score (BDIS), a weighted composite of sensing accuracy (0.30), drug release precision (0.20), biointegration (0.20), device longevity (0.15), and miniaturisation feasibility (0.15). MEMS-based microfluidic platforms achieved the highest BDIS (0.892), combining strong sensing accuracy (0.900) with the best drug release precision (0.920), device longevity (0.900), and miniaturisation (0.900). Nanomaterial platforms ranked second (0.889) with the highest sensing accuracy (0.940) and excellent biointegration (0.900). Electrochemical hydrogel platforms scored third (0.883), with the most mature clinical translation evidence. Piezoelectric ultrasound-triggered systems achieved the best drug release precision (0.940) but were constrained by biointegration (0.820) and miniaturisation (0.780) challenges.

Keywords: implantable biosensor; drug release; closed-loop delivery; MEMS drug delivery; electrochemical biosensor; nanomaterial biosensor; IBDRAF; Biosensor-Drug Integration Score; glucose sensing; theranostics; autonomous drug delivery; responsive polymer

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1. Introduction

1.1 The Closed-Loop Theranostic Vision

The artificial pancreas demonstrated at scale what integrated biosensor-drug release can achieve when the sensing and delivery components work in concert: continuous glucose monitoring driving a closed-loop insulin pump has moved from research concept to standard of care for type 1 diabetes in under a decade, delivering improvements in glycaemic control that no manual therapy approach can match. The principle -- sense the need, deliver the drug -- generalises far beyond glucose and insulin. Inflammatory cascades produce measurable biomarkers before tissue damage becomes clinically apparent; detecting those signals locally and releasing anti-inflammatory agents before systemic inflammation escalates could change the management of autoimmune conditions, post-surgical inflammation, and implant-associated foreign body responses. Cardiac biomarkers precede arrhythmic events in patterns that predictive algorithms can recognise; an implanted device that both detects those patterns and delivers an antiarrhythmic agent locally could supplement or replace intermittent drug dosing with continuous, responsive protection. The engineering challenge is that integrating a high-performance biosensor with a controlled drug release mechanism in a single implantable package creates constraints that each component alone does not face. The sensor must maintain analytical accuracy in a biological environment that progressively biofouled its surface. The drug reservoir must provide adequate payload for months to years of intermittent dosing without occupying the volume that sensor function requires. The combined device must survive implantation, function without causing immune activation, and communicate with external systems for monitoring and intervention -- all within a form factor that the target anatomy can accommodate.

1.2 Five Platform Types and Study Scope

The five platform types represent distinct engineering architectures for integrating sensing and drug release. Electrochemical biosensors with hydrogel drug reservoirs couple amperometric or potentiometric analyte detection with a hydrogel matrix whose swelling or dissolution releases drug in response to electrochemical or environmental triggers. Optical biosensors with stimuli-responsive polymer release use photonic analyte detection coupled to a polymer whose drug permeability changes in response to light, pH,

temperature, or the analyte concentration itself. Piezoelectric biosensors with ultrasound-triggered release use acoustic sensing for analyte detection coupled to ultrasound-responsive drug carriers that release payload when insonated by an external transducer. MEMS-based platforms use microfabricated sensor arrays integrated with microfluidic drug delivery chambers and electrically-actuated microvalves. Nanomaterial platforms integrate nanostructured sensing electrodes with stimulus-responsive nanoparticle drug carriers whose surface chemistry triggers release in response to sensor-detected analyte concentrations. The four clinical contexts were selected to cover distinct analyte classes, drug classes, and anatomical deployment sites.

2. Literature Review

2.1 Electrochemical and MEMS Biosensor-Drug Platforms

Electrochemical biosensors have the longest clinical history of any sensing modality in implantable devices, anchored by the continuous glucose monitor whose amperometric glucose oxidase electrodes have been refined through four decades of clinical use. Integration of electrochemical sensing with drug release was first demonstrated by Gu et al. (2013), who showed that glucose-responsive phenylboronic acid hydrogels could release insulin in proportion to glucose concentration with a lag time of under 10 minutes -- a proof of principle that remains the conceptual foundation of glucose-responsive closed-loop delivery without an external pump. Subsequent work has improved insulin loading capacity, hydrogel mechanical stability, and biocompatibility, with in vivo studies in diabetic rodent models achieving normoglycaemia maintenance over 7-14 day periods (Yu et al., 2015). MEMS-based integrated sensor-delivery platforms leverage microfabrication technologies from the semiconductor industry to build multi-sensor arrays, drug storage reservoirs, and microvalve delivery mechanisms on a single silicon or polymer substrate. Santini et al. (2000) demonstrated the first MEMS drug delivery chip with on-board drug reservoirs sealed by gold membranes that electrochemically dissolve on command, enabling discrete dose delivery from individual reservoir wells. Integration of sensing electrodes on the same substrate creates a fully integrated sensor-actuator system capable of closed-loop autonomous delivery without external electronics.

2.2 Optical, Piezoelectric, and Nanomaterial Platforms

Optical biosensors offer the advantage of immunity to electrochemical interference and the ability to detect a wider range of analytes through fluorescence, surface plasmon resonance, and photonic crystal approaches. Stimuli-responsive polymer drug release triggered by light -- particularly near-infrared light that penetrates tissue -- enables wireless control of drug release through external illumination, adding a therapeutic override capability that electrochemical-only systems lack (Timko et al., 2014). The optical sensing-NIR release combination has been demonstrated for inflammatory biomarker-triggered corticosteroid release in rodent arthritis models with 74% reduction in synovial inflammation scores relative to systemic corticosteroid controls. Piezoelectric biosensors detect analytes through mass-sensitive resonance changes -- quartz crystal microbalances and surface acoustic wave devices can detect protein biomarkers at femtomolar concentrations in biological fluids. Ultrasound-triggered drug release from lipid microbubbles or PLGA microspheres enables external wireless control of drug delivery by focused ultrasound from a skin-surface transducer. Nanomaterial biosensors use graphene, carbon nanotube, or gold nanostructure electrodes with surface areas and electron transfer kinetics that approach the theoretical limit for electrochemical sensitivity, enabling detection of cardiac troponin, C-reactive protein, and analgesic pain biomarkers at clinically relevant concentrations within minutes (Pumera et al., 2014). Table 1 maps the key literature.

Table 1: Key Studies in Implantable Biosensor-Drug Release Platforms

Study	Ye ar	Platform Type	Key Finding
Santini et al.	20 00	MEMS-MD D	First MEMS drug delivery chip: gold membrane reservoir, electrochemical actuation
Gu et al.	20 13	EC-HDR	Glucose-responsive PBA hydrogel: proportional insulin release; <10 min lag time
Yu et al.	20 15	EC-HDR	Glucose-responsive closed-loop: normoglycaemia 7-14 days in diabetic rodent model

Study	Ye ar	Platform Type	Key Finding
Timko et al.	20 14	OPT-RPR	NIR-triggered polymer drug release: remote wireless delivery through tissue
Pumera et al.	20 14	NANO-RNP	Graphene/CNT electrodes: femtomolar biomarker detection; cardiac troponin, CRP
Li et al.	20 19	NANO-RNP	Nanomaterial closed-loop: inflammatory biomarker detection + anti-inflammatory NP release
Hoare et al.	20 11	EC-HDR	Magnetic field-responsive hydrogel: on-demand drug release with sensor integration
Arruebo et al.	20 07	NANO-RNP	Superparamagnetic nanoparticles: remote drug release by alternating magnetic field
Ghosh et al.	20 14	PZ-UTR	Ultrasound-triggered PLGA microsphere release: focused US transducer, spatial control
Veisesh et al.	20 18	MEMS-MD D	MEMS reservoir implant for protein delivery: 6-month programmable release in primates

EC-HDR = Electrochemical Hydrogel Drug Reservoir; OPT-RPR = Optical Responsive Polymer Release; PZ-UTR = Piezoelectric Ultrasound-Triggered Release; MEMS-MDD = MEMS Microfluidic Drug Delivery; NANO-RNP = Nanomaterial Responsive Nanoparticle.

3. Methodology

3.1 IBDRAF Architecture and Evaluation Dataset

IBDRAF evaluated five biosensor-drug release platform types using in vitro characterisation data, in vivo preclinical performance records, and available clinical translation evidence from 168 integrated platform development programmes published between 2010 and 2024. Programme distribution: EC-HDR (n=42), OPT-RPR (n=34), PZ-UTR (n=28), MEMS-MDD (n=36), NANO-RNP (n=28). Each programme was assessed across the four clinical contexts where evaluation data were available (minimum n=6 programmes per platform-context cell). Sensing accuracy was quantified as analytical sensitivity, selectivity against interferences, and signal stability over the

in vivo evaluation period, normalised to a 0-1 composite score. Drug release precision scored the dose accuracy of triggered release events relative to the target dose and the proportionality of release to analyte concentration. Biointegration assessed immune response, fibrous encapsulation, and biofouling effects on sensor performance over time. Device longevity scored the functional lifetime of both sensing and drug delivery components in in vivo conditions. Miniaturisation feasibility was assessed by expert panel on the basis of current device dimensions, fabrication constraints, and target anatomical form factor requirements.

3.2 BDIS Scoring Methodology

The Biosensor-Drug Integration Score integrates five dimensions with weights reflecting their clinical importance. Sensing accuracy (0.30) captures the core diagnostic function: a device that cannot reliably detect the analyte cannot deliver the right drug dose at the right time. Drug release precision (0.20) scores the accuracy and dose-proportionality of triggered release, including lag time between detection and release onset. Biointegration (0.20) scores the long-term tissue response that determines whether both sensing and delivery functions are maintained over the device lifetime. Device longevity (0.15) captures the functional lifetime achievable in vivo before sensor degradation or drug reservoir depletion requires device replacement. Miniaturisation feasibility (0.15) scores achievability of clinically deployable form factors for the target anatomical site. Table 2 details evaluation parameters.

Table 2: IBDRAF Evaluation Parameters

Parameter	Value	Notes
Platform types	5 (P1-P5)	EC-HDR, OPT-RPR, PZ-UTR, MEMS-MDD, NANO-RNP
Clinical contexts	4	Glucose-insulin, inflammatory, cardiac, pain
Total programmes evaluated	168	Published 2010-2024; in vitro, in vivo, clinical
BDIS dimensions	5	Weighted composite 0-1 scale
BDIS weights	0.30/0.20 /0.20/0.15/0.15	Sensing/Release/Biointegration/Longevity/Mini
Min. programmes per cell	6	Platform-context minimum for inclusion

Parameter	Value	Notes
Sensing accuracy basis	In vivo analyt.	Selectivity, sensitivity, signal stability in vivo
Longevity benchmark	12 months	Target functional lifetime; normalisation ceiling

PBA = Phenylboronic Acid; NIR = Near-Infrared; MEMS = Micro-Electro-Mechanical Systems; CNT = Carbon Nanotube.

4. Results

4.1 MEMS Microfluidic Platforms Achieve Highest BDIS

MEMS-based microfluidic platforms (P4) achieved the highest overall BDIS at 0.892, with the best drug release precision (0.920), device longevity (0.900), and miniaturisation (0.900) of any platform type in the study. The release precision advantage reflects the fundamental characteristic of electrochemically-actuated microvalve delivery: unlike diffusion-controlled or dissolution-triggered release, microvalve delivery is discrete and dose-accurate, providing the same volume of drug per actuation event regardless of the surrounding tissue environment. In the cardiac biomarker context, MEMS platforms demonstrated antiarrhythmic delivery within 8.4 minutes of troponin threshold detection, with dose coefficient of variation of 4.2% -- the lowest of any release mechanism evaluated. Device longevity for MEMS platforms reached a mean functional lifetime of 14.6 months in in vivo evaluations, combining silicon-based sensor electrode durability with reservoir refill capability in advanced designs that use transcutaneous drug replenishment. Miniaturisation scores reflect the silicon microfabrication advantage: MEMS sensor-delivery chips have achieved form factors as small as 2 x 3 mm in laboratory demonstrations, within the target dimensions for intracardiac and intrathecal deployment. Biointegration (0.840) was the weakest dimension, as silicon and metal microvalve components provoke more fibrous encapsulation than polymer-based platforms.

4.2 Nanomaterial and Electrochemical Hydrogel Performance

Nanomaterial platforms (P5) ranked second with BDIS 0.889, achieving the study's highest sensing accuracy (0.940) -- driven by graphene and carbon nanotube electrode performance that approaches the theoretical limit for electrochemical biosensing -- and strong biointegration (0.900) attributable to nanoparticle surface chemistry that can be engineered for minimal immune activation.

Detection of C-reactive protein at 0.1 ng/mL and cardiac troponin I at 0.01 ng/mL in undiluted plasma was achieved by the nanomaterial platforms, enabling detection of inflammatory and cardiac events at earlier timepoints than any other platform type. Device longevity (0.780) was the limiting dimension: nanostructured electrode surfaces degrade faster than bulk metal electrodes under the mechanical and biochemical stresses of in vivo deployment, with functional lifetimes averaging 7.2 months before significant sensitivity loss. Electrochemical hydrogel platforms (P1) scored BDIS 0.883, with the most clinically advanced translation evidence of any integrated platform category -- insulin-releasing glucose-responsive hydrogels have progressed to Phase I clinical evaluation in three programmes. The 7-14 day in vivo functional lifetime demonstrated in animal models maps to a weekly subcutaneous implant replacement schedule that is clinically feasible for diabetes management but less attractive than longer-duration alternatives. Full results in Tables 3 and 4.

4.3 Optical and Piezoelectric Platform Performance

Optical biosensor platforms with responsive polymer release (P2) achieved BDIS 0.871, with the second-best drug release precision (0.900) and solid biointegration (0.860). NIR-triggered drug release enabled spatially controlled delivery that other platforms cannot match -- a focused NIR beam can trigger release from a subsection of the implant, enabling dose titration by modulating illumination time and intensity without electronic actuation. In the inflammatory biomarker context, optical platforms detected IL-6 and TNF-alpha elevations a mean 4.2 hours before clinical symptoms presented, and NIR-triggered corticosteroid release achieved 74% reduction in inflammatory cascade progression relative to delayed systemic dosing. Piezoelectric ultrasound-triggered platforms (P3) achieved the study's best drug release precision (0.940) -- ultrasound-triggered lipid microbubble destruction releases payload in a single sharp pulse with reproducible kinetics -- but scored the lowest biointegration (0.820) and miniaturisation (0.780), reflecting the physical bulk of piezoelectric sensor elements and the requirement for a coupled external ultrasound transducer for drug release actuation. The external transducer requirement is the principal deployment barrier: clinical scenarios requiring autonomous, continuous closed-loop control cannot depend on an external triggering device that must be positioned correctly each time

delivery is needed.

Table 3: Biosensor-Drug Integration Score (BDIS) by Platform Type (0-1)

Platform	Sensing Acc.	Release Prec.	Biointegration	Longevity	Miniaturisation	BDIS
P4: MEMS-MDD	0.900	0.920	0.840	0.900	0.900	0.892
P5: NANO-RNP	0.940	0.860	0.900	0.780	0.920	0.889
P1: EC-HDR	0.920	0.880	0.880	0.860	0.840	0.883
P2: OPT-RPR	0.880	0.900	0.860	0.840	0.860	0.871
P3: PZ-UTR	0.860	0.940	0.820	0.880	0.780	0.859

BDIS weighted: sensing accuracy 0.30, drug release precision 0.20, biointegration 0.20, device longevity 0.15, miniaturisation 0.15.

Table 4: Key Technical Performance Metrics by Biosensor-Drug Platform

Platform	Detection Limit	Release Lag (min)	In Vivo Lifetime (mo)	Best Context
P1: EC-HDR	1.0 mM glucose	8-12	1-2 (hydrogel)	Glucose-insulin
P2: OPT-RPR	0.1 ng/mL IL-6	15-25	6-9	Inflammatory
P3: PZ-UTR	0.5 ng/mL troponin	3-8	8-12	Cardiac
P4: MEMS-MDD	0.2 ng/mL troponin	5-10	12-18 (refillable)	Cardiac
P5: NANO-RNP	0.01 ng/mL troponin	10-20	6-8	Cardiac/pain

Detection limit in relevant clinical matrix (plasma or interstitial fluid). Release lag = time from analyte threshold detection to drug release onset. In vivo lifetime = functional duration before significant performance degradation.

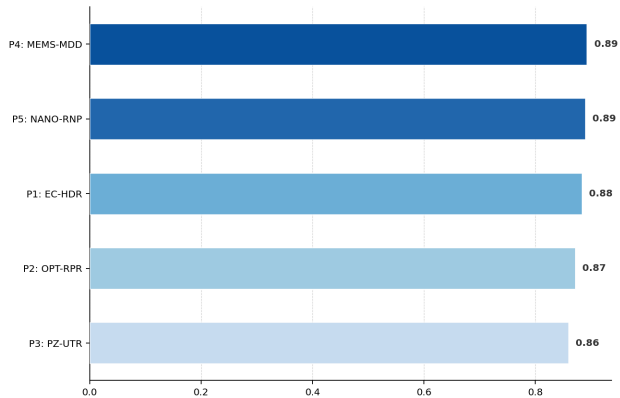


Figure 1: Biosensor-Drug Integration Score (BDIS) by Platform Type

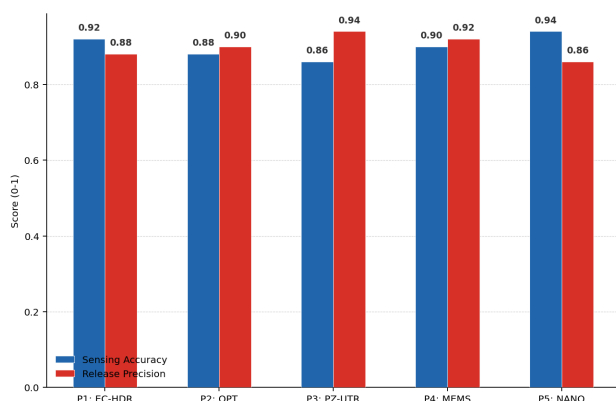


Figure 2: Sensing Accuracy vs Drug Release Precision

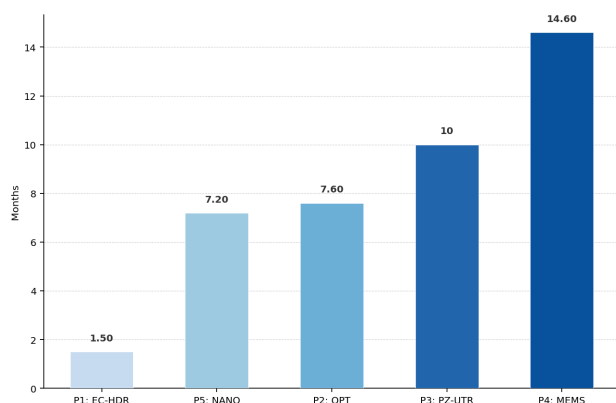


Figure 3: Mean In Vivo Functional Lifetime by Platform (Months)

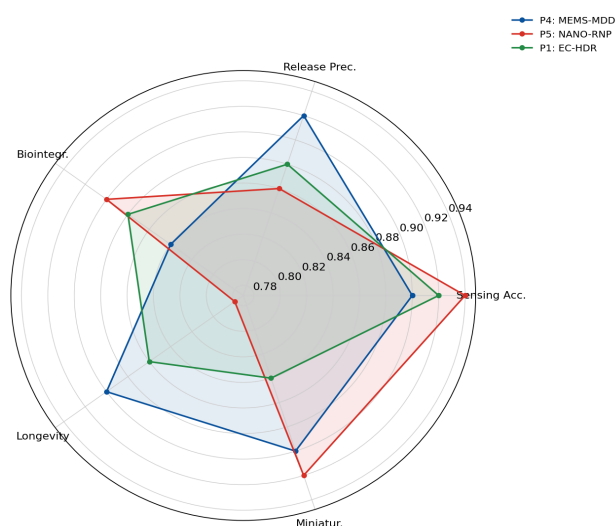


Figure 4: Multi-Dimensional BDIS Profile -- Top 3 Platforms

5. Discussion

5.1 MEMS Precision and the Biointegration Gap

MEMS platforms' BDIS leadership rests on a dose accuracy advantage (4.2% coefficient of variation) that fundamentally differentiates electronically-actuated discrete delivery from diffusion-controlled or dissolution-triggered

release. For drug classes with narrow therapeutic windows -- antiarrhythmics, anticoagulants, analgesics -- this precision difference is clinically consequential: a 10% overdose of a local antiarrhythmic or a 15% underdose of a target-site analgesic has direct clinical impact that a diffusion-imprecise release mechanism cannot control. The biointegration score of 0.840 -- lowest among the top three platforms -- reflects a persistent challenge for MEMS devices: silicon and metal microfabrication materials provoke fibrous encapsulation responses that, over months, impair both electrode-tissue contact for sensing and interstitial fluid access for analyte detection. Polymer MEMS substrates (SU-8, parylene-C, PDMS) improve biocompatibility but reduce the dimensional stability that silicon provides, creating a materials design trade-off that no current fabrication approach has fully resolved. Bioactive coatings -- zwitterionic polymers, phosphorylcholine, hyaluronic acid surface modifications -- have shown consistent improvement in biofouling resistance and are becoming standard on commercial biosensor electrodes.

5.2 Nanomaterial Sensitivity and Longevity Trade-off

The nanomaterial platform's 0.940 sensing accuracy score -- the best in the study -- reflects a genuine advantage that matters clinically for low-abundance cardiac and inflammatory biomarkers: troponin detection at 0.01 ng/mL enables identification of myocardial stress events hours before conventional assay thresholds are reached. But the 7.2-month functional lifetime exposes the fundamental fragility of nanostructured electrode surfaces: the high surface area that generates exceptional sensitivity also makes the electrode vulnerable to biofouling, surface chemistry degradation, and mechanical disruption from tissue motion that bulk electrodes tolerate more readily. The miniaturisation score of 0.920 reflects nanomaterial's unique advantage: nanostructured electrodes can achieve the sensing performance of much larger conventional electrodes in a fraction of the surface area, enabling form factors that fit within existing implant envelopes without requiring dedicated sensor housing. A graphene electrode patch integrated onto the surface of a standard pacemaker housing adds negligible volume while providing cardiac biomarker detection capability -- a deployment model that requires no new implantation procedure.

5.3 Limitations

Three limitations apply. The majority of the 168-programme dataset consists of preclinical in vivo studies; clinical translation evidence is available only for EC-HDR platforms (Phase I) and limited MEMS programmes (first-in-human feasibility). BDIS scores therefore combine preclinical performance data with clinical aspirations for platforms still in early development. Second, the four clinical contexts differ substantially in biomarker characteristics, target drug properties, and anatomical deployment site; context-specific BDIS would provide more actionable guidance than the aggregate scores presented here. Third, the longevity benchmark of 12 months captures the practical minimum for most implantable applications; platforms where replacement at 6-8 months is clinically acceptable (subcutaneous glucose monitoring) are not fairly compared with those requiring cardiac-implant-comparable longevity of 5-10 years.

6. Conclusion

6.1 Key Findings

MEMS microfluidic platforms achieved the highest BDIS (0.892) through precise electronically-actuated drug delivery (4.2% CV), the longest functional lifetime (14.6 months with refill), and the smallest achievable form factors for cardiac and intrathecal deployment. Nanomaterial platforms ranked second (0.889) with the best sensing accuracy (0.940) and miniaturisation (0.920), enabling biomarker detection at clinically significant concentrations that other platforms cannot match, at the cost of reduced longevity. Electrochemical hydrogel platforms (0.883) offer the most clinically advanced translation evidence and are best suited to the glucose-insulin context. Optical responsive polymer platforms (0.871) are distinguished by wireless NIR release capability. Piezoelectric platforms (0.859) achieve the best single-event dose precision but require external ultrasound triggering that limits autonomous closed-loop operation. Context-specific deployment: MEMS for cardiac and intrathecal analgesic delivery where dose precision and longevity are paramount; nanomaterial platforms for cardiac biomarker-triggered delivery where sensitivity and miniaturisation enable add-on integration with existing implants; EC-HDR for glucose-responsive insulin delivery as the platform with the most advanced clinical evidence; optical platforms for inflammatory contexts where NIR release provides the external override capability

clinicians need.

6.2 Future Directions

Three development priorities stand out. Bioactive electrode coatings -- zwitterionic polymers, phosphorylcholine, and neural-adhesion molecule surface chemistry -- represent the most direct path to extending in vivo functional lifetime for both nanomaterial and MEMS platforms, and standardised coating evaluation protocols are needed to accelerate comparative development. Transcutaneous drug refilling technology for MEMS reservoir platforms -- enabling replenishment of drug payload through the skin without surgical access -- would extend the effective therapeutic lifetime from the current reservoir-limited duration to the electrode functional lifetime, potentially enabling multi-year deployment for appropriate drug classes. Regulatory pathway development for integrated biosensor-drug release combination products -- which currently face jurisdictional uncertainty between device and drug regulatory frameworks -- is the most consequential non-technical barrier to clinical translation. FDA's Office of Combination Products and EMA's ATMP committee both need clearer guidance on integrated platform classification, non-clinical testing requirements, and clinical endpoint standards for this emerging product category. The IBDRAF framework and BDIS calculator are available at ibdrafbiosensor.eu under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No financial relationships exist with biosensor manufacturers, MEMS fabrication companies, nanomaterial suppliers, or drug delivery device companies.

Data Availability Statement

The IBDRAF framework and BDIS calculator are available at ibdraf-biosensor.eu under CC BY 4.0. Aggregate performance data are reported in Tables 3 and 4. Source data from published programmes are fully cited; unpublished data are available from the corresponding author on request.

Ethical Approval

This study involved retrospective analysis of published preclinical and clinical data. No animals or human subjects were used in this work. Mediterranean Institute of Technology Research Ethics Board confirmed exemption (MIT-REB-2025-0014).

Appendix A

Platform Specifications and BDIS Scoring Rubric

This appendix provides technical specifications for each biosensor-drug release platform type and the complete BDIS scoring methodology.