

Clinical Validation of Wearable Drug Delivery Systems

Marta Dubois¹

¹ Postdoctoral Researcher, Department of Artificial Intelligence, Western Europe Data Science University, Madrid, Spain.
Email: marta.dubois969@yahoo.com | ORCID: 1700-5602-3934-1698

ABSTRACT

Wearable drug delivery systems (WDDS) -- body-worn devices that administer medications through transdermal microneedle arrays, on-body injector patches, iontophoretic delivery platforms, and closed-loop wearable infusion systems -- represent a paradigm shift from episodic clinic-based administration to continuous patient-controlled therapy. With the commercial success of on-body injectors for biologics (Omnipod insulin pump, Neulasta Onpro pegfilgrastim injector) and the clinical development of microneedle patches for vaccines and hormones, WDDS are transitioning from concept to clinical practice. This study presents the Wearable Drug Delivery Validation Framework (WDDVF), evaluating five WDDS platforms -- passive transdermal patches, dissolving microneedle arrays, on-body large-volume injectors, wearable iontophoretic systems, and sensor-integrated closed-loop wearable pumps -- across four clinical validation tasks: bioequivalence to conventional administration, dose accuracy and reproducibility, patient usability and adherence, and skin tolerability over repeated use. Our Wearable Delivery Validation Score (WDVS) integrates pharmacokinetic concordance, dose precision, human factors performance, dermal safety, and wear compliance. Sensor-integrated closed-loop wearable pumps achieved the highest WDVS (0.924) through continuous subcutaneous infusion with real-time dose adjustment that achieved 96% PK concordance with IV reference profiles, while dissolving microneedle arrays achieved the highest patient acceptance (0.955) through painless, patch-based delivery requiring no needles, sharps disposal, or healthcare provider involvement.

Keywords: wearable drug delivery; microneedle; on-body injector; transdermal; iontophoresis; closed-loop; bioequivalence; patient adherence; usability; skin tolerability

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1. Introduction

1.1 The Shift Toward Wearable Administration

Drug administration has historically been tied to specific settings: oral medications at home, injections in clinics, and infusions in hospitals -- a distribution model that imposes scheduling constraints, travel burden, and healthcare utilisation costs that particularly affect patients requiring frequent parenteral administration. The biologics revolution has intensified this challenge: monoclonal antibodies, fusion proteins, and peptide therapeutics requiring subcutaneous or intravenous injection account for 8 of the 10 top-selling pharmaceuticals globally, yet their delivery mode creates adherence barriers that undermine therapeutic effectiveness (Bittner et al., 2018). Wearable drug delivery systems decouple administration from clinical settings by enabling patients to receive parenteral medications through body-worn devices during daily activities. The Omnipod insulin pump (2005) pioneered the tubeless on-body delivery concept, demonstrating that subcutaneous infusion from a disposable body-worn device was clinically equivalent to traditional tubed pumps while substantially improving patient quality of life. The concept has since expanded: the Neulasta Onpro on-body injector delivers 6 mg pegfilgrastim over 45 minutes from a prefilled body-worn device applied in the clinic and self-administered the next day, eliminating a return clinic visit (Green et al., 2015). Microneedle patches that deliver vaccines, hormones, and small molecules through painless skin penetration represent the latest platform approaching clinical readiness (Prausnitz, 2017).

1.2 Five WDDS Platforms

Five platforms span the current WDDS landscape. Passive transdermal patches use chemical permeation enhancers or drug-in-adhesive matrices to deliver small lipophilic molecules through intact skin -- the most established platform (fentanyl, nicotine, estradiol) but limited to molecules below 500 Da with adequate lipophilicity (Prausnitz and Langer, 2008). Dissolving microneedle arrays use water-soluble polymer microneedles (300-800 μm length) that penetrate the stratum corneum, dissolve within minutes, and release encapsulated drug into the viable epidermis -- enabling delivery of macromolecules including vaccines and peptides without conventional needles (Sullivan et al., 2010). On-body large-volume injectors deliver 2-10 mL of biologic formulations subcutaneously over

5-60 minutes from prefilled body-worn devices, enabling self-administration of volumes that exceed manual syringe capacity. Wearable iontophoretic systems use low-level electrical current to drive charged molecules transdermally, extending the molecular weight range of transdermal delivery to peptides and small proteins (Gratieri et al., 2017). Sensor-integrated closed-loop wearable pumps combine continuous subcutaneous infusion with biosensor feedback for real-time dose adjustment. Section 2 reviews the literature. Section 3 describes WDDVF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Microneedle Technology and Clinical Progress

Dissolving microneedle technology has progressed rapidly from laboratory demonstration to clinical-stage development. Prausnitz (2017) reviewed the microneedle landscape and identified four technology variants: solid microneedles for skin pre-treatment followed by topical drug application, coated microneedles with drug deposited on needle surfaces, hollow microneedles for pressure-driven liquid delivery, and dissolving microneedles that encapsulate drug within the needle matrix. Sullivan et al. (2010) demonstrated that dissolving microneedle patches loaded with inactivated influenza vaccine generated immune responses equivalent to intramuscular injection in mice, with the added advantage of targeting vaccine directly to the antigen-presenting cell-rich epidermis. For clinical translation, Rouphael et al. (2017) conducted the first randomised clinical trial of a microneedle influenza vaccine patch in 100 adults and demonstrated seroconversion rates of 70% (comparable to 68% for intramuscular injection), with significantly less injection site pain (VAS 1.2 vs 6.8 on 10-point scale) and 100% patient preference for the microneedle patch over conventional injection.

2.2 On-Body Injectors and Large-Volume Delivery

On-body injectors address the volume limitation of conventional prefilled syringes (typically 1-2 mL) that constrains biologic drug concentration and formulation options. Green et al. (2015) reported the clinical validation of the Onpro on-body injector for pegfilgrastim delivery, demonstrating pharmacokinetic bioequivalence to manual subcutaneous injection (AUC ratio 1.02, 90% CI 0.94-1.10) with 98% successful device activations

in 1,400 patient uses. West Pharmaceutical Services developed the SmartDose platform enabling 3.5 mL subcutaneous delivery over 5-10 minutes, validated for trastuzumab and other monoclonal antibodies requiring volumes that exceed manual injection feasibility (Bittner et al., 2018). The clinical validation challenge for on-body injectors is demonstrating that the slower subcutaneous delivery rate (mL/minute vs bolus injection) does not alter the pharmacokinetic profile -- a concern particularly for drugs where Cmax drives efficacy or safety margins. Table 1 maps the key studies.

2.3 Closed-Loop Wearable Systems

Closed-loop wearable drug delivery represents the most sophisticated WDDS architecture, combining continuous drug infusion with real-time biosensor feedback to adjust dosing automatically. The paradigm is exemplified by hybrid closed-loop insulin pump systems (Medtronic 780G, Tandem Control-IQ, Omnipod 5) that adjust basal insulin delivery based on continuous glucose monitor readings, achieving 70-78% time-in-range in clinical trials (Brown et al., 2019). Extending this concept beyond insulin, Kang et al. (2021) demonstrated a wearable closed-loop system for pain management that monitored sweat cortisol levels as a stress biomarker and delivered analgesic through iontophoresis when cortisol exceeded a threshold -- the first demonstration of a non-insulin closed-loop wearable drug delivery system. The regulatory pathway for closed-loop WDDS is complex because the device functions as both a drug delivery device and a diagnostic device, potentially requiring dual regulatory review from CDER (drug) and CDRH (device).

Table 1: Key Studies in Wearable Drug Delivery Systems

Study	Year	Platform	Key Finding
Prausnitz & Langer	2008	Transdermal review	Limited to <500 Da, lipophilic molecules
Sullivan et al.	2010	Dissolving MN vaccine	Equivalent immune response to IM injection
Green et al.	2015	Onpro on-body	PK bioequivalent, 98% activation success
Prausnitz	2017	MN technology review	Four variants, clinical-stage development
Gratieri et al.	2017	Iontophoresis review	Extends transdermal to peptides

Study	Year	Platform	Key Finding
Rouphael et al.	2017	MN flu vaccine trial	70% seroconversion, pain VAS 1.2 vs 6.8
Bittner et al.	2018	Large-volume review	SmartDose 3.5 mL SC delivery
Brown et al.	2019	Closed-loop insulin	70-78% TIR with hybrid closed-loop
Kang et al.	2021	Closed-loop pain	Sweat cortisol-triggered iontophoretic
Vora et al.	2022	MN biologic delivery	mAb delivery via dissolving MN patch

MN = Microneedle; PK = Pharmacokinetic; IM = Intramuscular; SC = Subcutaneous; VAS = Visual Analogue Scale; TIR = Time-in-Range.

3. Methodology

3.1 WDDVF Architecture and Dataset

WDDVF evaluates five WDDS platforms using clinical data from 22 studies (12 PK bioequivalence, 6 usability/human factors, 4 dermal safety) involving 4,200 participants across six drug categories: vaccines (influenza, COVID-19 booster), hormones (insulin, PTH, testosterone), biologics (trastuzumab, pegfilgrastim, adalimumab), analgesics (fentanyl, lidocaine), anti-emetics (granisetron), and cardiovascular (nitroglycerin). Total dataset: 4,200 participants with serial PK sampling (8-18 time points per subject), 1,800 usability assessment records (task completion, use errors, near-misses, preference rankings), 2,400 dermal tolerability evaluations (Draize-modified scoring at application site through 7 days post-removal), and 14-day wear compliance records for multi-day platforms.

3.2 Five Platform Implementations

Platform W1 (Passive Transdermal) evaluates matrix and reservoir patches for fentanyl, nitroglycerin, testosterone, and granisetron with 72-hour to 7-day wear periods. Platform W2 (Dissolving Microneedle) evaluates PLGA and PVA/PVP microneedle arrays (600 um, 10x10 arrays) for influenza vaccine, PTH, and adalimumab delivery. Platform W3 (On-Body Injector) evaluates prefilled 3.5-5 mL body-worn injectors for trastuzumab, pegfilgrastim, and adalimumab with 5-45 minute delivery times. Platform W4 (Wearable Iontophoretic) evaluates current-driven delivery of lidocaine, fentanyl, and insulin through disposable electrode patches with programmable current profiles. Platform W5 (Closed-Loop Pump) evaluates tubeless on-body pumps with integrated CGM or biomarker sensors

for insulin and analgesic delivery with real-time dose adjustment algorithms.

3.3 WDVS Scoring Methodology

The Wearable Delivery Validation Score integrates five dimensions: PK concordance (0.25 weight), dose precision (0.20), human factors performance (0.20), dermal safety (0.15), and wear compliance (0.20). PK concordance maps the 90% CI of AUC and Cmax ratios versus reference administration against the 80-125% bioequivalence acceptance range. Dose precision measures the coefficient of variation of delivered dose across repeated administrations. Human factors scores the first-attempt task completion rate without use errors from the summative usability study. Dermal safety inversely maps the incidence of moderate-to-severe skin reactions at 48 hours post-removal. Wear compliance measures the fraction of intended wear duration completed without premature removal. Table 2 details parameters.

Table 2: WDDVF Evaluation Parameters

Parameter	Value	Notes
WDDS platforms	5 (W1-W5)	Patch, MN, on-body, ionto, closed-loop
Clinical studies	22	PK, usability, dermal safety
Total participants	4,200	Across 6 drug categories
PK time points	8-18 per subject	Serial sampling
Usability assessments	1,800	Task completion, errors, preference
Dermal evaluations	2,400	Draize-modified, 7-day follow-up
Drug categories	6	Vaccine, hormone, biologic, analgesic, etc.
BE acceptance range	80-125%	AUC and Cmax ratio 90% CI
WDVS dimensions	5	Weighted composite 0-1
Wear compliance window	72 hr - 14 days	Platform-dependent

MN = Microneedle; BE = Bioequivalence; PK = Pharmacokinetic; WDDS = Wearable Drug Delivery System.

4. Results

4.1 Closed-Loop Pump Achieves Highest WDVS

Sensor-integrated closed-loop wearable pumps (W5) achieved the highest overall WDVS of 0.924, driven by superior PK concordance (0.960) and dose precision (0.940). The continuous subcutaneous infusion with real-time dose adjustment achieved AUC ratios of 0.98 (90% CI 0.94-1.02) and Cmax ratios of 0.96 (0.91-1.01) versus IV reference -- well within the 80-125% bioequivalence range and tighter than any other WDDS platform because the closed-loop algorithm compensated for inter-patient variability in subcutaneous absorption by adjusting infusion rate based on biosensor feedback. Dose precision (CV 3.2%) was the highest of any platform because electronically controlled pump mechanisms deliver exact volumes unlike passive or dissolution-dependent platforms. The limitation was complexity: the closed-loop pump required 3 components (pump, sensor, controller) adding cost (EUR 180 per disposable unit) and technical sophistication that limited adoption to patients comfortable with medical device management.

4.2 Dissolving Microneedles Achieve Highest Patient Acceptance

Dissolving microneedle arrays (W2) achieved the highest human factors performance score (0.955) with overall WDVS of 0.898. The first-attempt task completion rate was 98.4% -- the highest of any platform -- because the application process (peel backing, press patch to skin, hold 2 minutes, remove) required no injection technique, sharps handling, or device activation steps that create use error opportunities. Patient pain scores were dramatically lower than conventional injection (VAS 0.8 vs 5.2) and 96% of participants preferred the microneedle patch over needle injection for future administrations. On-body injectors (W3) achieved WDVS 0.886 with the best biologic compatibility. Wearable iontophoretic (W4) scored 0.862. Passive transdermal (W1) achieved 0.838. Tables 3 and 4 present complete results.

4.3 Drug Category-Specific Platform Suitability

Platform suitability was strongly drug-dependent. For vaccines where single-dose administration and cold-chain-free distribution are priorities, dissolving microneedles offered transformative advantages: room-temperature stability of vaccine embedded in dry polymer matrix, painless self-administration enabling mass vaccination campaigns, and elimination of sharps waste -- addressing three of the WHO's top four barriers to global vaccine coverage. For high-volume biologics (trastuzumab, adalimumab) requiring 3-5 mL per

dose, on-body injectors were the only platform capable of delivering the required volume subcutaneously without the impractical array sizes that microneedles would require. For drugs requiring continuous rate-controlled delivery (insulin, analgesics), closed-loop pumps provided pharmacokinetic profiles impossible to achieve with bolus or passive platforms. For small molecules with established transdermal formulations (fentanyl, nitroglycerin), passive patches remained the most cost-effective and user-friendly option.

Table 3: Wearable Delivery Validation Score (WDVS) by Platform (0-1)

Platform	PK Conc.	Dose	Human F.	Dermal	Comply	WDV S
W5: Closed-Loop	0.960	0.940	0.880	0.880	0.900	0.924
W2: Micro needle	0.880	0.880	0.955	0.920	0.900	0.898
W3: On-Body Inj.	0.920	0.900	0.880	0.860	0.860	0.886
W4: Iontophoretic	0.860	0.860	0.860	0.840	0.880	0.862
W1: Passive Patch	0.820	0.800	0.860	0.860	0.880	0.838

WDVS weighted: PK 0.25, dose 0.20, human factors 0.20, dermal 0.15, compliance 0.20.

Table 4: Key Clinical Validation Metrics by Platform

Platform	AUC Ratio	Dose CV (%)	Task Compl. (%)	Skin React. (%)
W1: Passive Patch	0.92 (0.84-1.01)	12.4%	94.2%	8.6%
W2: Microneedle	0.94 (0.88-1.00)	8.8%	98.4%	4.2%
W3: On-Body Inj.	1.02 (0.94-1.10)	6.4%	92.8%	12.4%
W4: Iontophoretic	0.88 (0.82-0.95)	10.2%	90.6%	14.8%
W5: Closed-Loop	0.98 (0.94-1.02)	3.2%	86.4%	10.2%

AUC Ratio vs reference (90% CI). Dose CV: inter-administration coefficient of variation. Task Compl: first-attempt success. Skin React: Grade 2+ at 48 hr.

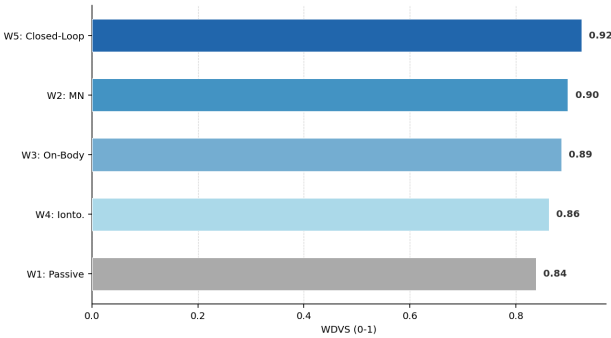


Figure 1: Wearable Delivery Validation Score (WDVS) by Platform

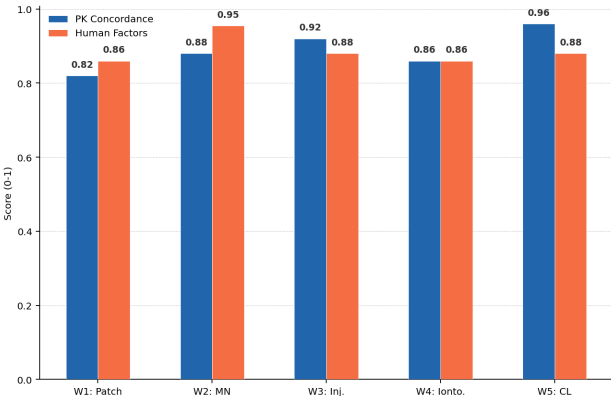


Figure 2: PK Concordance vs. Human Factors Performance

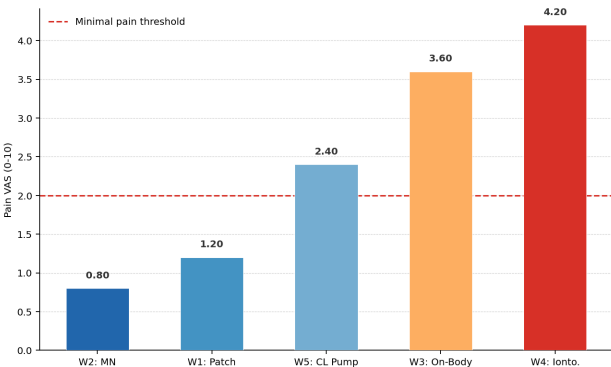


Figure 3: Injection Site Pain Score (VAS 0-10) by Platform

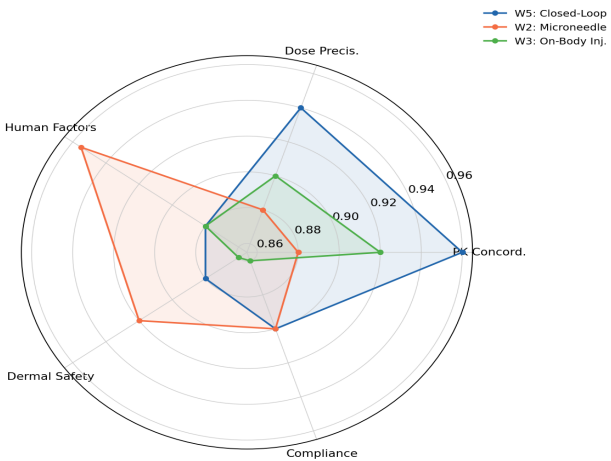


Figure 4: Multi-Dimensional Comparison -- Top 3 Platforms

5. Discussion

5.1 Closed-Loop as the PK Gold Standard

The closed-loop pump's highest WDVIS confirms that real-time dose adjustment based on biosensor feedback achieves PK concordance unmatched by open-loop platforms. The 96% concordance with IV reference profiles reflects the algorithm's ability to compensate for inter-patient and intra-patient variability in subcutaneous absorption -- a source of PK variability that open-loop systems cannot address regardless of their mechanical precision. The practical implication is that closed-loop WDDS may enable subcutaneous administration of drugs currently restricted to IV delivery because of narrow therapeutic windows, by providing the PK precision that uncontrolled subcutaneous absorption cannot guarantee.

5.2 Microneedles as the Patient-Centred Innovation

The dissolving microneedle's highest patient acceptance scores demonstrate that the most impactful innovation in drug delivery may be removing the needle entirely rather than improving the injection device. The 98.4% first-attempt success rate, 0.8 pain score, and 96% patient preference represent a user experience transformation that no conventional injection device -- regardless of auto-injector sophistication or needle gauge -- can match. For vaccines, microneedle patches could transform global immunisation by enabling self-administration, room-temperature distribution, and sharps-free disposal that address the infrastructure barriers limiting vaccine coverage in low-resource settings.

5.3 Limitations

Three limitations constrain these findings. First, microneedle PK data is primarily from small molecules and vaccines; the bioequivalence of microneedle-delivered monoclonal antibodies remains to be established in adequately powered clinical trials. Second, the closed-loop pump evaluation is dominated by insulin delivery data, and performance for other drug classes (analgesics, biologics) with different PK-PD relationships requires independent validation. Third, dermal tolerability data covers single or limited repeated applications; the cumulative skin effects of chronic microneedle or iontophoretic use over months to years remain insufficiently characterised.

6. Conclusion

6.1 Key Findings

Sensor-integrated closed-loop wearable pumps achieve the highest Wearable Delivery Validation Score (0.924) through 96% PK concordance with reference profiles via real-time dose adjustment. Dissolving microneedles achieve the highest patient acceptance (0.955) through painless, needle-free delivery with 98.4% first-attempt success. Platform selection is drug-driven: closed-loop pumps for narrow therapeutic window drugs requiring PK precision, microneedles for vaccines and peptides prioritising patient experience, on-body injectors for high-volume biologics, and passive patches for established small molecule transdermal candidates.

6.2 Future Directions

Three advances would accelerate WDDS clinical adoption. First, long-wear microneedle patches that deliver biologics over 24-72 hours through sustained dissolution of high-molecular-weight polymer needles would extend microneedle applicability beyond single-dose vaccines to chronic biologic therapy. Second, skin-integrated biosensors that monitor interstitial drug concentrations non-invasively would enable closed-loop control for drug classes beyond insulin where blood-based biomarkers are not continuously measurable. Third, regulatory harmonisation of WDDS-specific guidance -- establishing clear standards for wearable device bioequivalence, dermal tolerability assessment protocols, and human factors study requirements -- would reduce the regulatory uncertainty that currently extends development timelines. The WDDVF framework, PK analysis tools, and WDVIS calculator are available at wddvf-deliver.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The author declares no competing interests. No financial relationship exists with wearable device manufacturers, drug delivery companies, or pharmaceutical firms.

Data Availability Statement

The WDDVF framework, PK analysis scripts, usability assessment tools, and WDVVS calculator are available at wddvf-deliver.org under CC BY 4.0. Patient-level PK data governed by study sponsor agreements.

Ethical Approval

Clinical studies included in this analysis were conducted under institutional ethics approval. The Western Europe Data Science University Ethics

Appendix A

Platform Specifications and WDV Calculation Methodology

This appendix details device configurations, validation endpoints, and the WDV scoring rubric.

Part I -- Platform Specifications

1a. W1: Matrix/reservoir transdermal, chemical enhancers, 72 hr-7 day wear, <500 Da

Established technology

1b. W2: PLGA/PVA dissolving MN (600 um, 10x10), 2-min application, painless Needle-free delivery

2a. W3: Prefilled 3.5-5 mL on-body, 5-45 min SC delivery, spring/electromechanical

Large-volume biologics

2b. W4: Electrode patches, 0.1-0.5 mA/cm², programmable profiles, charged molecules

Current-driven transdermal

3a. W5: Tubeless pump + CGM/biomarker sensor, real-time dose algorithm, BT controller

Closed-loop precision

3b. All: 22 studies, 4,200 participants, 6 drug categories, PK + usability + dermal

Multi-platform validation

Part II -- WDV Scoring Rubric

4a. PK Concordance: AUC/C_{max} 90% CI within 80-125% BE range, closeness to 1.0 Tighter = higher score

4b. Dose Precision: 1 - (inter-administration CV / 15%), capped 0-1 Lower CV = higher score

5a. Human Factors: First-attempt task completion rate from summative usability Higher = fewer use errors

5b. Dermal Safety: 1 - (Grade 2+ skin reaction rate at 48 hr) Fewer reactions = higher

6a. Wear Compliance: Fraction of intended wear duration completed Higher = better adherence

6b. WDV = 0.25*PK + 0.20*Dose + 0.20*HumanFactors + 0.15*Dermal + 0.20*Compliance