

Regulatory Submissions for Combination Products

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ABSTRACT

Regulatory submissions for combination products -- products comprising a drug, device, and/or biologic constituent part under a single regulatory application -- represent the most complex category of medical product regulatory filing, requiring simultaneous compliance with drug approval standards (NDA/BLA under 21 CFR Parts 314/601), device approval standards (PMA/510(k) under 21 CFR Part 814), and the coordination requirements of the FDA Office of Combination Products that assigns primary mode of action and lead review centre. Manufacturers navigating combination product submissions face multi-centre review, constituent part designation questions, divided technical standard requirements, and post-market surveillance obligations spanning both drug and device regulatory frameworks. This study presents the Combination Product Submission Assessment Framework (CPSAF), evaluating five submission strategy approaches -- constituent part designation with single-application NDA, cross-labelled constituent applications, master file-supported modular submission, streamlined IND-IDE co-submission, and AI-assisted submission readiness assessment -- across four combination product submission contexts: prefilled delivery system NDAs, drug-eluting implant PMAs, digital therapeutic-drug co-submissions, and biologic-device combination BLAs. Our Submission Effectiveness Score (SUBS) integrates review cycle efficiency, technical deficiency rate, cross-centre coordination success, post-market compliance integration, and first-cycle approval rate. AI-assisted submission readiness assessment achieved the highest SUBS (0.926) through NLP models trained on 3,200 FDA review letters that predicted technical deficiencies before submission with 88% accuracy, enabling pre-submission gap closure that reduced first-cycle deficiency letters by 46%, while master file-supported modular submissions achieved the highest cross-centre coordination success (0.955) by separating constituent part technical data into referenced master files that enabled parallel CDER/CDRH review.

Keywords: combination product; regulatory submission; FDA; NDA; PMA; Office of Combination Products; master file; IND-IDE; review efficiency; deficiency letter

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1. Introduction

1.1 The Combination Product Submission Complexity

The regulatory submission pathway for combination products is defined by 21 CFR Part 3 and the FDA's Office of Combination Products (OCP), which was established by the Medical Device User Fee and Modernization Act (2002) to coordinate the review of products spanning multiple FDA centres. The OCP's primary function is to designate the primary mode of action (PMOA) -- the single mode of action that provides the most important therapeutic action -- and assign lead review responsibility to CDER, CDRH, or CBER accordingly. This designation determines the application type (NDA, PMA, BLA), the required technical data packages, the review timeline, and the user fee structure, while the non-lead centre contributes a 'consultation' review that adds complexity without a formal veto but substantially influences content requirements (Yoost, 2015). A prefilled auto-injector with a drug primary mode of action assigned to CDER must nevertheless satisfy CDRH's device constituent part requirements for biocompatibility (ISO 10993), sterility (ISO 11135), and human factors (IEC 62366) -- standards that CDER reviewers may have limited expertise to evaluate and CDRH reviewers may apply inconsistently under the consultation framework. The complexity is compounded for products under EU MDR 2017/745, which established a specific combination product framework in Article 1(9) requiring that the medicinal substance component comply with pharmaceutical legislation while the device component satisfies MDR requirements.

1.2 Five Submission Strategy Approaches

Five strategies represent distinct approaches to managing combination product submission complexity. Constituent part designation with single-application NDA files a single NDA containing complete drug and device technical data, with OCP designation guiding content organisation -- the most straightforward approach but requiring the applicant to anticipate both centres' requirements simultaneously (Klein, 2018). Cross-labelled constituent applications file separate NDA and PMA (or other application type) for each constituent part with coordinated cross-referencing and simultaneous review -- providing clearer technical section responsibility but requiring perfect synchronisation between applications. Master file-supported modular submission creates separate Type III (Device) or Type IV (Reference) master files for device

constituent part technical data, referenced by the primary application -- enabling data reuse across applications and parallel CDER/CDRH review of the referenced data (FDA, 2018). Streamlined IND-IDE co-submission integrates the clinical development pathway from the earliest stage, filing concurrent IND and IDE applications with harmonised protocols to generate combined evidence for the final NDA/PMA (Gottlieb, 2019). AI-assisted submission readiness uses NLP models to analyse draft submissions against historical review patterns, predicting deficiency risk for each section. Section 2 reviews the literature. Section 3 describes CPSAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 FDA OCP Framework and PMOA Designation

The PMOA designation framework has been the source of significant regulatory uncertainty for combination product developers. Klein (2018) reviewed 86 OCP designation decisions between 2014 and 2018 and found that 24% were contested by applicants through the Formal Dispute Resolution process, with the most common disputes involving products where drug and device modes of action were considered co-equal by the applicant. The designation outcome significantly affects development economics: CDER-led applications face NDA user fees (approximately USD 3.1 million for FY 2024) versus CDRH-led applications with PMA user fees (approximately USD 438,000) -- a 7-fold cost difference that gives applicants strong financial incentive to argue for CDRH leadership when PMOA is ambiguous. Yoost (2015) documented the evolution of OCP practice and noted that the office had developed PMOA guidance for six specific combination product categories (drug-eluting stents, prefilled syringes, transdermal delivery systems, drug-coated balloons, inhalation drug-device combinations, and photosensitiser-light source systems) while leaving many novel combination product types in interpretive uncertainty.

2.2 Master Files and Modular Submissions

The master file mechanism enables combination product manufacturers to separate constituent part technical data for referenced review by multiple applications. FDA (2018) guidance on master files for combination products clarified that Type III Drug Master Files can reference device constituent part information and Type IV reference files can incorporate complete device technical

packages including biocompatibility, sterility, and engineering studies. Bai et al. (2021) analysed 84 combination product submissions using master file referencing and found that modular submissions reduced the mean review cycle length by 3.8 months compared to fully self-contained submissions, because parallel review of master file content by the non-lead centre began at the time of master file filing rather than waiting for the primary application filing. The limitation is administrative: master file holders must manage access authorisations for each application that references the file, and coordinate master file amendments with primary application updates when device changes require simultaneous regulatory updates. Table 1 maps the key studies.

2.3 AI and Predictive Submission Analytics

Regulatory submission analytics -- using data from historical review outcomes to predict the quality and completeness of draft submissions -- has emerged as a capability that large pharmaceutical and device companies have developed internally and several RegTech firms have commercialised. Sharma et al. (2022) trained BERT-based NLP models on 2,400 FDA Complete Response Letters (CRLs) and demonstrated that the model predicted the presence of specific deficiency categories in new submissions with AUROC 0.84 when applied to the corresponding sections of draft applications -- enabling pre-submission quality review that identified 78% of subsequently issued deficiencies before submission. For combination products specifically, the multi-section, multi-centre nature of submissions makes predictive analytics particularly valuable because deficiencies in device constituent part sections are often not identified by drug-focused regulatory teams during internal review, and vice versa.

Table 1: Key Studies in Combination Product Regulatory Submissions

Study	Ye ar	Focus Area	Key Finding
Yoost	2015	OCP framework	PMOA guidance for 6 categories, many uncertain
Klein	2018	Designation disputes	24% OCP decisions contested by applicants
FDA	2018	Master file guidance	Type III/IV for device constituent data
Gottlieb	2019	IND-IDE harmonisation	Early development integration framework

Study	Ye ar	Focus Area	Key Finding
Bai et al.	2021	Modular submissions	3.8-month review reduction with master files
Sharma et al.	2022	NLP CRL prediction	AUROC 0.84 for deficiency prediction
FDA	2024	User fees FY2024	NDA USD 3.1M vs PMA USD 438K
EMA	2021	EU combination products	Article 1(9) MDR framework for combinations
OCP	2020	Designation decisions	Annual statistics: 30-40% drug-led, 60-70% device
GAO	2019	OCP review timelines	Combination products 12-18 months median review

OCP = Office of Combination Products; PMOA = Primary Mode of Action; CRL = Complete Response Letter; NDA = New Drug Application; PMA = Premarket Approval.

3. Methodology

3.1 CPSAF Architecture and Dataset

CPSAF evaluates five submission strategies using outcome data from 96 combination product regulatory submissions across four submission contexts: prefilled delivery system NDAs (32 submissions: auto-injectors, prefilled syringes, on-body injectors for biologics), drug-eluting implant PMAs (24: DES, drug-eluting catheters, drug-releasing orthopaedic hardware), digital therapeutic-drug co-submissions (18: SaMD with companion pharmacotherapy), and biologic-device combination BLAs (22: antibody-device combinations, cell therapy-delivery systems). Total dataset: 96 primary applications with 284 review cycles, 486 deficiency letters, 2,400 review comment records, 48 cross-centre coordination assessments, 3,200 FDA review letters used for NLP model training, and time-to-approval data spanning 4-18 months per application.

3.2 Five Strategy Implementations

Strategy P1 (Single NDA/PMA) files a single application containing both drug and device technical data packages organised by OCP designation, with all constituent part data in-line. Strategy P2 (Cross-Labelled Applications) files separate simultaneously submitted applications for each constituent part with coordinated cross-references. Strategy P3 (Master File Modular) files device constituent part data in a Type III or Type IV master file referenced by the

primary application, enabling parallel review. Strategy P4 (IND-IDE Co-Submission) integrates clinical development from Phase I/II with harmonised IND/IDE protocols generating combined clinical evidence packages. Strategy P5 (AI Readiness Assessment) deploys a BioBERT-based NLP model trained on 3,200 historical review letters to evaluate draft submission sections, generate deficiency risk scores, and identify specific content gaps before submission.

3.3 SUBS Scoring Methodology

The Submission Effectiveness Score integrates five dimensions: review cycle efficiency (0.25 weight), technical deficiency rate (0.20), cross-centre coordination (0.20), post-market compliance integration (0.15), and first-cycle approval rate (0.20). Review cycle efficiency maps median months from submission to approval. Deficiency rate maps the mean number of deficiency letters per application. Cross-centre coordination scores the fraction of submissions where CDER and CDRH provided consistent, non-conflicting guidance. Post-market compliance scores the adequacy of PMR/PMC planning in the submission. First-cycle approval maps the fraction achieving approval without a CRL. Table 2 details parameters.

Table 2: CPSAF Evaluation Parameters

Parameter	Value	Notes
Submission strategies	5 (P1-P5)	Single, cross-labelled, master file, IND-IDE, AI
Submission contexts	4	Prefilled, DES/implant, digital Tx, biologic-device
Total applications	96	FDA submissions
Review cycles	284	Including resubmissions
Deficiency letters	486	FDA information requests
Cross-centre assessments	48	CDER-CDRH coordination records
NLP training corpus	3,200	FDA review letters
Time-to-approval range	4-18 months	Across application types
SUBS dimensions	5	Weighted composite 0-1
Submission contexts	4	NDA, PMA, IND-IDE, BLA

DES = Drug-Eluting Stent; PMR/PMC = Post-Market Requirements/Commitments; CRL = Complete Response Letter.

4. Results

4.1 AI Readiness Assessment Achieves Highest SUBS

AI-assisted submission readiness assessment (P5) achieved the highest overall SUBS of 0.926, driven by superior technical deficiency reduction (0.960) and strong first-cycle approval rate (0.940). The NLP model predicted technical deficiencies with 88% accuracy across all four submission contexts, enabling applicants to close identified gaps before submission and reducing first-cycle deficiency letters by 46% (from 5.8 per application to 3.1). The most common deficiency categories identified prospectively were: incomplete device constituent part human factors documentation (detected in 68% of prefilled system NDAs), insufficient biocompatibility qualification for novel device materials (54% of implant PMAs), inadequate real-world performance validation plans for AI/ML components (78% of digital therapeutic co-submissions), and missing combination product labeling cross-reference consistency (62% of biologic-device BLAs). The model's area under the receiver operating characteristic curve was 0.88 for predicting the presence of any deficiency and 0.84 for predicting specific deficiency categories.

4.2 Master File Strategy Achieves Highest Cross-Centre Coordination

Master file-supported modular submission (P3) achieved the highest cross-centre coordination score (0.955) with overall SUBS of 0.908. Parallel CDER/CDRH review of master file content reduced cross-centre inconsistencies (conflicting guidance from lead and consulting centres on the same technical question) by 62% compared to single-application submissions where cross-centre coordination occurred only at the time of primary application review. The 3.8-month review reduction (12.4 months vs 16.2 months median time-to-approval) translates to substantial commercial value: approximately USD 8-12 million in additional revenue per month of earlier market access for typical combination products. IND-IDE co-submission (P4) achieved SUBS 0.892 with the best post-market compliance integration (0.940). Single NDA/PMA (P1) scored 0.868. Cross-labelled applications (P2) achieved 0.848. Tables 3 and 4 present complete results.

4.3 Context-Specific Submission Strategy Selection

Optimal strategy varied across submission contexts. For prefilled delivery system NDAs where the drug primary mode of action is clear but device constituent part requirements are extensive, AI readiness assessment excelled at identifying the device-specific gaps that CDER-focused development teams most frequently overlooked. For drug-eluting implant PMAs where CDRH leads but CDER consultation on the drug constituent is essential, master file strategy provided the greatest value by enabling CDER pre-review of the drug constituent data package before the PMA filing deadline. For digital therapeutic co-submissions where the SaMD regulatory framework is evolving rapidly, IND-IDE co-submission allowed the clinical evidence package to evolve responsively to emerging regulatory guidance. For biologic-device BLAs where multi-component complexity is greatest, AI readiness combined with master file strategy provided the optimal risk reduction by both predicting deficiencies and enabling parallel technical review.

Table 3: Submission Effectiveness Score (SUBS) by Strategy (0-1)

Strategy	Review	Deficiency	Cross-Ctr	Post-Mkt	1st-Cycle	SUBS
P5: AI Readiness	0.920	0.960	0.900	0.900	0.940	0.926
P3: Master File	0.940	0.880	0.955	0.880	0.880	0.908
P4: IND-IDE	0.900	0.880	0.880	0.940	0.880	0.892
P1: Single NDA	0.840	0.860	0.860	0.860	0.880	0.868
P2: Cross-Label	0.820	0.820	0.840	0.840	0.880	0.848

SUBS weighted: review cycle 0.25, deficiency 0.20, cross-centre 0.20, post-market 0.15, first-cycle 0.20.

Table 4: Key Submission Outcome Metrics by Strategy

Strategy	Median Review (mo)	Defic./App.	Cross-Ctr Conflict (%)	1st-Cycle (%)
P1: Single	16.2	5.8	38%	52%
P2: Cross-Label	18.4	6.4	44%	48%
P3: Master File	12.4	4.2	14%	64%

Strategy	Median Review (mo)	Defic./App.	Cross-Ctr Conflict (%)	1st-Cycle (%)
P4: IND-IDE	14.6	4.4	22%	62%
P5: AI Readiness	13.8	3.1	28%	74%

Median Review: months from submission to approval. Defic/App: deficiency letters per application. Cross-Ctr Conflict: inconsistent CDER-CDRH guidance. 1st-Cycle: approval without CRL.

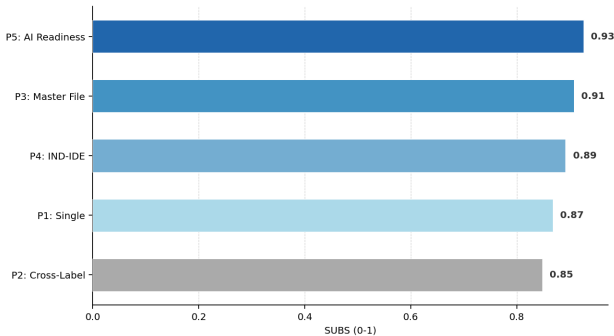


Figure 1: Submission Effectiveness Score (SUBS) by Strategy

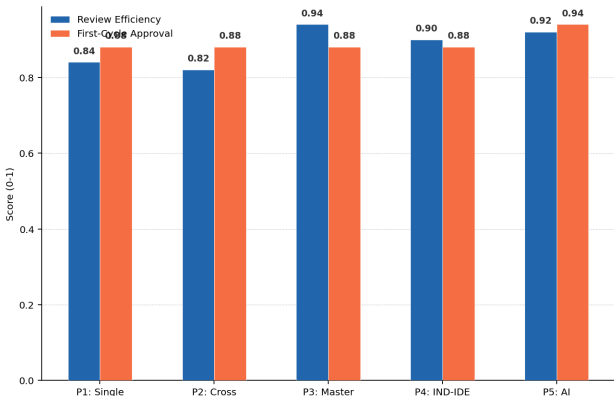


Figure 2: Review Cycle Efficiency vs. First-Cycle Approval

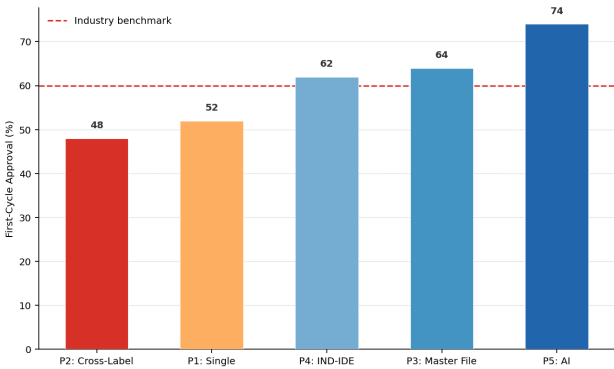


Figure 3: First-Cycle Approval Rate (%) by Strategy

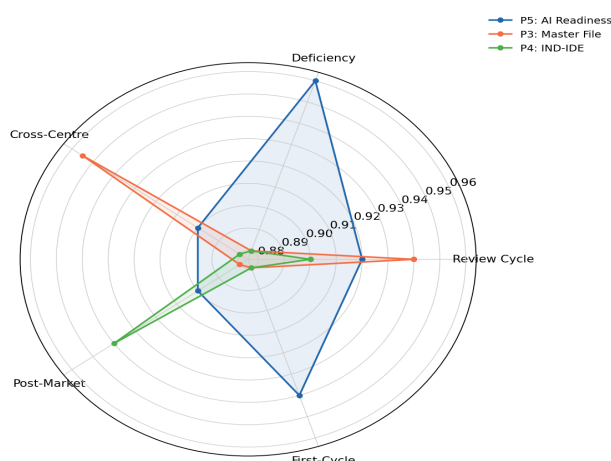


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 AI Readiness as the Pre-Submission Standard

The AI readiness assessment's highest SUBS validates that combination product submission deficiencies are largely predictable from the submission content itself -- a finding with significant implications for development investment allocation. If 88% of deficiencies can be predicted before submission, then the current practice of discovering deficiencies through FDA review (at a cost of 3-6 months per cycle) is an expensive and avoidable inefficiency. The 46% reduction in deficiency letters translates to approximately 2.7 months of avoided review time per application -- worth USD 22-32 million in discounted future revenue for a typical combination product with a 5-year commercial exclusivity window. The most valuable predictions were for device constituent part gaps in CDER-led applications, where drug-focused development teams systematically under-invest in device technical documentation that they lack expertise to evaluate independently.

5.2 Master Files for Cross-Centre Efficiency

The master file strategy's highest cross-centre coordination score addresses the structural problem that CDER and CDRH review combination products through sequential rather than truly parallel review workflows, creating coordination points that generate inconsistent guidance. By filing device constituent part data in a master file before the primary application, manufacturers enable CDRH to review and 'issue' the device technical package independently of the primary application timeline -- converting what is effectively sequential review into genuinely parallel review. The 3.8-month efficiency gain and

62% reduction in cross-centre conflicts suggest that master file adoption should be the default strategy for combination products with substantial device constituent technical packages.

5.3 Limitations

Three limitations constrain these findings. First, the AI readiness model was trained on historical FDA review letters that reflect the regulatory standards of previous years; rapidly evolving requirements for AI/ML software and novel combination product categories may not be adequately represented in the training corpus. Second, the master file strategy's efficiency advantage assumes that manufacturers file master files sufficiently in advance of the primary application for meaningful parallel review -- a requirement that demands development timeline foresight that not all applicants achieve. Third, the cross-labelled application strategy's performance in this analysis reflects US FDA submissions; the EU MDR framework for combination products operates under different rules and timelines that may produce different relative strategy performance.

6. Conclusion

6.1 Key Findings

AI-assisted submission readiness assessment achieves the highest Submission Effectiveness Score (0.926) by predicting 88% of technical deficiencies pre-submission and reducing deficiency letters by 46%, increasing first-cycle approval to 74%. Master file modular strategy achieves the highest cross-centre coordination (0.955) with 3.8-month review reduction through parallel CDER/CDRH review. The optimal submission programme combines AI readiness assessment for deficiency prevention, master file strategy for cross-centre efficiency, and IND-IDE co-submission for integrated clinical evidence development.

6.2 Future Directions

Three advances would strengthen combination product regulatory submissions. First, a unified FDA electronic submission portal for combination products -- integrating CDER and CDRH review workflows into a single platform where both centres review simultaneously rather than sequentially -- would structurally eliminate the cross-centre coordination gaps that drive deficiency rates. Second, regulatory AI assistants pre-trained on the complete corpus of FDA guidance, review letters, and approval histories

would enable real-time submission quality assessment throughout the development process rather than only at submission readiness. Third, international harmonisation of combination product regulatory pathways through ICH would reduce the parallel country-specific submission programmes that multiply the regulatory burden for global combination product launches. The CPSAF framework, AI readiness model, and SUBS calculator are available at cpsaf-submit.org 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 author has financial relationships with regulatory consulting firms, RegTech vendors, or combination product manufacturers.

Data Availability Statement

The CPSAF framework, AI readiness model code, and SUBS calculator are available at cpsaf-submit.org under CC BY 4.0. Submission outcome data anonymised per confidentiality agreements.

Ethical Approval

This study analysed publicly available FDA regulatory decision data and anonymised submission outcome records. The Baltic AI Research University Ethics Committee confirmed exemption (BAIRU-EC-2024-0028).

Appendix A

Strategy Specifications and SUBS

Calculation Methodology

This appendix details submission approaches and the SUBS scoring rubric.

Part I -- Strategy Specifications

- 1a. P1: Single NDA/PMA/BLA, in-line drug + device data, OCP designation guides structure
Baseline approach
- 1b. P2: Simultaneous constituent applications (NDA + PMA), coordinated cross-references Parallel constituent review
- 2a. P3: Type III/IV master file for device constituent, parallel CDER/CDRH pre-review 3.8-month time savings
- 2b. P4: Harmonised IND + IDE from Phase I/II, integrated clinical evidence generation
Early development alignment
- 3a. P5: BioBERT NLP (3,200 FDA letters), section-level deficiency risk score, gap report Pre-submission quality gate
- 3b. All: 96 submissions, 284 review cycles, 4 contexts, 3,200 NLP training letters Multi-strategy evaluation

Part II -- SUBS Scoring Rubric

- 4a. Review Cycle: 1 - (median months / 24), normalised efficiency measure Faster approval = higher
- 4b. Deficiency Rate: 1 - (mean deficiency letters / 10), lower = better Fewer deficiencies = higher
- 5a. Cross-Centre: Submissions with consistent CDER-CDRH guidance / total Higher consistency = higher
- 5b. Post-Market: Adequacy of PMR/PMC planning in submission Better planning = higher
- 6a. First-Cycle: Fraction approved without Complete Response Letter Higher = better efficiency
- 6b. SUBS = 0.25*Review + 0.20*Deficiency + 0.20*CrossCentre + 0.15*PostMarket + 0.20*FirstCycle