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Early Unblinding to Pharmacokinetics (PMx) Data: Challenges, Practices and Benefits

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ABSTRACT

Pharmacometrics (PMx) analyses play a critical role in Model-Informed Drug Development (MIDD), supporting dose selection, trial design, benefit–risk assessment, and regulatory decision-making. However, PMx analyses depend on pharmacokinetic (PK) concentration data, exposure, and baseline covariates of interest. Of these, PK data can act as a surrogate for treatment assignment and hence can imply the treatment assignment, resulting in restricted access until formal study unblinding. This paper describes the scientific rationale, business need, benefits, and risks associated with controlled early access to PMx data prior to unblinding. Drawing on industry practices shared through the ISOP PMx Data Programming Special Interest Group (SIG), we summarize governance models, firewalled team structures, and standard operating procedures (SOPs) used to mitigate risks of unintentional unblinding and bias. Practical considerations—including documentation, approval of pathways, secure environments, vendor engagement, and data reconciliation strategies—are discussed. We will discuss the increasing need for safety/efficacy data for MIDD decisions. When implemented with appropriate controls, early access to PMx data enables parallel workflows, improves data quality, and supports timely regulatory submissions while preserving study integrity.

PHARMACOMETRICS (PMX) DATA AND ANALYSES

Pharmacometrics (PMx) integrates pharmacokinetics (PK), pharmacodynamics (PD), and patient-level covariates to quantitatively characterize drug exposure, response, and variability. Analyses such as population PK, population PK/PD, and exposure–response (ER) form a core component of Model-Informed Drug Development (MIDD), which supports dose selection, trial design optimization, extrapolation to special populations, and evaluation of efficacy and safety relationships. Global health authorities, including the FDA and EMA, increasingly encourage MIDD approaches, as outlined in the ICH M15 guidance.

ICH M15 provides harmonized principles for planning, model evaluation, and documentation to inform regulatory and development decisions, emphasizing that model rigor should match the impact of the decision. Regulatory mechanisms, such as the FDA's MIDD Paired Meeting Program, allow sponsors to align early on MIDD strategy and receive guidance on applying models within specific development programs.

For the purposes of early-access governance, "PMx data" includes (1) PK concentrations, (2) dosing information, (3) baseline covariates required for model development, and, in some cases, (4) anti-drug antibody (ADA), PD, or response endpoints when exposure–response analyses are planned. PK data are often particularly sensitive, as concentration–time profiles can differ by treatment arm, dose, or formulation (Zong & Sisco, 2018). Consequently, PK concentrations are typically masked in blinded studies. Many sponsors consider PK data potentially unblinding and restrict broad access until formal study unblinding, allowing controlled early access only under additional safeguards to preserve study integrity.

Access to unblinded pharmacometric (PMx) data varies by study phase and design. In Phase 1 studies, PMx programmers and Clinical Pharmacologists generally have timely access to unblinded data,

facilitating efficient analysis. In contrast, access to unmasked pharmacokinetic (PK) data in double-blind or sponsor-blinded Phase 2 and Phase 3 trials is often restricted, delaying PMx analyses until later in the clinical development lifecycle. As development timelines become increasingly compressed and organizations aim to shorten submission cycle times, these delays can reduce the strategic value of Model-Informed Drug Development (MIDD). Consequently, late availability of PMx insights may limit their impact on key development decisions and create downstream bottlenecks for regulatory submissions.

RATIONALE AND BUSINESS NEED FOR EARLY ACCESS

In this paper, “early access” refers to access to unmasked PK and dosing data before study database lock (DBL). The business case for early PMx access is strongest when PMx deliverables are on the critical path for key development decisions or regulatory milestones. Early unmasking is often needed to enable timely use of Phase 2 data to inform downstream study design decisions, such as dose optimization, PK sampling schedules, and sample size planning. Similarly, early unmasking of Phase 3 studies is frequently required to keep PMx activities aligned with accelerated submission timelines.

These business needs reflect the reality that PMx work cannot always be initiated “at DBL” and still be completed with the rigor expected for high-impact decisions and downstream deliverables. PMx activities typically require substantial lead time for analysis dataset programming and quality-control readiness, iterative model development and validation, sensitivity analyses, and internal cross-functional review cycles. Teams also often need time to identify and resolve data issues that are difficult to address late in the process—particularly when resolution benefits from unblinded review workflows and clear role separation (e.g., designated unblinded reviewers supporting issue identification and remediation while minimizing the risk of inadvertent unblinding). Initiating these activities only after DBL can compress timelines for quality control and validation, increase rework, and elevate the risk of delays and errors.

From an operational perspective, early access to unmasked PMx data represents a targeted, exception-based approach that allows essential PMx activities to proceed under defined governance, documentation, and access controls. By frontloading the minimum necessary PMx activities in a restricted environment, modeling and analyses are execution-ready at DBL, while preserving the blind for the broader study team.

BENEFITS OF CONTROLLED EARLY ACCESS

Controlled early access to PMx data provides multiple advantages. Parallelization of workflows allows population PK/PD models to be developed concurrently with safety and efficacy analyses, eliminating post-unblinding delays. Early access accelerates regulatory submissions by ensuring that exposure–response analyses and dose justification are available alongside clinical results. Additional time for data cleaning, sensitivity analyses, and model validation improves overall data quality and robustness. Early PMx insights also support strategic development decisions, such as dose optimization, identification of relevant covariates, and evaluation of special populations. Collectively, these benefits enhance alignment with regulatory expectations for MIDD.

RISKS ASSOCIATED WITH EARLY ACCESS

Despite its benefits, early access to unmasked PMx data introduces serious risks. The primary risk is unintentional unblinding: PK/PD patterns, dose information, or linkable identifiers may reveal treatment assignment, which can bias trial conduct or interpretation (Zong & Sisco, 2018). Additional risks include inappropriate communication of patient-level or group-level results to blinded staff, data security failures when sensitive data are stored or transferred outside restricted environments, and compliance/audit concerns when early access is not formally documented. These risks can be mitigated by establishing an explicit firewall, limiting the number of unblinded personnel, segregating storage locations, controlling printouts, requiring confidentiality acknowledgements, and delaying dissemination of modeling outputs until after official unblinding and materiality determination.

INDUSTRY PRACTICES FOR CONTROLLED EARLY ACCESS

To balance benefits and risks, the industry has adopted a range of controlled early access practices. The ISOP PMx Data Programming SIG conducted a survey with participation from 12 large pharmaceutical, biotechnology, and contract research organizations (CROs). Survey insights indicate variability in the scope of early data release, ranging from unmasked PK concentration data only to PK data combined with treatment assignments and limited safety or efficacy information. The different early access scenarios are summarized in Table 1.

Table 1 Summary of Early Data Access Scenarios

Scenario	Unmasked PK Data	Unmasked Dosing Data	Actual Treatment Codes	Safety/Efficacy Data Access
1	Yes	Yes	No	No
2	Yes	Yes	Yes	No
3	Yes	Yes	Yes	Yes

Accessing safety and efficacy data alongside unmasked PK data before study unblinding is challenging, as it can compromise study integrity. Across the industry, various approaches are employed to manage this scenario (Scenario 3), aiming to minimize risk, frontload dataset and analysis preparation, and meet regulatory timelines.

a) Limited number of patients safety/efficacy data
b) Scrambled patient ids in safety/efficacy datasets
c) Dummy safety/efficacy data
d) Safety/Efficacy data access provided to external vendor
e) Independent PMx programmers and modelers accessing Unmasked PK and Safety/Efficacy data. Members who have access to unmasked PK do not get access to study Safety/Efficacy data

Another difference we observed across organizations is accessing actual (unblinded) treatment codes vs. some using dummy codes and defer unblinding until database lock.

Early access to actual treatment codes can:

- Reduce post–database lock rework
- Minimize confusion from placeholder values

However, it also:

- Requires additional governance and approvals
- Involves handling sensitive artifacts (e.g., allocation schedules, IXRS files)
- Increases operational complexity

From an analytical perspective, the absence of actual treatment codes prior to database lock generally does not impact PK or PMx modeling, as treatment derivations can be completed after unblinding. The use of dummy codes is therefore primarily an operational consideration and requires:

- Clear documentation
- Effective communication to avoid misinterpretation

Due to differences in processes, risk tolerance, and timelines, there is no one-size-fits-all approach. These practices emphasize key trade-offs to guide decisions tailored to each organization. Decision-making should be aligned with the study type, study phase, and analysis requirements, with the most

restrictive scenario typically applied to Phase3 studies.

PRACTICAL CONSIDERATIONS FOR IMPLEMENTATION

Based on the survey and discussions within the ISoP PMx Data Programming SIG, practical considerations for enabling early access to PMx data prior to study DBL were identified and are summarized in Table 2.

Table 2 Summary of Practical Considerations for implementation

Category	Theme	Summary of Responses
Request/Approval of Early Data Access	Process and Documentation of early unblinding	All companies have developed internal well governed processes to request and approve PMx data early before DBL
Study Types with Early Access	Later-phase studies	Early access is needed in Phase 2 and/or Phase 3 studies, especially those supporting regulatory submissions or faster filing.
Timing of Early Data Access	Variability in early access timing	Early access typically occurs 4–8 weeks before DBL, or ~80% of PK/ADA data are cleaned, with most companies reporting access at around 6 weeks prior.
	Constraints on actual treatment code	Some respondents explicitly noted that actual treatment code from ADSL is restricted until DBL due to blinding or governance policies.
Functions Providing Data	Centralized data programming teams	SDTM/ADaM datasets are typically provided by statistical programming teams.
	Cross-functional collaboration	Strong collaboration noted among clinical pharmacology, bioanalytical data manager, statistician, statistical programmer, PMx programmer.
SDTM Domains Shared Early	Common domains provided	Frequently mentioned domains include PC (Pharmacokinetics), IS (Immunogenicity), EX (Exposure), EC (Exposure as Collected), and DM (Demographics).
ADaM Datasets Shared Early	Common ADaM datasets needed	ADSL, ADEX, ADLB
	Baseline-only datasets	When shared, ADaMs are often restricted to baseline or partial datasets, excluding post-baseline or treatment-related information.
Time Savings in Modeling & Simulation (M&S)	Moderate efficiency gains	Respondents reported noticeable time savings, enabling teams to meet aggressive, accelerated submission timelines.
	Dependency on data readiness	Actual time saved depends on data quality, completeness, and how early access is granted.
Challenges & Limitations	Data completeness issues	Early datasets may be incomplete or subject to updates, requiring rework later.
	Governance and compliance	Access to certain data (especially efficacy/safety) is restricted due to regulatory and internal governance policies.

- Planning: Early-access activities should be carefully planned and documented to ensure traceability and audit readiness. Depending on the study's design and intended use, documentation may include elements in the protocol or Statistical Analysis Plan, and a Data Monitoring Committee charter.
- Early Access Request and Approval: The request process is typically initiated by the Clinical Pharmacologist and reviewed/approved by the Biostatistician and Global Filing Team. Implementation should start with a written rationale and a defined operating model. In many organizations this is captured in an unblinding plan or memo that specifies scope, data domains, personnel, secure storage location, communication restrictions, and a results dissemination plan. Core safeguards include:
    - Unblind only the minimum number of staff needed;
    - Prohibit sharing of patient-level data (and avoid patient-level discussions with blinded staff);
    - Store unblinded raw data in access-restricted folders separate from the project's blinded workspace;
    - Secure and destroy printouts when no longer needed;
    - Unblinded personnel should formally acknowledge confidentiality requirements
- Communication protocols: Strict guidelines if implemented then can prevent inadvertent sharing of real patient IDs or treatment codes with the broader study team. The communication protocols should also prohibit unblinded teams from discussing any future resources or budgets as that may reveal the study outcomes. Modeling outputs should be shared with blinded team members until official unblinding.
- Modeling and Simulation Analysis Plan (MAP): It is required to have a robust strategy for handling PMx analysis if data changes occur before and after unblinding. This includes
    - Pre-defined Procedures for Data Availability/Reconciliation: Clear procedures for managing data availability and any discrepancies.
    - Impact Assessment Protocol: Protocol for assessing data changes on models.
    - Version Control and Documentation: Rigorous tracking of datasets, scripts, and outputs.
    - Communication Plan: Promptly inform stakeholders of data changes.
    - Sensitivity Analyses: Understand how data changes influence predictions.
    - Robustness Checks: Assess model stability with data variations.
    - Justification for Discrepancies: Provide scientific rationale for any differences.
- External Vendors: External vendors may be engaged to perform early modeling using unblinded data before DBL. All vendor personnel must be formally authorized, comply with confidentiality and data protection requirements, and conduct work within an isolated environment according to a pre-specified MAP.
- Challenges: Early access to data introduces several operational and governance challenges that organizations must carefully manage. Initial datasets are often incomplete or subject to updates, which can necessitate downstream rework and impact efficiency. At the same time, access to critical data—particularly efficacy and safety endpoints—is frequently restricted due to regulatory requirements and internal governance policies, limiting flexibility in analysis. Establishing a secure and restricted working environment, along with controlled data flows, requires appropriate infrastructure and oversight. In addition, robust communication processes are essential to prevent inadvertent unblinding, especially in blinded study settings. Finally, teams must be adequately trained to handle restricted data access, ensuring compliance with protocols while maintaining data integrity and confidentiality.

CONCLUSIONS

The increasing formalization of MIDD evidence expectations (ICH M15) underscores the need for disciplined governance when accessing sensitive PMx data prior to official unblinding. In practice, access is often separated by data type: individuals handling PK data generally should not access unblinded efficacy or safety data unless explicitly approved and controlled, minimizing the risk that partial signals reveal treatment assignment. When implemented effectively—with minimal unblinding, secure infrastructure, strict communication controls, and delayed dissemination—controlled early access can

enhance the timeliness and quality of population PK and exposure–response analyses. Survey results from the ISOP PMx Data Programming SIG indicate that many organizations, guided by their risk tolerance and internal processes, have developed fit-for-purpose models and are formalizing these practices within structured frameworks to maximize benefits while maintaining study integrity.

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PMx Data Programming SIG - ISOP Website

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