National Council for Prescription Drug Programs
NCPDP

September 16, 2013

Division of Dockets Management (HFA–305)
Food and Drug Administration
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Subject: Docket No. FDA–2013–N–0502, Standardization and Evaluation of Risk Evaluation and Mitigation Strategies, Follow up from Public Meeting

Dear FDA and Adam Kroetsch,

The National Council for Prescription Drug Programs (NCPDP) is a not-for-profit American National Standards Institute (ANSI)-accredited Standards Development Organization (SDO) consisting of nearly 1700 members who represent drug manufacturers, chain and independent pharmacies, drug wholesalers, insurers, mail order prescription drug companies, claims processors, pharmacy benefit managers, physician services organizations, prescription drug providers, software vendors, telecommunication vendors, industry professional societies, service organizations, government agencies, and other parties interested in electronic standardization within the pharmacy services sector of the health care industry.

NCPDP currently has 3 Task Groups charged with standards development of various aspects of REMS standardization, prescribing, and prescription processing.

NCPDP provided oral comments to the FDA at its July 25th and 26th, 2013 Public Meeting on REMS standardization and evaluation. In addition to testimony, NCPDP is providing the following recommendations:

- Designate development and implementation of structured product labeling (SPL) standardization of REMS as one of the 4 Prescription Drug User Fee Act reauthorization (PDUFA V) priority projects
- Formally adopt SPL as the means for standardizing and providing central access to REMS data
- Continue to work closely with all stakeholders in further defining the full range of REMS data and content needed to automate all REMS activities and transactions from the point of prescribing to all steps of certification and approval to patient's prescription receipt and monitoring as well as reporting and tracking
- Designate NCPDP as an official ANSI-accredited SDO collaborator for REMS standardization
- Designate the National Library of Medicine as an official collaborator for REMS standardization via its central drug information repository (DailyMed)
- Continue engagement of stakeholders in further defining, structuring, and coding via SPL all relevant aspects of REMS data as well as in developing use cases and in testing
- Issue draft Guidance to industry on REMS standardization, including information on SPL as the electronic means and an electronic submission requirement similar to that in effect for prescribing information (professional labeling), preferably in first quarter 2014
- With industry collaboration, improve adoption with the use of standards and compliance with REMS.

- Expand adoption of NCPDP Telecommunication Standard – Retail Pharmacy REMS, with ETASU components, should be approved (new) or migrated (existing) to the use of the NCPDP Telecommunication Standard for information exchanges.
- Review and assess data reporting requirements – The NCPDP Telecommunication Standard should evolve to support REMS reporting requirements.
- Pursue alignment with other programs – The NCPDP Telecommunication Standard should evolve to align REMS participation requirements with other business functions, including DEA dispensing requirements and Prescription Drug Monitoring Program (PDMP) reporting requirements.

NCPDP will now expand on its recommendations concerning REMS standardization by providing written comments on "Docket No. FDA–2013–N–0502, Standardization and Evaluation of Risk Evaluation and Mitigation Strategies (REMS), Public Meeting". We will expand on the critical importance of establishing as one of the 4 priority projects outlined by PDUFA V the implementation of a standardized, highly structured and codified electronic submission requirement for REMS using the SPL model and public access via DailyMed. Also included in our written comments is an expanded description of why SPL should be the preferred path to achieving the goal of REMS standardization aimed at better integration with, and a resultant reduction in burden to, the existing and evolving healthcare system and why NCPDP should be recognized by FDA as an official SDO collaborator in meeting its PDUFA V commitments, particularly as they relate to downstream automation via integration into NCPDP's Telecommunication and SCRIPT Standards and industry adoption.

Background

In its capacity as an SDO focused on electronic data standards affecting prescription and other drug-related transactions and messaging, NCPDP has been working closely with FDA through its Work Group 2 SPL Activities Task Group (formerly Work Group 2 Guiding Coalition) for over 4 years in advising the agency of potential enhancements to SPL that focus on meaningful downstream uses of these data by the healthcare information technology sector. From this work arose the November 2010 recommendation to investigate the merits of using SPL as the preferred path for capturing and representing REMS data in a highly structured and codified format suitable for automated extraction and incorporation into various electronic applications.

Recognizing the critical importance of first establishing a standardized electronic data structure and codification mechanism for REMS data (consistent with FDA's identified need for a "common language"), NCPDP designated the WG2 SPL REMS Requirements Task Group as the lead for its SPL REMS activities in August 2011. These REMS activities include all aspects of prescription processing from the point of prescribing to the ultimate receipt of the drug by the patient as well as associated authorization messaging, tracking, and reporting. NCPDP's WG11 REMS and ePrescribing Task Group is addressing REMS integration into electronic prescribing transactions among prescribers, pharmacies, intermediaries, payers, sponsors, and REMS administrators. The WG1 Safe Use Processing (FDA REMS) Task Group developed a Reference Guide that defined how to use Telecommunication Standard Version 5.1, and subsequently Version D.0 of the Telecommunication Standard to support a complex REMS program. The Reference Guide provided industry guidance on how to implement a pharmacy workflow friendly REMS solution that leverages the pharmacy financial transaction infrastructure. In fact, the Telecommunication Standard currently supports the class-wide transmucosal immediate release fentanyl (TIRF) REMS. Additionally, the WG1 Safe Use Processing (FDA REMS) Task Group developed and successfully balloted REMS enhancements. These enhancements support additional REMS processing capabilities that the pharmacy industry can use when a new version of the NCPDP Telecommunication Standard is adopted by HIPAA.

NCPDP as a Standards Development Organization

NCPDP's diverse membership provides leadership and healthcare information technology solutions through education and standards development, created using a broad-based ANSI-accredited consensus-building process. NCPDP standards and role as an SDO have been named in federal legislation, including the Health Insurance Portability and Accountability Act (HIPAA); the Medicare Prescription Drug, Improvement, and Modernization Act (also called the Medicare Modernization Act or MMA); and the Health Information Technology for Economic and Clinical Health (HITECH) Act. NCPDP members have created standards such as the Telecommunication Standard and Batch Standard, the SCRIPT Standard for electronic prescribing (including prior authorization transactions for the prescription benefit processing), the Formulary and Benefit Standard, the Pharmacy and/or Combination ID Card Implementation Guide, the Manufacturers Rebate Standard, and more to improve communication within the pharmacy and electronic prescribing industry. (See http://www.ncpdp.org.)

FDA specifically stated in their May 22, 2013 Federal Register Notice in advance of the Public Meeting their interest in collaborating with SDOs in the development and implementation of standardized REMS and as a means to ensure their adoption. Since the principal goal of FDA's REMS-specific PDUFA V commitments is standardization, it is logical for FDA to seek an appropriate SDO(s) for collaboration in developing needed electronic data and messaging standards. NCPDP strongly supports FDA's stated desire to work closely with SDOs like NCPDP, and specifically recommended in its oral comments at the July 25th and 26th, 2013 Public Meeting that it be designated officially as an SDO collaborator on standardizing REMS.

NCPDP believes that its long-standing history in working closely with FDA on meaningful downstream SPL use by the healthcare information technology sector, its more than 2-year effort investigating with FDA and a broad stakeholder base the merits of SPL as a means of standardizing REMS data and associated content, its efforts in leveraging SPL-standardized REMS data within the NCPDP SCRIPT and Telecommunication Standards, and its role as a consensus-development convener of a diverse group of stakeholders affected by REMS make it uniquely qualified to serve in an official capacity as a designated collaborator in achieving the PDUVA V commitments for REMS standardization.

NCPDP was the organization that originally proposed SPL as a means to standardize REMS and already has engaged 3 of its own Task Groups and other stakeholders in broad-based expert and stakeholder feedback and consensus development. Through these efforts, NCPDP also already has begun modeling and enhancing REMS integration into affected electronic prescribing and other prescription transaction and processing standards.

Relevant stakeholder participants in NCPDP's REMS standardization activities include FDA itself, the National Library of Medicine (NLM), other federal agencies (e.g., Centers for Medicare & Medicaid Services [CMS]), professional practice and trade associations, pharmacies, drug database publishers, healthcare information technology vendors, prescription transaction processors, pharmacy benefits managers (PBMs), health information networks, claims adjudicators, physicians services organizations, As a result, FDA collaboration with NCPDP can ensure a broad base of REMS standardization adoption, which is a goal of the agency in working with an SDO and other third parties.

Finally, NCPDP's established record of working closely with FDA on SPL activities is acknowledged on the agency's Structured Product Labeling Resources website (http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm).

Standardization of Data and Content of REMS

An often cited characteristic of REMS is that "if you've seen one REMS program, you've only seen one REMS program". During the course of FDA's recent two-day public meeting, FDA staff and speaker after speaker described as a central problem the lack of REMS standardization and the resultant burdens this places on their integration into evolving healthcare systems and on healthcare providers and patients.

Standardization of the codification and structure of REMS is critically important for downstream automation as a major strategy in reducing the burdens on integration into healthcare systems and prescription processing as well as on healthcare providers and patients themselves. At its core,

standardized definitions of all REMS–associated concepts and data elements and associated standardized codification—creating a common standardized language and structure—are necessary to allow the full range of needed automation focusing on reducing these burdens and enhancing seamless integration into workflow. Such standardization is a key requirement to achieve efficient REMS management for all aspects of prescription processing. These efficiencies accrue for electronic prescribing, the validation processes for patients and providers, the documentation of the prescription approval and all other tracking and reporting elements intended to ensure safe use.

NCPDP believes that access to, and repurposing of, highly structured and codified REMS data will play a critical role in the downstream achievement of more efficient, highly integrated prescription processing and patient monitoring for affected drug products. Workflow involving the prescriber, dispenser, drug manufacturer (sponsor) and distributor, REMS administrator, registries, processors, and adjudicators will benefit from NCPDP's SPL standardization strategy for REMS. Implementation of various NCPDP standards on electronic prescribing (SCRIPT Standard) and other drug product transactions (Telecommunication Standard) involving REMS depend on timely implementation of REMS data standardization. (See discussions below on REMS Standardization and Electronic Prescribing and on REMS Standardization and Prescription Processing and Reporting.)

FDA has stated publically its strong desire to standardize REMS, creating in 2011 the REMS Integration Initiative charged with determining as one of its goals how best to design REMS that can be better integrated into the existing and evolving healthcare system. Steps toward REMS standardization already identified by FDA include the following: fully characterizing the diverse structure and content of existing REMS, identifying best practices, and developing and implementing a strategy for actual standardization. Because of the diversity in individual drug product REMS, even established stakeholders expend undo time and resources integrating new and sustaining existing REMS into workflow. To address this inefficiency, FDA is seeking to minimize unnecessary variation by making REMS more consistent, predictable, and easier to understand without sacrificing warranted customization based on specific drug and clinical situation.

One critical component of achieving this goal is to create a standardized "common language" and structured codification to describe REMS concepts, documents, associated materials (e.g., training), and all REMS-specific requirements (e.g., need for certification). FDA staff expressed publicly their support for NCPDP's concept of employing SPL as the means to better characterize and share REMS information. NCPDP has worked closely with staff from FDA's Health and Regulatory Data Standards group as well as those from the REMS Integration Initiative in characterizing REMS components and requirements, with a focus on creating a standardized method for codification, structured representation, and capture via SPL. The agency is to be commended on its efforts to date in exploring with NCPDP and other stakeholders the critical importance of standardizing REMS data and the merits of SPL as the preferred path. (See the discussion below on Structured Product Labeling (SPL) as the Preferred Path to REMS Data Standardization.)

Structured Product Labeling (SPL) as the Preferred Path to REMS Data Standardization

SPL is an international document markup standard (eXtensible Markup Language, XML) approved by Health Level Seven (HL7) that specifies the structure and semantics of the content of authorized published information about medicines licensed by a country's licensing authority (e.g., FDA). SPL has been adopted in the US by FDA as the mechanism for exchanging drug product and facility information, including but not limited to information known as product labels, package inserts, and prescribing information. In the US, all written, printed, or graphic material accompanying a medicinal product is called labeling (21 CFR 201.57).

While often described as electronic labeling, SPL is far more than just an electronic file of professional prescribing information—what commonly is referred to as labeling or the package insert. Instead, it has been positioned by FDA to continue to expand into a robust repository of highly structured data about drugs and their associated products that can drive a myriad of automated processes and applications, including integrated electronic prescribing and prescription processing systems and alerts and other safety mechanisms. NCPDP believes that as much data as possible about medications and their

products should be captured through SPL to enhance reliable downstream access to, and application of, these data in healthcare information systems.

Currently, most REMS information is available electronically as portable document format (PDF) files. Almost 10 years ago, FDA recognized the limitations of electronic PDFs as a source of information about drugs, particularly concerning automated downstream use of such drug data. In moving from PDFs to required submission of labeling content via SPL in 2005, FDA stated that:

> "SPL allows the exchange of information between computer systems in a way that cannot be accomplished with PDF. For example, the information in SPL can be used to support health information technology initiatives for improving patient care."
>
> (Guidance for Industry: Providing regulatory submissions in electronic format—content of labeling. April 2005)

Thus, using SPL to capture and codify REMS information would meet FDA's stated goal of employing this standard to support health information technology initiatives for improving patient care. Currently, only one component of REMS requires SPL submission, i.e., medication guides.

The purpose of SPL is to facilitate the review, editing, storage, dissemination of, and access to official information about medications in a highly structured and granular form. It is an existing, widely used standard that is well suited to serve as the preferred path for standardizing REMS data and content. SPL is intended to:

- provide a single source for access to critical drug product information
- facilitate provision of the content of medication information both electronically and in human readable format, being structured in such a way that it can be exchanged meaningfully (e.g., from a conceptual perspective) across systems without the need for additional transformation steps
- improve drug product information dissemination to all potential users, focusing on provision of the most up-to-date information in a timely manner so critical to improving risk management of regulated drug products
- facilitate more efficient evaluation of product information changes and to promote more coordinated data collection throughout the regulatory agency and by others, improving all aspects of processing, storage, and archiving
- improve access to REMS information
- enhance the ability to query and report on a wide scope of drug product-specific information, thus allowing better support for specific data analyses such as sub-population assessments of differences
- improve interoperability among a diverse array of heath information systems and technology, including regulatory agency, sponsor, prescription processing, and clinical information systems
- enhance the system integration of clinical data by applying established standards
- enhance patient safety by providing healthcare providers and patients with improved access to information needed to make better risk management decisions in a format that is designed to enhance integration with other technical and clinical applications
- support retention of legacy and other historical information in a database structure

SPL documents are highly adaptable and may be transmitted in a variety of ways, including via standardized messaging protocols (e.g., HL7, NCPDP) among systems, Internet, physical media, PDF, electronic transfer of word-processing applications, and many others. As an HL7 standard, SPL is designed for interoperability within health information technology, with a focus on improving care delivery, optimizing workflow, reducing ambiguity, and enhancing knowledge transfer among all stakeholders, including healthcare providers, government agencies, the health information technology vendor community, other SDOs, and patients.

In the December 11, 2003 Federal Register (68 FR 69009), FDA published final regulations requiring that the content of labeling be submitted electronically for new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs),3 and annual reports (see 21 CFR 314.50(l), 314.94(d), 601.14(b), and 314.81(b), respectively). CDER subsequently announced in public docket number 92S-0251 that became effective October 31, 2005 CDER that the content of labeling submissions would no longer be accepted in PDF format. Instead, applicants were to use the SPL standard when submitting content of labeling to FDA in XML with original submissions, supplements, and annual reports. CBER took a similar action that went into effect on October 15, 2008. In addition, CDER, CBER and the Center for Veterinary Medicine finalized their intention to begin using the SPL standard for electronic drug establishment registration and drug product listing in a Guidance to Industry that was issued at the end of May 2009.

SPL documents (files) contain both the content of labeling (all text, tables, and figures) for a product along with additional machine readable information (including drug listing data elements and clinical data elements). Drug listing data elements include coded information about the product (including product and generic names, ingredients, ingredient strengths, dosage forms, routes of administration, appearance, DEA schedule) and the packaging (package quantity and type). Clinical data elements include coded information about the clinical use of the product (including indications and use, contraindications, drug interactions, warning and precautions and use in special populations, limitations to use such as those associated with REMS).

SPL is a broadly applied standard for capturing structured information about drugs. It serves as a reliable, standardized source of this information, which can be extracted easily, automatically, and electronically from an SPL document and associated indexing.

In addition to the absence of a standardized electronic structure and codification, there also currently is no central repository for REMS data that can be reliably accessed to drive needed automation and seamless integration of REMS processes into prescription workflow and patient management. Instead, stakeholders attempting to integrate REMS into workflow must rely on a diverse set and location of data whose validity and currency may be questionable. By integrating REMS into SPL as another key drug product-related concept and ensuring its validity and currency, the process of REMS integration will be greatly simplified and stakeholders can be assured that they are accessing the most current, credible and relevant data contemporaneously.

There are several compelling reasons to use SPL, as the means for standardizing the exchange of REMS data, versus other means, including:

- SPL is an existing, adaptable standard already in wide use for exchanging meaningful medication information electronically
- it is well suited for highly granular data like REMS
- SPL formatting allows for a mix of coding and text
- SPL has a highly adaptable, flexible substructure
- mechanisms already exist for addressing issues, best practices, standards, and future development
- an existing, effective publically accessible SPL data repository in the National Library of Medicine's (NLM's) DailyMed
- use of existing SPL expertise and infrastructure
- drug manufacturers (sponsors) already have extensive experience in submitting SPL data electronically to this central repository

NCPDP and a broad base of stakeholders believe that SPL is the preferred path for REMS data standardization. Such standardization of data codification and structure is absolutely critical for downstream automated solutions directed at seamlessly integrating REMS into health-system workflow and greatly reducing the current burden heavily weighted by manual and often redundant non-interoperative processes.

Codification of the unique components of REMS with SPL is a way to organize, standardize, and centralize the content associated with drug products. It would standardize REMS format and content for electronic submission to FDA and would simplify integration into electronic prescribing and prescription processing systems, allowing for easy inclusion within existing standards such as the NCPDP electronic prescribing (SCRIPT) and prescription adjudication and reporting (Telecommunication) standards. It also would allow for automatic population of public information sites and improve FDA and sponsor REMS tracking activities.

As an XML data structure, SPL also affords great flexibility in context-specific, meaningful presentation of information since it is structured conceptually rather than literally. For example, in patient portals, REMS data extracted from SPL can be presented using consistent patient-centric terminology regardless of the words employed in the actual REMS and even at different levels of health literacy. Thus, a sponsor's use of the term "Patient and Healthcare Professional Acknowledgement Form" could be described more simply as "Patient Consent Form," "What are the Risks and Benefits to Me," or some other patient-centric translation in a patient portal. Likewise, inconsistent terminology employed by sponsors can be harmonized and presented in a standard way regardless of the terms used to describe the same concept. For example, FDA provided at the recent public meeting 5 examples of different sponsor wording for the same concept of patient and provider agreement and enrollment forms. Conceptual tagging employed through SPL would permit easy location of all these forms simultaneously regardless of the actual words used by the sponsor to describe them.

One of the key components of FDA's REMS Integration Initiative is the efforts of its REMS Design and Standardization Workgroup aimed at developing an analytically rigorous approach to designing, standardizing, and integrating REMS programs. Standardization of REMS data using SPL is a key element in achieving this. FDA acknowledged that a "common language" to describe REMS variation must first be established before REMS standardization can occur and stated that the agency already has concluded that inclusion of REMS information in SPL will better characterize and improve how REMS information is captured and shared across the health system. NCPDP was a key stakeholder involved in FDA reaching these conclusions, working closely with various groups and individuals within the agency to build consensus. NCPDP also worked closely with a broad range of other stakeholders as part of the consensus-building process concerning SPL.

Benefits of SPL standardization of REMS include:

- Standardized and more efficient REMS submissions by sponsors
- More efficient and simplified REMS review by FDA
- More efficient and standardized REMS prescription processing
    - Facilitating and documenting certification of prescribers, dispensers, healthcare settings, etc.
    - Facilitating and documenting the registration and qualification of patients
    - Facilitating electronic prescribing via SCRIPT Standard
    - Documenting prescription REMS approval & facilitating dispensing
    - Facilitating and documenting other elements to ensure safe use (ETASU)
- More efficient and standardized searching of all REMS data by leveraging SPL's highly granular, codified structure, including global searches across different REMS
- More efficient and simplified REMS tracking at all levels
- Standardized and optimized REMS reporting and analysis
- Leverages existing SPL expertise, standards, infrastructure, and publically accessible central repository

Summarized below are key consensus-building activities led by NCPDP over the past 3 years concerning SPL's role in standardizing REMS. NCPDP clearly has exhibited a strong commitment to exploring the merits of SPL and building consensus.

- November 2010, NCPDP's WG2 Guiding Coalition (now WG2 SPL Activities Task Group) begins exploring SPL as means for REMS standardization

- May 2011, NCPDP's WG2 creates SPL REMS Requirements Task Group to focus on REMS standardization via SPL; continues to build consensus at its quarterly Work Group meetings and conference calls throughout 2011-2013
- Summer 2011, NCPDP develops schema (model) of all REMS concepts, requirements, and decision/transaction trigger points using FDA's 2009 Draft Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications
- Summer 2011 NCPDP meets with FDA's Health and Regulatory Data Standards group (Randy Levin, Lonnie Smith) to explore further the merits of SPL for REMS standardization; agreement to pursue and build consensus
- September 2011 NCPDP begins more in-depth engagement of pharmaceutical sponsors and other SPL experts through the SPL Working Group Leadership Team; engagement continues
- October 2011 NCPDP coordinates session on Possible Uses of SPL in REMS as part of a Drug Information Association (DIA) conference on The Future of SPL: What's Next?; extensive stakeholder participation by pharmaceutical manufacturer staff involved with SPL and other SPL services experts
- October 2011 NCPDP meeting with National Library of Medicine (NLM) Medical Subject Headings group (Stuart Nelson, John Kilbourne) to discuss the Library's preferred SPL REMS pathway from DailyMed perspective; NLM strongly preferred a composite approach where REMS content was integrated as a new element within a given drug product's existing SPL rather than a separate document type that would require resource-intensive maintenance of links among SPL files
- January 2012 initial meeting between NCPDP and FDA's REMS Integration Initiative (Adam Kroetsch and other FDA staff); subsequent meetings throughout 2012 and 2013; FDA begins building use cases and further characterizing all REMS
- March 2012 NCPDP (WG2 and WG11 representatives) meet with FDA staff from the Office of Planning and Informatics to discuss status of FDA efforts in exploring further SPL REMS standardization
- March 2012 NCPDP hosts invitational stakeholder meeting—Standardization of REMS Requirements Focus Group —in Scottsdale; FDA participates as invited speaker
- May 2012 NCPDP Standardization Co-chairs designate WG2 SPL REMS Requirements Task Group as lead on REMS initiatives with participation from REMS Task Groups from WG1 and WG11
- Summer and Fall 2012 FDA REMS Integration Initiative continues in-depth analysis of exiting REMS and begins building an internal database of REMS concepts, including materials and types, components, product information, requirements, and associated values, filling the gaps from NCPDP's initial schema
- January 2013 NCPDP conference call with REMS Integration Initiative
- April 2013 NCPDP meeting with FDA's REMS Integration Initiative
- August 2013 NCPDP provides oral comments on REMS Standardization via SPL: Critical Codification & Structure for Downstream Automation at FDA's Public Meeting on Standardizing and Evaluating REMS

NCPDP remains fully committed to assisting FDA as a formal collaborator in pursuing standardization of REMS using SPL, and to continued engagement of the Council's ANSI-accredited standards development processes to facilitate integration within existing and future healthcare information systems development and adoption within the healthcare information technology industry.

Designating SPL REMS Standardization as One of the PDUFA V Priority Projects

NCPDP recommends that FDA designate SPL REMS standardization as one of the PDUFA V priority projects. Although much work has already been done gaining consensus on NCPDP's proposed approach, far more work is needed to actually define and implement the proposed SPL solution. As noted above, successful execution of SPL standardization of the content and structure of REMS is the most critical step in achieving the needed downstream means for automation of all aspects of REMS. Everything hinges on its effective achievement as a first step. Without it, FDA will not achieve its PDUFA V commitments for standardizing REMS in a way that will ensure seamless integration into, and the resultant substantial reduction in burden to, the existing and evolving healthcare system.

Key focuses of this prioritization include but are not limited to:

- Completion of FDA's characterization of REMS content and data types
- Completion of FDA's internal REMS Database
- Regulatory analysis, focusing on e-submissions guidance and agreements under PDUFA V aimed at enhancing the quality and efficiency of FDA review through required electronic submission and standardization of electronic drug data
- Consensus development of a "common language" to describe all aspects of REMS
- Engagement by FDA of an expert SPL consultant to model the full range of REMS via an SPL schema
- Stakeholder engagement to provide feedback on proposed REMS SPL definitions and structure and FDA's draft schema
- Testing
- Stakeholder engagement on use cases
- Issue a new FDA draft Guidance to Industry on the content and structure of REMS, with a strong focus on SPL, standardization, and electronic submission
- Collaboration with NCPDP to ensure optimal integration into electronic prescribing and prescription processing standards
- Collaboration with NLM to ensure easy public access to all REMS data as part of Daily Med

As a focus among the 4 domains identified by FDA for priority projects, the SPL REMS standardization priority project would apply primarily to pharmacy systems and practice settings, but also would benefit each of the other areas (prescriber education and providing benefit/risk information to patients) because of the central role that SPL codification would serve in providing timely, ready access to, and communication of, all information associated with each REMS. In addition, SPL data, structure, and definition standardization is expected to have a beneficial effect of promoting standardization of individual REMS programs, to the extent possible.

REMS Standardization and Electronic Prescribing

NCPDP is currently working on standardizing the REMS process using electronic prescribing transactions. The purpose of the new electronic prescribing transactions is to streamline the electronic processing of REMS prescriptions from prescriber creation to pharmacy dispensing. All processes will be completed electronically without deviating from workflow once all steps are standardized. The transaction is "triggered" when the prescriber's electronic health record (EHR) system recognizes the drug as a REMS product from the information obtained from the SPL.

NCPDP is also modifying the SCRIPT Standard (used to transmit refill approvals and new prescriptions) to provide for a real-time sharing of REMS information among the stakeholders. While this process would not be used to report the dispensing of a REMS product, it would provide a clean prescription to the pharmacy that, when filled, would then be reported to the REMS Administrator.

The following transactions are being covered by this process:

- REMS eligibility of the patient, prescriber, and pharmacy, as required
- Verification requirements of any special REMS, including lab values
- Refill requests

- Transfers of REMS prescriptions from pharmacy to pharmacy
- Changes in drug therapy from one REMS drug to another

The NCPDP WG11 REMS and ePrescribing Task Group continues to work diligently on these transactions. There is still work to be accomplished before the transactions are finalized and ready for publication, such as:

- Use cases and error codes have been defined, additional fields and appropriate transactions have been identified and the flow charts are currently being finalized (see draft flows below).
- The implementation guide sections can be written once the flow charts are completed and the following gaps have been closed:
    - Communicating lab values to the REMS Administrator
    - Determining what information will be contained in the SPL

The efficiency of the electronic prescribing REMS transactions relies heavily on the final content of the SPL. REMS information must be integrated into the SPL in such a way that it is readily retrievable and consumable by prescriber systems at the onset of order entry and the pharmacy at dispensing.

Proposed Draft REMS Electronic Prescribing Transaction Flows

Prescriber System to Intermediary Option for NewRx

This flow separates the REMS requirements from the NewRx process.

Prescriber chooses patient, medication. The selected medication triggers the REMS "eligibility process". (*Solution requires prescriber system to recognize medications requiring REMS. Structured Product Label (SPL) is assumed to provide this information.)* A query to the drug database (or other control mechanism) indicates that a REMS approval is needed for this medication. The REMSInitiationRequest is from the prescriber to the REMS Administrator to verify REMS is needed. The REMSIntiationResponse is from the REMS Administrator answering if REMS is required, and if yes, the REMS questions to be answered or information to be provided. The REMSRequest is from the prescriber system to the REMS Administrator with the fulfillment information to the questions/information to produce a REMS approval. The REMS Administrator generates a REMSResponse. If Approved, the prescribing system can generate the NewRx. If Denied, the prescribing system must alert the prescriber to modify something and submit a new REMSRequest.

Sets patient expectations before they leave prescriber of whether they are accepted for the REMS before the NewRx is generated.

If an Intermediary is involved, the Intermediary would need a table of which medications are handled by which REMS Administrator. There is a 1 medication to 1 administrator relationship. 1 REMS Administrator may handle many medications. The Intermediary cannot perform REMS transactions on behalf of prescribing system because they would not have the information to fulfill the questions.

ASSUMPTION: ALL transactions are real-time and synchronous. (Mailbox could be used.) If no intermediary involved, see Prescriber or Dispensing Provider Direct diagrams.

Prescriber system recognizes need for REMS based upon selected product (SPL)
1) Prescriber system sends REMSInitiationRequest to Intermediary.
2) Intermediary sends REMSInitiationRequest to REMS Administrator
3) REMS Administrator sends REMSInitiationResponse to Intermediary.
4) Intermediary sends REMSInitiationResponse to Prescriber system.
5) Prescriber system sends REMSRequest to Intermediary
6) Intermediary sends REMSRequest to the REMS Administrator
7) REMS Administrator sends REMSResponse to intermediary (approved or denied)
8) Intermediary sends REMSResponse to Prescriber system

If Approved:
9) Prescriber system sends NewRx with REMS, with REMS flag/code/auth # to Intermediary
10) Intermediary sends NewRx with REMS flag/code/auth # to Dispensing Provider system
11) Dispensing Provider system sends Status/Error back to Intermediary
12) Intermediary sends Status/Error back to Prescriber system

Other Considerations:

Goal: use of RxNorm as the code set for the medication.

Need to include guidance that to support REMS, the entities have to support the version that supports REMS.

Patient/Dispensing Provider/ Prescriber/Medication – REMS program determines which piece is a failure (one or more than one piece).

REMS Administrator might be able to suggest an alternative Dispensing Provider if the one chosen is not approved.

SPL is working on standardized information from the manufacturers.

2 = New transaction
9 = Current transaction

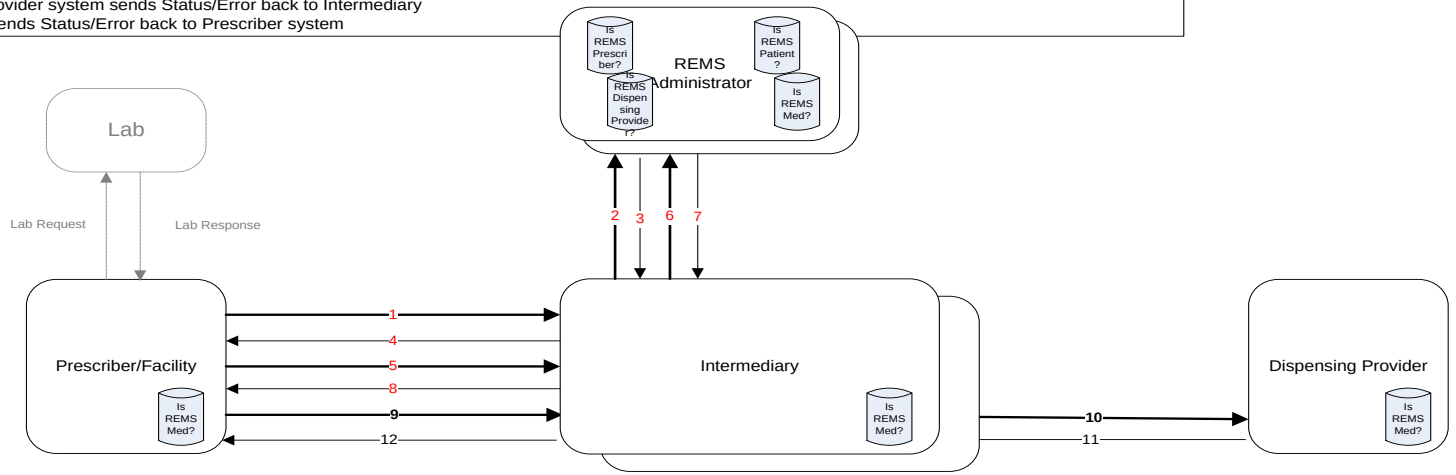

Figure 1. Prescriber via Intermediary Checks REMS

Prescriber System Direct Option for NewRx

This option assumes the prescribing system chooses to interact with the REMS Administrator directly. The prescribing system chooses to interact with the dispensing provider via an intermediary.
This flow separates the REMS requirements from the NewRx process.

Prescriber chooses patient, medication. The selected medication triggers the REMS "eligibility process". (*Solution requires prescriber system to recognize medications requiring REMS. Structured Product Label (SPL) is assumed to provide this information.)* A query to the drug database (or other control mechanism) indicates that a REMS approval is needed for this medication. The REMSInitiationRequest is from the prescriber to the REMS Administrator to verify REMS is needed. The REMSIntiationResponse is from the REMS Administrator answering if REMS is required, and if yes, the REMS questions to be answered or information to be provided. The REMSRequest is from the prescriber system to the REMS Administrator with the fulfillment information to the questions/information to produce a REMS approval. The REMS Administrator generates a REMSResponse. If Approved, the prescribing system can generate the NewRx. If Denied, the prescribing system must alert the prescriber to modify something and submit a new REMSRequest.

Sets patient expectations before they leave prescriber of whether they are accepted for the REMS before the NewRx is generated.

There is a 1 medication to 1 administrator relationship. 1 REMS Administrator may handle many medications. The prescriber system needs to know which REMS Administrator to send the REMSRequest.

ASSUMPTION: ALL transactions are real-time and synchronous. (Mailbox could be used.)
Prescriber system recognizes need for REMS based upon selected product (SPL)
1) Prescriber system sends REMSInitiationRequest to REMS Administrator.
2) REMS Administrator sends REMSInitiationResponse to Prescriber system.
3) Prescriber system sends REMSRequest to REMS Administrator.
4) REMS Administrator sends REMSResponse to Prescriber system (approved or denied)

If Approved:
5) Prescriber system sends NewRx with REMS, with REMS flag/code/auth # to Intermediary
6) Intermediary sends NewRx with REMS flag/code/auth # to Dispensing Provider system
7) Dispensing Provider system sends Status/Error back to Intermediary
8) Intermediary sends Status/Error back to Prescriber system

Other Considerations:

Goal: use of RxNorm as the code set for the medication.

Need to include guidance that to support REMS, the entities have to support the version that supports REMS.

Patient/Dispensing Provider/ Prescriber/Medication – REMS program determines which piece is a failure (one or more than one piece).

REMS Administrator might be able to suggest an alternative Dispensing Provider if the one chosen is not approved.

SPL is working on standardized information from the manufacturers.

2 = New transaction
9 = Current transaction

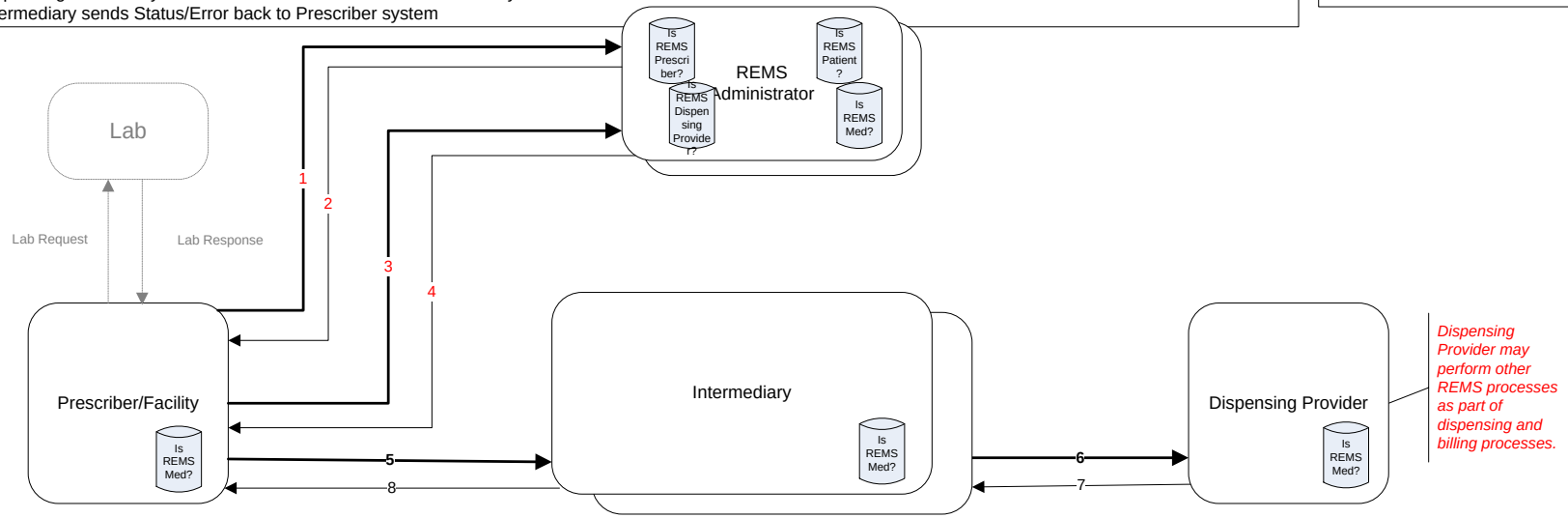

Figure 2. Prescriber Checks REMS

Dispensing Provider System Receives NewRx without REMS Designation Option	**Other Considerations:**
This option assumes the prescribing system sends the NewRx without the REMS flag/code/auth #. The Dispensing provider system assumes the prescribing system or their Intermediary on prescriber's behalf did not check since the REMS flag/code/auth# are not sent. The Dispensing provider system chooses to check REMS before claim billing. (It is recognized that pharmacies may opt to have the REMS checking during claims processing, but this option shows that the dispensing provider can use the REMS transactions as well. There may be instances where the dispensing provider has to fulfill information on the REMS process.) This flow separates the REMS requirements from the NewRx process. Prescriber chooses patient, medication. There is no REMS checking. The prescribing system generates the NewRx. The NewRx may/not go through an Intermediary. The NewRx is received by the Dispensing provider system. The medication triggers the REMS processing. (*Structured Product Label (SPL) is assumed to provide this information.)* A query to the drug database (or other control mechanism) indicates that a REMS approval is needed for this medication. The Dispensing provider system recognizes that no REMS information has been provided. The REMSInitiationRequest is from the Dispensing provider system to the REMS Administrator to verify REMS is needed. The REMSIntiationResponse is from the REMS Administrator answering if REMS is required, and if yes, the REMS questions to be answered or information to be provided. The REMSRequest is from the Dispensing provider system to the REMS Administrator with the fulfillment information to the questions/information to produce a REMS approval. The REMS Administrator generates a REMSResponse. If Approved, the Dispensing provider system proceeds with dispensing processes. This scenario does not set patient expectations before they leave prescriber of whether they are accepted for the REMS before the NewRx is generated. There is a 1 medication to 1 administrator relationship. 1 REMS Administrator may handle many medications. The prescriber system needs to know which REMS Administrator to send the REMSRequest. **ASSUMPTION: ALL transactions are real-time and synchronous.** (Mailbox could be used.) Dispensing provider system recognizes need for REMS based upon selected product (SPL) 1) Prescriber system sends NewRx without REMS flag/code/auth # to Intermediary 2) Intermediary sends NewRx without REMS flag/code/auth # to Dispensing Provider system 3) Dispensing Provider system sends Status/Error back to Intermediary 4) Intermediary sends Status/Error back to Prescriber system 5) If Status (not Error), Dispensing Provider system sends REMSInitiationRequest to REMS Administrator. This assumes that the Dispensing Provider either has the information or is able to obtain the information to fulfill the REMSRequest (from own system, from Prescriber, from lab, etc.) 6) REMS Administrator sends REMSInitiationResponse to Dispensing Provider system. 7) Dispensing Provider system sends REMSRequest to REMS Administrator. 8) REMS Administrator sends REMSResponse to Dispensing Provider system (approved or denied) If Approved Dispensing provider system continues dispensing functions. End of flow. If Denied: 9) Dispensing provider system sends Error to Intermediary. 10) Intermediary sends Error to Prescribing system. 11) Prescribing system sends Status in response to Intermediary. 12) Intermediary sends Status response to Dispensing provider system.	Goal: use of RxNorm as the code set for the medication. Need to include guidance that to support REMS, the entities have to support the version that supports REMS. Patient/Dispensing Provider/Prescriber/ Medication – REMS program determines which piece is a failure (one or more than one piece). REMS Administrator might be able to suggest an alternative Dispensing Provider if the one chosen is not approved. SPL is working on standardized information from the manufacturers. 2 = New transaction 9 = Current transaction

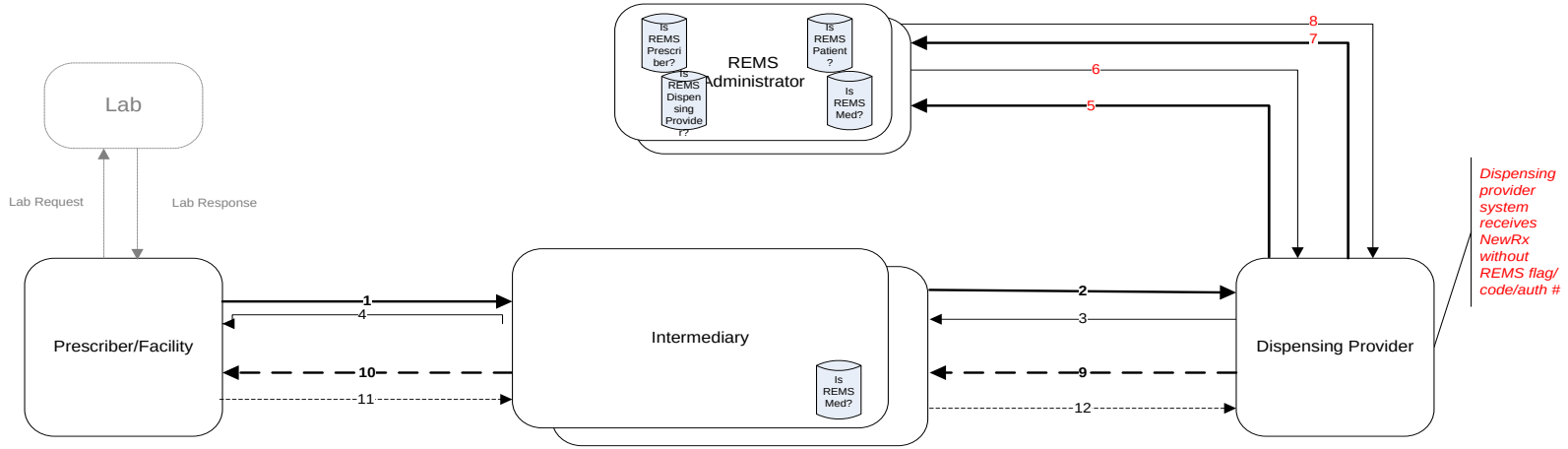

Figure 3. Dispensing Provider Checks REMS

REMS Standardization and Prescription Processing and Reporting

The NCPDP Safe Use Processing (FDA REMS) Task Group developed guidelines for adopting the Telecommunication Standard as a mechanism to support REMS program participation requirements by pharmacies. The guidelines were used by pharmacy practice management system developers and operators to provide a consistent and standardized process for implementing a REMS program using the NCPDP Telecommunication Standard. The use of the NCPDP Telecommunication Standard to support REMS programs recognizes the following:

- The nearly ubiquitous use of the NCPDP Telecommunication Standard for prescription claims processing, and therefore patient access to participating retail pharmacies,
- The work-flow friendly messaging capabilities of the NCPDP Telecommunication Standard,
- The development and maintenance cost advantages of piggy-backing REMS program activities on an existing and widely adopted technology infrastructure, and
- Recognition that NCPDP is an ANSI-accredited SDO adhering to a consensus building process by all interested parties.

The NCPDP Telecommunication Standard will shortly support three REMS programs. One of the three existing programs (i.e. TIRF REMS) is class-wide. As currently deployed, these three REMS programs, utilizing the NCPDP Telecommunication Standard, support the following REMS capabilities:

- Ability to auto-enroll a patient into a specified REMS program and thereby eliminate this burdensome task from participating providers
- Ability to confirm patient enrollment and program participation training for a specified REMS program ahead of billing and dispensing a medication
- Ability to confirm pharmacy enrollment and program participation training for a specified REMS program ahead of billing and dispensing a medication.
- Ability to confirm prescriber enrollment and program participation training for a specified REMS program ahead of billing and dispensing a medication
- Ability to assess clinical appropriateness of REMS medication by editing against any combination of prescription claim attributes, including days supply, quantity dispensed, date of birth, patient gender code, and deliver a clinical alert to the pharmacy ahead of billing and dispensing a medication

By FDA collaborating closely with NCPDP, the Telecommunication Standard also can be further enhanced to support REMS requirements with the following:

- Expand adoption of NCPDP Telecommunication Standard – Retail Pharmacy REMS programs, with ETASU components, should be approved (new) or migrated (existing) to the use of the NCPDP Telecommunication Standard for information exchanges. Specifically, programming messages should be automated and delivered prior to dispensing a medication and delivered in a standard manner, without having to access a web portal.
- Pursue codification of REMS data – REMS, with or without ETASU components, should align with a standard code set that captures the program participation requirements. The standardized code set, enabled by SPL, should be a common data set that is used by the NCPDP Telecommunication Standard and SCRIPT Standard.
- Review and assess data reporting requirements – The NCPDP Telecommunication Standard should evolve to support REMS reporting requirements. This should include any data that is captured from patient interactions.
- Pursue alignment with other programs – The NCPDP Telecommunication Standard should evolve to align REMS participation requirements with other business functions, including DEA dispensing requirements and Prescription Drug Monitoring Program (PDMP) reporting requirements. As an example, these programs should facilitate the capture and alignment of a Prescriber ID.

The efficiency of the electronic REMS transactions rely heavily on the final content of the SPL. REMS information must be integrated into the SPL in such a way that it is readily retrievable and consumable by the pharmacy at dispensing.

Sample REMS Model for Drugs Dispensed by Outpatient Pharmacies

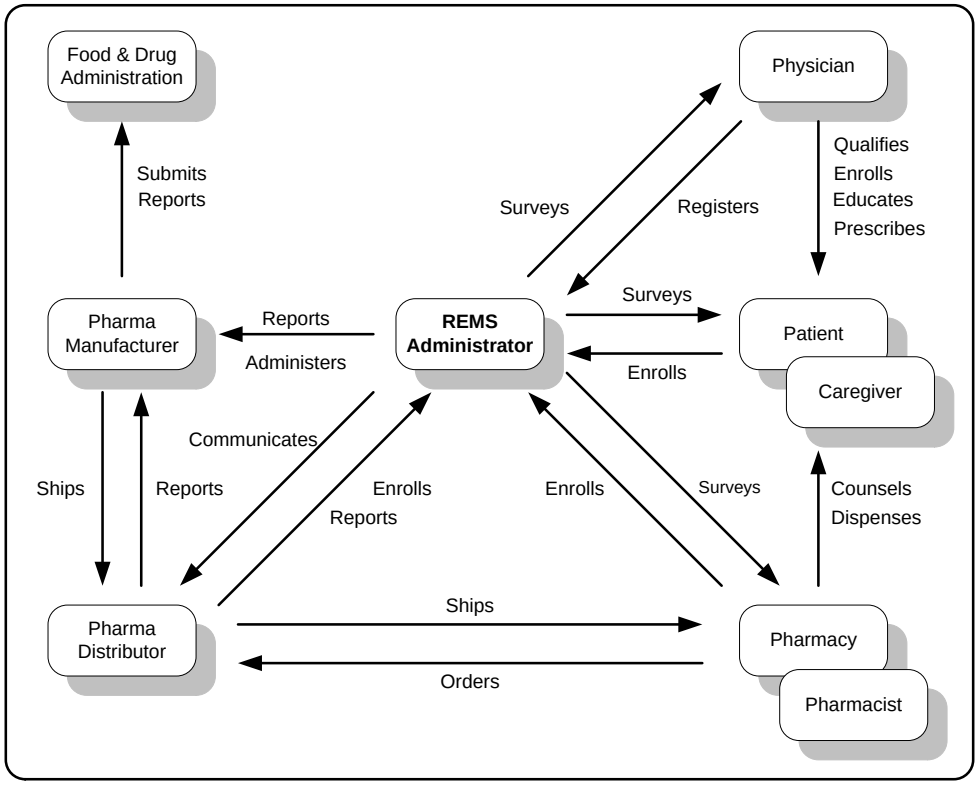

Figure 4.

Providers, Switches, and REMS Administrators

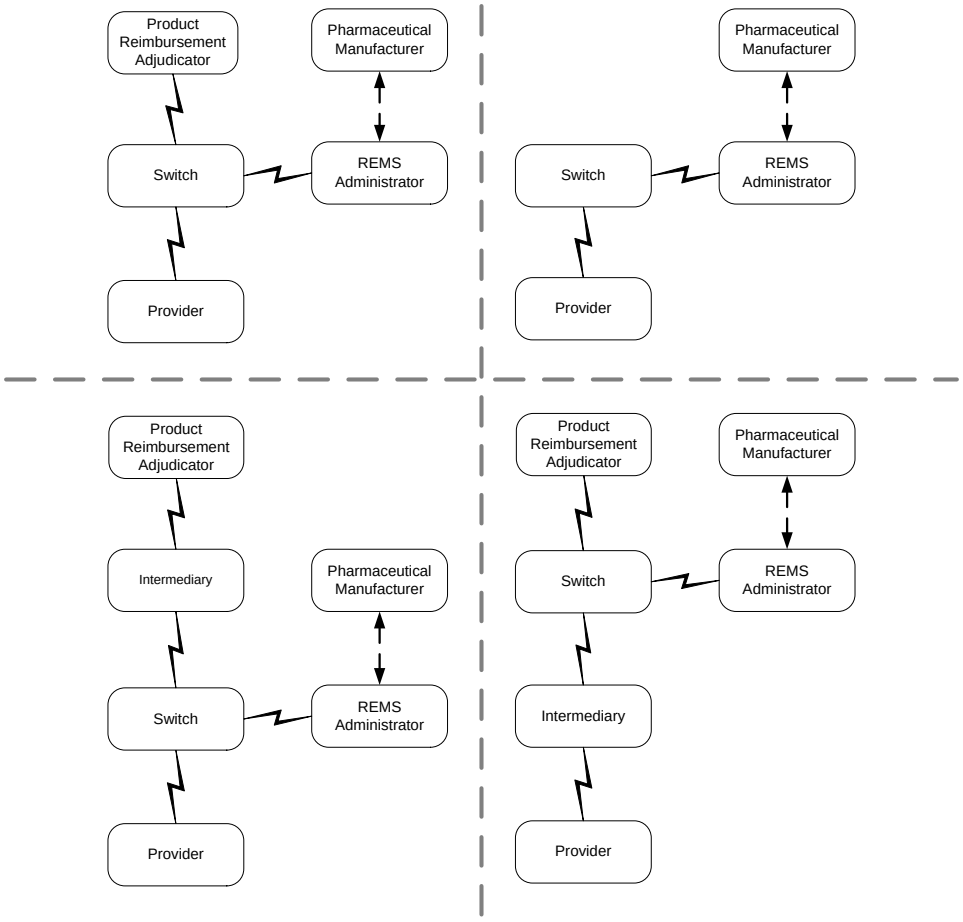

Figure 5.

Conclusions

Thank you for the opportunity to submit recommendations. NCPDP looks forward to future collaboration with FDA in order to ensure that the proposed SPL solution be identified as one of the 4 PDUFA V priority projects. Achieving standardization of data content and format is crucial to downstream applications such as the Telecommunication and SCRIPT Standards and will be realized by the adoption of the proposed SPL solution.

Respectfully,

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President
NCPDP

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