Observational post-marketing studies to assess abuse in real-world use: an industry perspective

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OPC

Opioid PMR Consortium (OPC) Participating Companies Conducting PMRs

As mandated by the FDA, the following eight companies are sponsoring the observational PMR studies.

Boehringer Ingelheim Roxane Laboratories

PURDUE

Actavis

endo

Pfizer

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Mallinckrodt

Zogenix®

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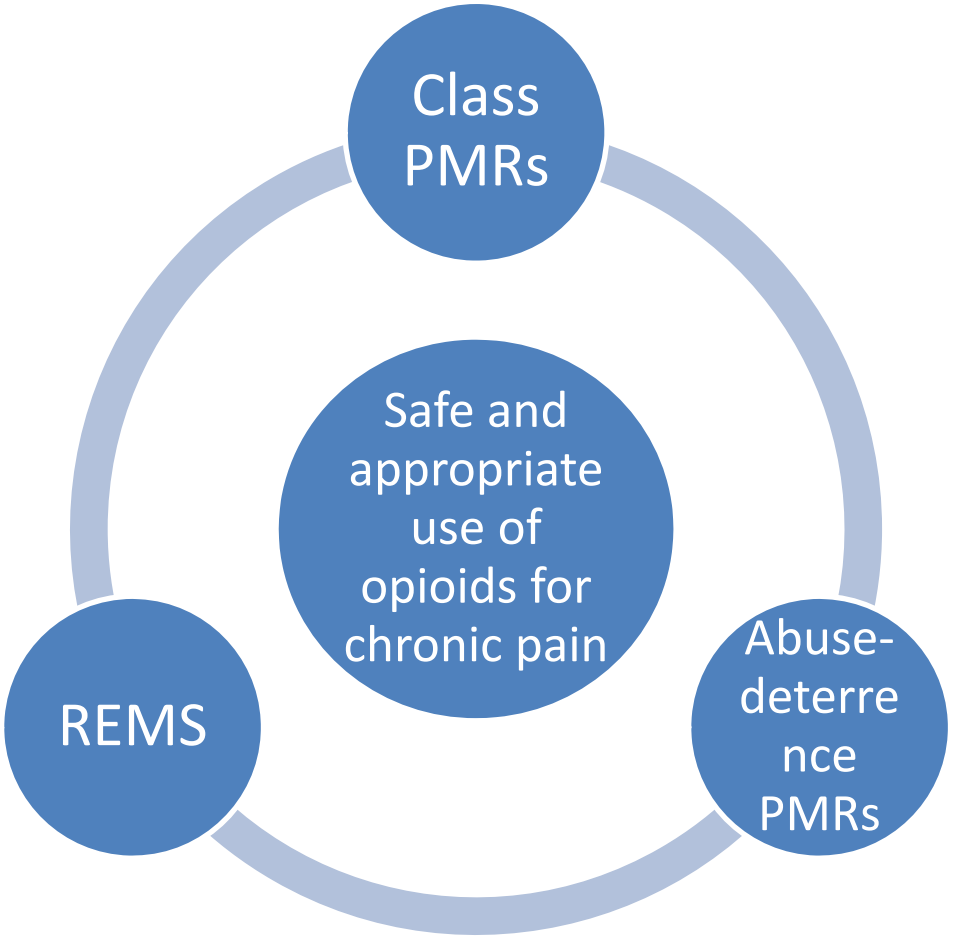
Three Legs of Post-Marketing Requirements



Types of FDA-Required Postmarketing Studies to Assess Abuse of ER/LA Opioid Analgesics

1. Shared post-marketing studies for ER/LA opioids
    1. Focus on pain patients with long-term opioid treatment
    2. Shared by brand ER and LA opioid manufacturers
    3. Assess incidence of and risk factors for abuse

Focus of this talk

2. Product-specific post-marketing studies for products with abuse-deterrent claim in the label
    1. Not limited to pain patients
    2. Assess changes in abuse and related outcomes

3. Shared assessments of the ER/LA Opioid Analgesic REMS
    1. Not limited to pain patients
    2. Shared by both brand and generic ER and LA opioid manufacturers
    3. Assess changes in abuse and related outcomes

ER/LA opioids = extended-release and long-acting opioids

Outcomes Required by FDA in PMRs

- Misuse
- Abuse
- Addiction
- Overdose
- Death

- Doctor shopping being validated
- Hyperalgesia/long-term analgesic efficacy

FDA Letter Received in September 2013 by Brand ER/LA Opioid Companies

- FDA's analyses of the medical literature and the input of FDA stakeholders are considered to be "new safety information" as defined in section 505-1(b)(3) of FDCA
- Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limited to specific products
- The role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death should be assessed
- Because many of risk factors cannot be captured using administrative databases alone, FDA is unlikely to find administrative database studies alone as adequate
- Only a clinical trial will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioids
- We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies and clinical trial

Required Shared Studies in FDA's Letter

PMRs in FDA's letter	FDA's Focus
2065-1	Assess incidence and predictors of misuse, abuse, addiction, overdose & death among patients prescribed ER/LA opioid products.
2065-2	Develop and validate measures of misuse, abuse, addiction, overdose & death
2065-3	Validate coded medical terminologies to identify misuse, abuse, addiction, overdose & death in databases used for studies
2065-4	Define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse, and addiction
2065-5	Conduct a clinical trial to assess hyperalgesia with at least one year's use of ER/LA opioids to treat chronic pain. Assess tolerance development too. Include assessment of risks relative to efficacy.

Ten Shared Observational PMR Studies

PMRs in FDA's letter	FDA's Focus	OPC Study	Study Title
2065-1	Assess incidence and predictors of misuse, abuse, addiction, overdose & death among patients prescribed ER/LA opioid products	**Study 1A**	A prospective investigation of the risks of opioid misuse, abuse, and addiction among patients treated with extended-release/long acting (ER/LA) opioids for the treatment of chronic pain
		Study 1B	Incidence and predictors of opioid overdose and death among ER/LA opioid analgesics users as measured by diagnoses and death records—a retrospective database study
2065-2	Develop and validate measures of misuse, abuse, addiction, overdose & death	**Study 2A Qualitative**	A qualitative study to assess the content validity of the prescription opioid misuse and abuse questionnaire (POMAQ)
		Study 2A Quantitative	A quantitative study to assess the construct validity of the prescription opioid misuse and abuse questionnaire (POMAQ)
		Study 2B	Validation of PRISM-5-Op, measure of addiction to prescription opioid medication
2065-3	Validate coded medical terminologies to identify misuse, abuse, addiction, overdose & death in databases used for studies	**Study 3A**	Study to validate coded medical terminologies used to identify opioid-related overdose in the postmarketing databases employed in PMR Study 1B
		Study 3B	An observational study to develop computable algorithms for identifying opioid abuse and addiction based on administrative claims data
2065-4	Define and validate ''doctor/pharmacy shopping'' as outcomes suggestive of misuse, abuse, and addiction	**Study 4A**	Cross-sectional study to define and validate doctor/pharmacy shopping as outcomes suggestive of abuse and/or addiction
		Study 4B	Study to evaluate the relation between doctor/pharmacy shopping and outcomes suggestive of misuse, abuse, and/or diversion
		Study 4C	Retrospective cohort study to evaluate the relation between doctor/pharmacy shopping and outcomes suggestive of misuse, diversion, abuse, and/or addiction by medical record review

Ten Shared Observational PMR Studies

PMRs in FDA's letter	FDA's Focus	OPC Study	Study Title
2065-5	Design and conduct a clinical trial to assess the known serious risk of hyperalgesia associated with the use of ER/LA opioid analgesics when used for at least one year to treat chronic pain. FDA encourages sponsors to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics	Study 5	Clinical trial to assess the known serious risk of hyperalgesia associated with the use of ER/LA opioid analgesics

Studies to Assess Incidence of Abuse, Misuse, Addiction, Overdose and Death

- A prospective cohort study of misuse, abuse, and addiction among patients treated with ER/LA opioids for chronic pain (#1A)
  - Sites/Research Partners: HMO Research Network , Veterans Affairs, Community based clinical trial network
- Incidence and predictors of opioid overdose and death among ER/LA opioid analgesics users as measured by diagnoses and death records—a retrospective database study (#1B)
  - Sites/Research Partners: Kaiser Permanente Northwest, Group Health Cooperative, United Healthcare/Optum, Tennessee Medicaid/Vanderbilt University

Interpretation of Cohort and Database Studies

Endpoint	Study 1A Patient Report	Study 1B Algorithms using coded terms	Comment
Misuse	√	-	Assessed by patient self-report using validated instrument
Abuse	√	√	Abuse and addiction assessed by patient self-report using validated instrument and aberrant behaviors in EHRs
Addiction	√		Abuse and addiction combined assessed by ICD-9 codes and validated diagnostic algorithm
Overdose	**Low #s**	√	Assessed by validated diagnostic algorithm using coded terms
Death	**Low #s**	√	Overdose deaths assessed by validated diagnostic algorithm

Potential Risk Factors for Abuse, Addiction and Overdose

Assessed in Study 1A and 1B

- Demographic characteristics
- Opioid use characteristics
  - Time from initiation, duration, daily dose, formulation (oral, transdermal, abuse-deterrent), type (eg, morphine), IR or ER
- Pain – level and type
- Functional Status (SF-12)
- Genetic samples obtained via saliva (in collaboration with NIDA)
- History of psychiatric and substance use disorders
- Alcohol, tobacco, and other drug use (PRISM)
- Sleep quality, stress level and social support
- Psychiatric disorders (depression, anxiety, bipolar disorder)
- Prescriber specialty for ER/LA opioid
- Psychotropic medication use

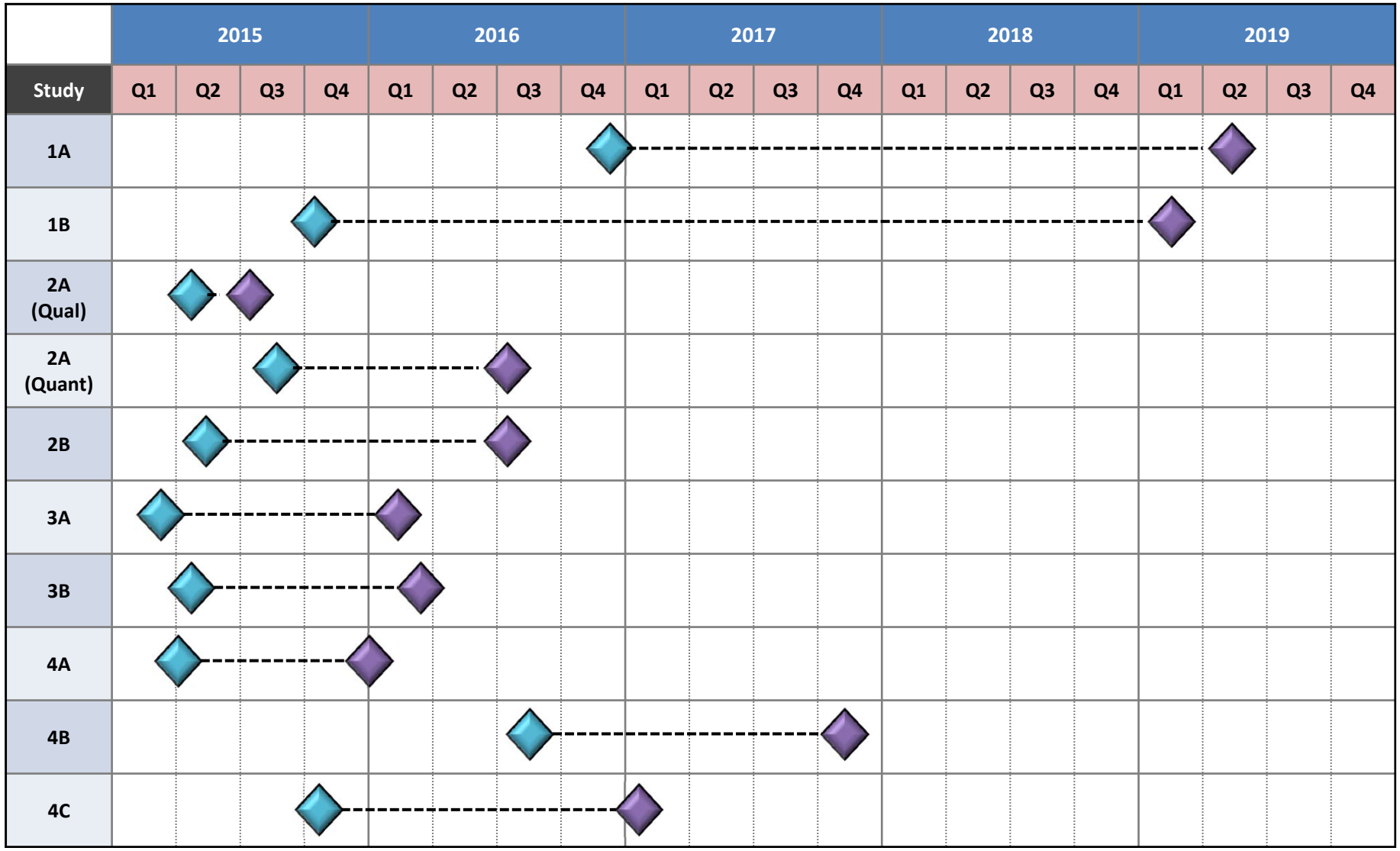
Validation Studies of Abuse, Addiction and Overdose

- Misuse and abuse questionnaire – POMAQ (#2A)
  - Evidera
- Addiction questionnaire – PRISM modified for pain patients (#2B)
  - Columbia University
- Overdose – diagnostic algorithm using coded terms (#3A)
  - Kaiser Permanente Northwest
- Abuse and addiction - diagnostic algorithm using coded terms (#3B)
  - Group Health Cooperative

Studies to define and validate "doctor/pharmacy shopping" as suggestive of misuse, abuse or addiction

- Relationship between doctor/pharmacy shopping categories versus:
  1) abuse/addiction algorithm used coded terms in insurance claims database developed in Study 3B
  2) misuse, abuse, or addiction measured by questionnaires/instruments evaluated in Study 2A and 2B
  3) outcomes suggestive of misuse, diversion, abuse, and/or addiction by medical record review

Timeline of PMR Observational Studies



Number of FDA-Required Postmarketing and REMS Assessment Studies

1. Shared post-marketing studies for ER/LA opioids
    1. N = 11

2. Product-specific post-marketing studies for products with abuse-deterrent claim in the label
    1. N=4 to 14

3. Shared assessments of the ER/LA Opioid Analgesic REMS
    1. N = 8

Sponsor has to conduct a low of 23 studies and a high of 33 studies for an ER/LA opioid analgesic with abuse-deterrent properties

Conclusions

- Program of 10 studies to assess misuse, abuse, addiction, overdose and death among patients with chronic pain using long-term opioid therapy
- Questionnaire instruments to measure 1) misuse and abuse and 2) addiction among pain patients are being developed and will be validated
- Diagnostic algorithms validated to be used in electronic health record or insurance claims databases to detect abuse/addiction and overdose/death associated with opioid analgesic use
- Doctor/pharmacy-shopping as a measure of abuse will be assessed and validated