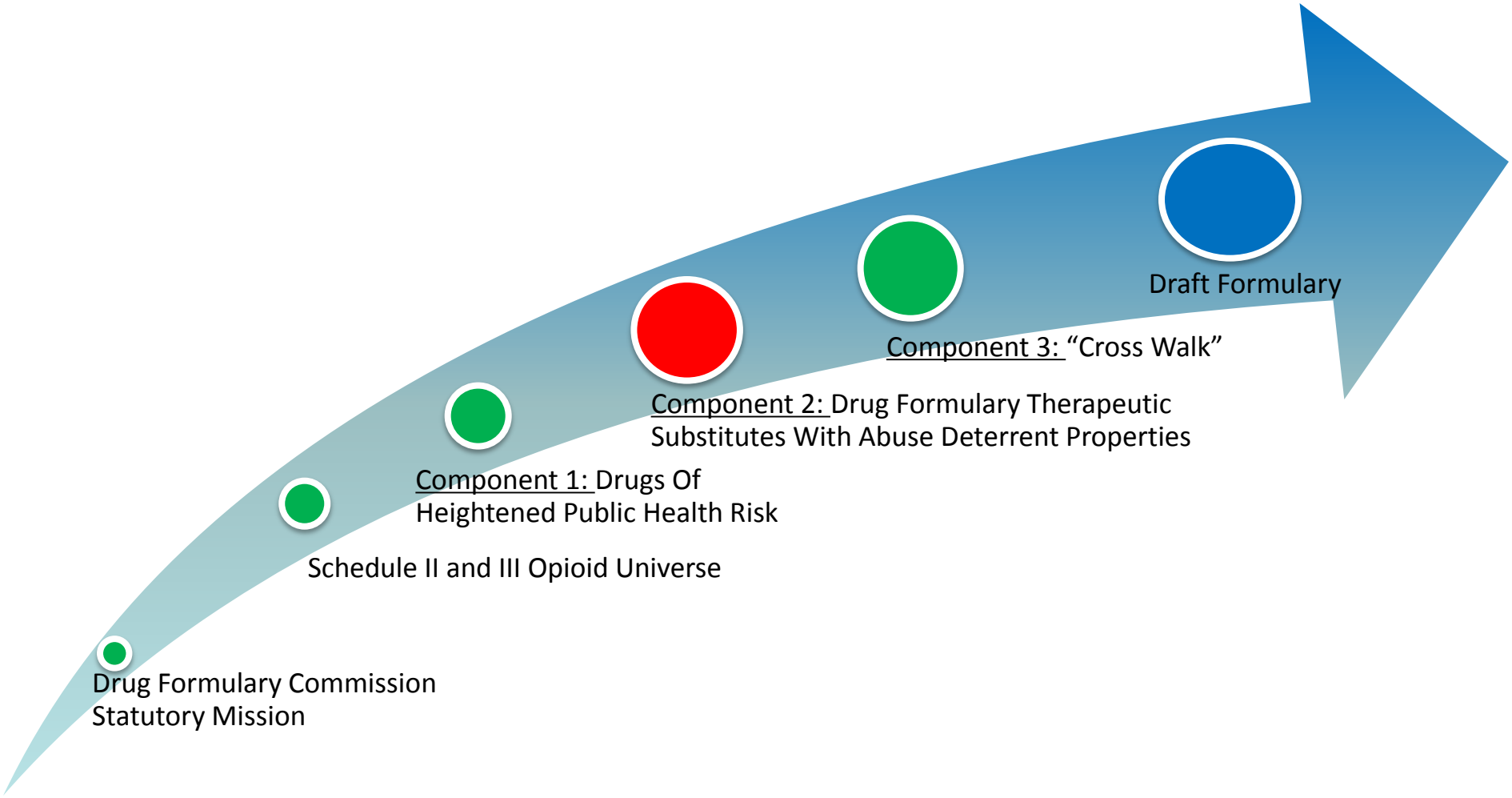
Drug Formulary Commission

Bureau of Health Care Safety and Quality
Department of Public Health
January 7, 2016

Opening Remarks



Presentation Agenda

- Review of December 17th meeting
  - Voted to approved Hysingla ER
  - Voted not to approve Targiniq ER
    ….or other drugs that are not marketed in the United States for inclusion as a potential substitute
  - Continued discussion OxyContin
  - Continued discussion Embeda

Monograph Review

Schedule II Opioids

FDA Approved Abuse Deterrent Labeling

Therapeutically Equivalent Substitutes
FDA Approved ADF Labeling

List of Medications with Abuse-Deterrent Claims in FDA-Approved Labeling

Product Name	Manufacturer	Ingredient(s)	Dose Form	Method of Abuse Deterrence	DFC Action
Targiniq ER	Purdue	Oxycodone ER and Naloxone	Tablet	Antagonist	Voted NOT to approve for Crosswalk consideration at December 17, 2015 meeting
OxyContin	Purdue	Oxycodone ER	Tablet	Crush-resistant Formulation	Deferred to January 7, 2016 meeting
Hysingla ER	Purdue	Hydrocodone ER	Tablet	Crush-resistant Formulation	Voted to approve for Crosswalk consideration at December 17, 2015 meeting
Embeda	Pfizer	Morphine ER and Naltrexone	Capsule	Antagonist	Deferred to January 7, 2016 meeting

Oxycontin CR ADF Monograph Review

- Oxycodone HCL
- ADF Property
  - physical chemical barrier
  - effective against injection, snorting
- FDA Approval April 2010
- FDA ADF labeling approved April 2013
- Available Strengths
  - 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg

OxyContin® ADF Technology

- Reformulated in 2010 with RESISTEC® technology[2]
- RESISTEC® technology[2]:
  - Increases tablet hardness
  - Forms a viscous gel under attempts to dissolve in aqueous solutions
  - Resists increased drug delivery rate when mixed with alcoholic beverages
- Abuse-deterrence studies[49-51]:
  - OxyContin® with RESISTEC® resisted crushing, breaking, extraction and dissolution using a variety of tools and solvents
  - Crushed OxyContin® with RESISTEC® was associated with less drug liking and willingness to take drug again when administered intranasally compared to crushed original OxyContin® and oxycodone powder

OxyContin® Information Requested by DFC

- Post-marketing data indicate a reduction in the abuse of OxyContin® after reformulation.[54-59]
- Post-marketing survey data also indicate that after reformulation some OxyContin abusers (n=88)[59]:
  - Switched from non-oral routes of abuse to oral abuse (n=38; 43%)
  - Successfully defeated the ADF mechanism to continue normal route of abuse (n=30; 34%)
  - Continued with previous oral abuse independent of formulation (n=20; 23%)
- Anecdotal reports from an internet forum identified methods to bypass the ADF mechanism by using tools such as a Dremel® rotary power tool or Pedi-Paws® pet nail trimmer, and subsequently utilizing a microwave and freezer to prevent complete gel formation. Conversely, some individuals reported difficulty abusing the tablets by methods other than the oral route due to inability to avoid gel formation.[60]
- Purdue Pharma, LP canceled their scheduled meeting on July 7, 2015 with the FDA intended to review findings of post-marketing OxyContin® abuse data, requesting more time for analysis of the data.[61]

OxyContin® Information Requested by DFC

- The first required postmarketing study results regarding abuse of OxyContin® are due to the FDA in June 2018.[61]
- OxyContin® is included in the extended-release/long-acting (ER/LA) shared Risk Evaluation and Mitigation Strategy (REMS) program.[48]
- Initial Dose (opioid naïve adults): 10 mg every 12 hours.[1]
- Initial Dose (pediatric): Pediatric patients should not start until they have tolerated other opioids equivalent to at least 20 mg oxycodone per day for at least five consecutive days.[1]
- Two FDA advisory committees voted 14 to 4 with one abstention in favor of approval of the reformulated OxyContin® (ADF).[46]

OxyContin® Information Requested by DFC

- Mean time to peak plasma concentration (T_{max}) for intact **OxyContin® ADF tablets** (oral administration):
  - Ranges from 4.15 to 5.11 hours, dependent upon dose[1]
- Median T_{max} for intact **OxyContin® ADF tablets** (oral administration):
  - 5 hours[52]
- Median T_{max} for crushed **OxyContin® ADF tablets** (oral administration):
  - 1.75 hours[52]
- Median T_{max} for finely crushed **OxyContin® ADF tablets** (insufflation):
  - 2.00 to 2.08 hours[50,51]
- Median T_{max} for coarsely crushed **OxyContin® ADF tablets** (insufflation):
  - 2.62 to 3.00 hours[50,51]
- Median T_{max} for finely crushed **original OxyContin® tablets**: (insufflation):
  - 1.00 to 1.10 hours[50,51]

Embeda Monograph Review

- morphine sulfate / naltrexone HCL
- ADF Property
  - antagonist
  - effective against crushing, snorting
- FDA Approval August 2013
- FDA ADF Approval October 2014
- Available Strengths 20 /.8, 30/1.2, 50/2, 60/2.4, 80/ 3.2, 100/4mg

Embeda® ADF Technology

- Embeda® is a μ-opioid receptor agonist (morphine) and μ-opioid receptor antagonist combination ADF.[1]
- Embeda® capsules contain pellets of extended-release morphine with naltrexone sequestered in the core of the pellets.[1]
- When Embeda® is taken as directed, the naltrexone is intended to have no clinical effect. If the pellets are crushed or chewed, up to 100% of the naltrexone may be released, which may antagonize opioid effects or precipitate withdrawal symptoms in physically dependent patients.[1]

Embeda® Information Requested by DFC

- Embeda® has been evaluated in multiple abuse liability studies:[6-9]
  - Crushed pellets and intact Embeda® administered as oral solutions were associated with less "drug likability" compared to morphine solution.[6]
  - There was no significant difference in drug likability between crushed and intact Embeda® administered as oral solutions.[6]
  - Crushed Embeda® pellets administered as an oral solution were associated with less "drug liking" and "drug high" compared to crushed morphine sulfate controlled-release (CR) administered as an oral solution.[7]
  - Crushed Embeda® pellets administered intranasally were associated with less drug liking and drug high compared to crushed morphine CR administered intranasally.[8]
  - Simulated Embeda® solution administered intravenously (IV) was associated with less of a high when compared to morphine solution for IV administration.[9]

Embeda® Information Requested by DFC

- The FDA expects formal epidemiologic studies to assess whether or not the ADF properties of Embeda® actually result in a meaningful reduction in abuse in the community by October 2020.[11]
- Anecdotal reports posted on an internet forum identified methods to bypass the abuse deterrent mechanism of Embeda® by the oral and intravenous routes; however, there were reports of precipitated withdrawal after abuse of crushed Embeda® pellets, as well.[12]
  - IV abuse report: User combined water and lemon juice, repeatedly used a hot water bath to heat the mixture and waited approximately 12 hours to prepare a solution for injection.
  - Oral abuse report: User placed Embeda® pellets into a shot glass full of water, and used repeated short microwave sessions to prepare a solution for ingestion, while avoiding ingestion of remainder of the pellets.

Embeda® Information requested by DFC

- Embeda® is subject to the requirements of the shared system extended-release/long-acting Risk Evaluation and Mitigation Strategies (REMS) program.[13]
- Initial Embeda® dosing (opioid naïve): 20 mg/0.8 mg every 24 hours.[1]
- Initial Embeda® dosing (converting from other opioids): 30 mg/1.2 mg every 24 hours.[1]
- Information regarding FDA advisory committee voting on Embeda® is not readily available. Of note, Embeda® was originally approved in 2009.[2]
- Median time to peak plasma concentration (Tmax)for intact Embeda.®[1]
- Morphine Tmax: 7.5 hours.
- Median Tmax for crushed Embeda® pellets administered orally.[1]
- Morphine and naltrexone: one hour.
- Median Tmax for crushed Embeda® pellets, insufflated.[1]
- Morphine and naltrexone: 36 minutes.
- The earliest deadline for the manufacturer to submit results of a post-marketing epidemiological study that assesses whether the ADF mechanism results in a meaningful deterrence to abuse or misuse in the community is October 2020.[11]

Meeting Summary

- Meeting Recap
- Review of takeaways
- Next steps
  - Anticipated materials
- Next Meeting
  - January 21, 2016 9:00AM-12:00PM