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**Minutes of the Drug Formulary Commission**

**Meeting of Thursday, June 2, 2016**

Division of Health Professions Licensure

239 Causeway Street, Room 417

Boston, MA 02114

**Date of Meeting:** Thursday, June 2, 2016

**Beginning Time:** 2:11 PM

**Ending Time:** 5:07 PM

**Advisory Council Members Present:** The following (13) appointed members of the Drug Formulary Commission attended on June 2, 2016, establishing the required simple majority quorum (9) pursuant to Massachusetts Open Meeting Law (OML): DPH Interim Director of the Bureau Health Care Safety and Quality, Eric Sheehan (Chair); Dr. Douglas Brandoff; Cheryl Campbell, Ray Campbell; Dr. Daniel Carr; Dr. Joanne Doyle-Petrongolo; Dr. Ken Freedman; Stephen Feldman, Dr. Paul Jeffrey; Dr. Virginia Lemay; Dr. Theoharis Theoharides; Tammy Thomas and Dr. Alexander Walker.

**1. Welcome and Introductions**

Department of Public Health (DPH) Bureau of Health Care Safety and Quality Interim Director Chair Eric Sheehan called the meeting to order at 2:11 PM following an Executive Session of the Commission.

Mr. Sheehan reminded the attendees that this is a recorded, public hearing, and confirmed that no one in audience was recording.

Mr. Sheehan summarized the May 5, 2016 meeting. He noted that the Commission at its last meeting began crosswalking the Abuse Deterrent Property (ADP) drug products it approved as potential substitutes with the drug products it determined have a Heightened Public Health Risk.

Data was presented on Embeda® and several drug products for which it may be substituted, based on statutory criteria, the definition approved for Chemically Equivalent Substitution and the form approved to determine the strength of evidence showing ADP Efficacy.

As requested by the Commission, additional data was presented to determine if the potential pairings fit the approved definition and produce a comparable biologic effect. The Commission voted to approve Embeda® as a chemically equivalent substitute for:

* Morphine Extended-Release, 24-hour capsule (generic Avinza®);
* Kadian®;
* Morphine Extended-Release, 12 or 24-hour capsule (generic Kadian®);
* MS Contin®, with additional guidance; and
* Morphine Extended-Release tablet (generic MS Contin®), with additional guidance.

These five Embeda® pairings will be placed on the Draft Formulary of Abuse Deterrent Opioids, with additional guidance provided for MS Contin® and its generic, given potential pharmacokinetic differences in the two drug products.

Mr. Sheehan called for approval of the minutes from the May 5, 2016 meeting. There were no changes offered by the members.

* + Motion to approve: Dr. Theoharides
  + Second: Dr. Walker
  + All in favor: 12 in favor; 0 opposed; 1 abstention.

Cheryl Campbell abstained as she was not present at the May 5th meeting.

**2. Opioid Bill**

Next, Mr. Sheehan gave an overview of other initiatives that support the work of the Commission and Department of Public Health in addressing opioid abuse into our communities. Mr. Sheehan provided information on the new Prescription Monitoring Program (PMP) system, known as the Massachusetts Prescription Awareness Tool (MassPAT) and mandates stemming from Chapter 52 of the Acts of 2016*, An Act Relative to Substance Use, Treatment, Education and Prevention*.

Mr. Sheehan tied these efforts into the conversation on cost impact of the Commission’s draft formulary. By reducing the number of units dispensed, these initiatives will likely serve to narrow the cost impact of the Commission’s approved substitutions.

Chapter 52 also requires the Drug Formulary Commission, by September 1, 2016, to publish, distribute, and update annually a list of FDA approved, non-opioid drug products that are effective pain management alternatives and have a lesser potential for abuse than Schedule II and III opioid drug products. Following the Commission’s approval, it will be published on the DPH website and distributed to everyone with an MCSR. The published list could be useful for prescribers, faced with a patient holding a voluntary non-opioid directive, to determine a non-opioid treatment alternative.

Mr. Jonathan Mundy presented a draft list for the Commission’s review.

Dr. Freedman asked how the list was created and what primary source references were used.

Tyson Thompson stated that MicroMedex drug compendia were used as a consensus guideline.

Mr. Feldman suggested that the list should be sorted by the type of pain indicated for use.

Dr. Freedman stated that a doctor would not prescribe without knowing that already. Eric Sheehan noted that it would be a prescriber’s responsibility to know what he is prescribing.

Dr. Theoharides suggested that the list note all brand names and any off label indications

Dr. Lemay agreed that brand names should be included if known.

Dr. Freedman suggested that there should be instructions for usage of the list.

Dr. Carr recited language he believed should be noted before the list online.

Dr. Carr asked whether the list should include custom compounded topical analgesics. He also suggested including ketamine, NSAIDs, MNDA receptor blockers like memantine and dextromethorphan, and herbal treatments like St. John’s Wart and feverfew.

Mr. Mundy noted that the legislation requires the list to be made up of FDA approved drugs only, and that compounded drugs and many alternative remedies are not so approved.

Dr. Brandoff stated his belief that a mere list would be discarded, but that it may be beyond the scope of the commission to get too deep in the weeds.

Dr. Campbell suggested that the statutory mandate to review this list annually would allow the commission to start with a bare bones list and add more later.

Dr. Carr agreed but stated that the addition of an introduction would make a smaller list more than just symbolic.

The members came up with the following introductory language through live editing:

***Non-Opioid Drug Products for Pain Management***

***The list that follows below is intended for informational purposes only and not intended to be either complete or to be used as guidance for opioid substitution.***

*Clinicians have reported favorable experience with many drug and non-drug interventions for pain. Not all of these observations are equally well supported by the best available evidence, and not all conditions or patients respond equally well to the same dose of the same agent. Competencies in the safe and effective diagnosis and treatment of painful conditions are a complex skill set. Appropriate clinical expertise should be sought in the individualized decision making required for optimal pain assessment and treatment.*

Members also asked that the list be put into XL format.

Additional drugs recommended for inclusion were anti-spazmotics, benzodiazepines, sodium channel blockers.

Mr. Sheehan asked for a motion to defer the vote on the final list until the next meeting.

* + Motion to defer: Dr. Theoharides
  + Second: Dr. Brandoff
  + All in favor: unanimous.

BREAK

Mr. Sheehan called for a break, which lasted from 3:30 PM – 3:43 PM.

**3. Evaluation**

Mr. Sheehan informed the Commission that the next agenda item was to reconsider Zohydro ER as a potential substitute. At the March 3, 2016 meeting, the Commission voted to defer the vote on Zohydro ER until the Department could present some additional information on its ADP efficacy. The Department obtained additional information to present from the manufacturer, with the goal of voting on this drug product today. Depending on the outcome, we may have another crosswalk opportunity to present later in the meeting.

Jonathan Mundy went through the presentation of Zohydro ER ADP efficacy; including the original monograph and an addendum.

Mr. Sheehan opened the discussion by asking the members to refer to the Evaluation Guide to determine if the monograph and addendum presented sufficient information to allow the commission to vote today.

Dr. Walker made a motion to approve Zohydro ER.

Dr. Feldman requested more discussion before voting. He asked the members whether they wanted to put up a drug that we may have to take back.

Dr. Jeffrey reminded the members that there is no non-abuse deterrent hydrocodone ER product on the market for which Zohydro ER would substitute. However, he noted that the commission had already approved Hysingla ER, which could substitute for Zohydro ER, if it were rejected.

Mr. Sheehan confirmed that if Zohydro ER were rejected, it would be placed on list A and could be crosswalked with a drug product on list B, as Hysingla ER is.

Dr. Jeffrey asked if there was an alternative to approving or rejecting Zohydro ER.

Mr. Sheehan responded that because a decision on this drug was already deferred by the commission in order to receive additional information, and because that information had now been presented, the only options at this time were to approve or reject Zohydro ER.

Dr. Brandoff asked if Zohydro ER would be placed on List A if it were rejected.

Mr. Sheehan confirmed and stated that List A Zohydro ER would be crosswalked with List B Hysingla ER.

Dr. Jeffrey asked whether the commission had voted to reject other ADF drug products that are now on List A.

Mr. Sheehan responded yes. Opana ER and Targiniq are on List A.

Dr. Walker asked if the committee fears that this bead technology is not up to a level of viscosity. Here we have a drug with a gel property, but if I have the option with the drug with a gel vs no gel, I will pick the gel formulation.

Dr. Theoharides wondered if the company could have blocked out whatever the gel is, and why they can’t give us all the information. He stated that he shouldn’t have to go the FDA for this information

Dr. Jeffrey stated that Hysingla ER has made a better determination that it is abuse deterrent than Zohydro ER. He noted that if the committee rejects Zohydro ER from List B, then we are saying that Hysingla ER is more abuse deterrent.

Dr. Carr stated that he did not see the components that the committee was looking for.

Dr. Theoharides wondered if the manufacturer understood the request.

Dr. Thompson confirmed that the company only provided the brief one-pager.

Dr. Jeffrey stated that, given the history of this company with the commonwealth, they had to understand that this was their opportunity to present the committee with evidence of abuse deterrence. They chose not to give us the information that will make us want to vote.

Dr. Brandoff noted the drugs unique history in the commonwealth leading to it being banned in 2013/2014. He explained that there are steps to be taken if someone wants to prescribe this right now. There are limitations and stop gaps. He asked to what degree does that factor into this conversation?

Ms. Nelson reminded the committee that when any drug on the formulary on list A is prescribed and it does not say no substitution, it will have to go back to the prescriber to get the substitution. For Zohydro, if it were approved and there were a substitute drug on List A, there would be even more steps.

Mr. Sheehan called again for a motion to approve or reject.

Dr. Jeffrey made a motion to reject Zohydro ER for inclusion on List B as a potential ADF substitute.

Mr. Sheehan asked if there was a motion to approve or reject Zohydro® as a potential substitute to move on to Component 3.

* Motion to reject: Dr. Jeffrey
* Second: Dr. Theoharides
* All in favor: Unanimous

**4. Crosswalk**

Mr. Sheehan stated that Section 13 of Chapter 17 of the General Laws guides the Commission’s work in Component 3 by offering four criteria by which we determine that a drug is a chemically equivalent substitution. In addition to the definition of the term “chemically equivalent substitution” itself, the Commission must consider accessibility, cost, drug effectiveness, and ADP efficacy.

As the Commission evaluates each pairing based on these criteria, it is important to note that the totality of the factors should determine whether a List B drug product should substitute for a List A products. Factors should be considered in order for the Commission to meet its goal of finding safer alternatives for Heightened Public Health Risk Drugs. This is especially true of cost.

Mr. Sheehan reminded the Commission that the Formulary is not mandatory for prescribers. Particularly, as we discuss cost impact, it is important to remember that a robust prescriber/patient relationship may lead a prescriber to exercise the option of noting “no substitution” when he or she believes that substituting for a safer alternative is not warranted in light of a cost increase.

Mr. Sheehan referred to the Commission’s approved definition for the term “Chemically Equivalent Substitution” as it applies to the creation of a drug formulary of abuse deterrent substitutes. He stated that the Department will present four pieces of pharmacokinetic data for each drug to provide support, in addition to FDA approval for the treatment of pain, of the comparable biologic effect produced by the designated substitute: Peak Concentration; Time to Peak Concentration; Elimination Half-Life; and Area Under the Curve.

Mr. Mundy began by facilitating the conversation about proposed Hysingla ER® pairings.

Mr. Sheehan asked if there were any questions following the presentation.

Dr. Jeffrey noted that this pairing was not a straight conversion because one is dosed every 12 hours and the other is dosed every 24 hours. He believes it creates a layer of confusion.

Mr. Mundy reminded the committee that other drug pairings had been approved with guidance.

Dr. Jeffrey agreed that guidance highlighting the difference in dosing regimen would be appropriate.

Dr. Theoharides asked why the kinetics are similar if the dosing is different.

Dr. Thompson explained that the time to peak is quicker for Zohydro ER.

Dr. Theoharides continued to question the kinetics.

Dr. Jeffrey discussed the biphasic release of this product as explanation.

Mr. Sheehan explained the difference between a motion to approve vs. a motion to approve with guidance.

Dr. Brandoff presented a hypothetical: If the dose were 40mg/day it would be Zohydro 20mg q12h vs Hysingla 40mg q24h. He asked if the PK would be different for this situation?

Dr. Thompson explained that the AUC would be similar.

Dr. Theoharides continued to state that the time to peak would be different.

Mr. Sheehan asked if there was a motion to approve the pairing of Hysingla ER® as a potential substitute for Zohydro®, with guidance.

* Motion to approve: Dr. Carr
* Second: Dr. Theoharides
* All in favor: Unanimous

Mr. Sheehan stated that the Commission would next review the proposed pairings involving Oxaydo®. He noted that as discussed in previous meetings, the work before the Commission is an evolving process based on new relevant data and information that is made available for review. Mr. Sheehan stated that the Commission would review the ADP efficacy form for Oxaydo®, which includes pertinent information about Oxaydo®, including review of the NDA review summary, as requested by the Commission.

Mr. Tyson Thompson reviewed the Oxaydo ADP efficacy form with the Commission. He noted a new study, which was not readily available for review during the evaluation phase. The FDA commented that procedures were incomplete because commercially available solvents were not used, the company did not attempt to use heat to produce reaction, and particle size reduction did not go far enough. FDA also questioned a finding that there was a statistically significant reduction in primary endpoint (drug liking, willingness to take drug again) because there was a sig sequence effect, as a result halved sample size, which made it no longer statistically significant.

Dr. Theoharides asked why the evidence of ADP efficacy was listed as a category 2. Seems it should be category 3.

Dr. Thompson explained that it was category 2 because published literature still accepted it as statistically significant, even if FDA disagreed in NDA review. Because the company was still allowed to cite the study in the package insert with a caveat, it still qualified as category 2. Oxaydo was approved as a product before any draft guidance on the issue, so they were allowed to cite study.

Dr. Theoharides stated that he wanted to change it to category 3.

Mr. Sheehan recognized a consensus to change to category 3.

Members expressed some confusion about the difference between the monograph and the ADP Efficacy form.

Ms. Nelson reminded the members that the monograph was not a comparison of one drug to another, but an evaluation of abuse deterrence of a single drug. Whereas, the ADP Efficacy Form is a tool to compare one drug to another using the four factors outlined in statute, one being the ADP efficacy of the substitute. ADP efficacy form was to help formalize documentation of our discussion of the evidence of ADP efficacy.

Mr. Mundy moved the presentation forward to compare the pharmacokinetics of Oxaydo IR and Roxicodone IR., oxycodone IR tablets and oxycodone IR capsules.

Mr. Sheehan opened it up to discussion for DFC members and reminded commission members to take into consideration cost, accessibility and ADP Efficacy.

Dr. Theoharides stated that if the question is whether to spend $1million more on a drug that is already 3 ADP, his vote was no.

Dr. Freedman, focusing on slide 8, stated that Oxycodone IR tablet would have the largest financial impact and have 99% of cost impact for all three drugs. Even if we agree with theoretical idea of abuse deterrent formulation, the $300 million dollars could be better utilized elsewhere. He suggested expanding drug recovery programs, AIDS prevention, etc.

Dr. Walker noted that an apples to apples comparison requires us to divide by person, which is $6000 per person, because of the high utilization.

Dr. Freedman accepted this point but cannot support this pairing.

Mr. Mundy provided context, stating that in the PMP, oxycodone has a high abuse potential, it is responsible for many fatalities on a daily basis. We are still trending up in deaths.

Dr. Carr reminded the members that Oxaydo’s ADP efficacy was just reclassified as category 3, which is not as strong evidence.

Dr. Feldman stated his concern that substitution would not save lives because the people dying are a different cohort than these. What do you get for $3,100 per patient? Is it worth it to spend the money?

Dr. Theoharides noted that, if the company comes back with more evidence, we can reconsider.

Mr. Sheehan confirmed.

Dr. Freedman stated that it was not clear if the opioid deaths are for ingestion vs injection. Most of the patients at his drug treatment clinic, are ingesting Rx drugs. Those who are abusing heroin, they switched because the opioids were too expensive. Sure there are some people that inject the Rx opioids, but most people are injecting heroin, not the Rx drugs. He asked if we knew how many of the total overdose deaths were from Heroin.

Dr. Thompson noted that the nature of additional Zohydro information and additional Oxaydo information is different in that Oxaydo included APD evidence that was interpreted more than one way, but Zohydro did nothing to show an assessment of clinical potential.

Dr. Walker asked if we could take Oxaydo off list B.

Mr. Sheehan noted that Zohydro was deferred and revisited when a lack of information followed by a request for additional information provided nothing. With Oxaydo, the right decision was made at the time of evaluation. This new information was presented because it may change things. New information can always change our formulary. It is a living breathing document. We could not vote on a re-evaluation of Oxaydo today because it is not on the agenda. So Oxaydo remains an approved potential substitute, that’s not changing today. We are voting on the crosswalk today.

Dr. Feldman stated the the context of cost kicks in big time here.

Eric asked if he was saying, because of the cost and that it’s category 3, there’s not enough justification to move vs. if it was category 1 or 2.

Dr. Feldman nodded.

Mr. Sheehan asked for any additional comments.

Mr. Sheehan asked if there was a motion to reject the pairing of Oxaydo® as a potential substitute for Oxycodone IR, capsule.

* Motion to reject: Dr. Theoharides
* Second: Dr. Jeffrey
* All in favor: unanimous

Mr. Sheehan asked if there was a motion to reject the pairing of Oxaydo® as a potential substitute for Roxicodone, tablet.

* Motion to reject: Dr. Feldman
* Second: Dr. Theoharides
* All in favor: Unanimous

Mr. Sheehan asked if there was a motion to reject the pairing of Oxaydo® as a potential substitute for Oxycodone IR, tablet.

* Motion to reject: Dr. Theoharides
* Second: Dr. Feldman
* All in favor: Unanimous

As part of closing remarks, Mr. Sheehan summarized the votes taken. The Commission voted to:

* Reject Zohydro® ER as a potential substitute to advance to Component 3.
* Approve Hysingla® ER as a chemically equivalent substitute for Zohydro® ER, capsule.
* Reject Oxaydo® as a chemically equivalent substitute for Oxycodone IR, capsule.
* Reject Oxaydo® as a chemically equivalent substitute for Roxicodone®, tablet.
* Reject Oxaydo® as a chemically equivalent substitute for Oxycodone IR, tablet, which is a generic of Roxicodone®.

With these votes, the Commission has now completed the work necessary for a completed draft Formulary of Abuse Deterrent Drugs. We have identified no further pairings for the drugs approved as potential substitutes in Component 3.

Some next steps involving the Commission include:

* Draft formulary and regulation review: After the votes today, the content for the first draft formulary is complete and ready for drafting by staff. The Department intends to have the draft ready to present for review at the next meeting.
* Future Meetings: The next meeting will be on Thursday, June 30 from 9:00-12:00 at 250 Washington Street. At this time, we do not anticipate needing to meet in July but ask that the members respectively continue to hold 9:00-12:00 on both July 14 and 28.

At the June 30th meeting, the Department will present a plan and schedule for the continuation of the Commission’s work. We will be setting up meetings for the Fall and Winter and will relay those dates and times at this meeting.

Having no further business before the Commission, Mr. Sheehan asked for a motion to adjourn.

* + Motion: Dr. Brandoff
  + Second: Dr. Theoharides
  + All in favor: Unanimous

The Drug Formulary Commission meeting concluded at 5:07 PM.

**Documents Presented to DFC at the *June 2, 2016* Meeting**

* DFC Minutes from May 5, 2016
* DFC PowerPoint presentation
* Draft Non-Opioid Pain Management List
* Zohydro Monograph
* Zohydro, Hysingla and Oxaydo ADF Efficacy Forms

Documents can be found at: <http://www.mass.gov/eohhs/gov/departments/dph/programs/hcq/drug-control/drug-formulary-commission.html>