Testimony of Sidney Wolfe, M.D.
Health Research Group of Public Citizen

FDA Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees

Arymo ER: extended release morphine sulfate

August 4, 2016

(I have no financial conflict of interest)

Is there a deficiency of ER Morphine products or use?

- “utilization of morphine ER remained relatively steady from 2011 through 2015”
- “morphine ER was the top dispensed drug (6.4. million prescriptions dispensed [2015]) of the ER/LA opioid analgesic market”
- The are currently 5 U.S. morphine ER products, the latter two with “abuse-deterrent” labels

Morphine ER	MS Contin	May 29,1987
	Kadian	July 3, 1996
	Avinza	Feb 20, 2002
	Embeda (morphine/naltrexone)*	Aug 13, 2009
	Morphabond**	October 2, 2015

FDA briefing document, PDF pages 44 & 47

FDA Summary at 10/21/10 AC Meeting Discussing Embeda Abuse Deterrent Labeling

- "premarketing assessment of abuse deterrent formulations using in *in vitro* manipulation and extraction studies, clinical pharmacokinetic studies and human abuse liability studies, provide information that suggests how and to what extent a product, purported to be abuse deterrent, may be manipulated and abused once the product is on the market."

- "Only post-marketing epidemiological studies will reveal the extent to which a product, purported to be abuse deterrent, will actually be manipulated and abused after the product has been on the market."

Label additions concerning “reduce abuse” (“revised April 2014”)

- “The in vitro and pharmacokinetic data demonstrate that crushing EMBEDA pellets results in the simultaneous release and rapid absorption of morphine sulfate and naltrexone hydrochloride. **These data along with results from the oral and intranasal human abuse potential studies indicate that EMBEDA has properties that are expected to reduce abuse via the oral and intranasal route.** However, abuse of EMBEDA by these routes is still possible.”

Highlights from Egalet First Quarter 2016

WAYNE, Pa., May 10, 2016 /PRNewswire/ -- Egalet Corporation (Nasdaq: EGLT

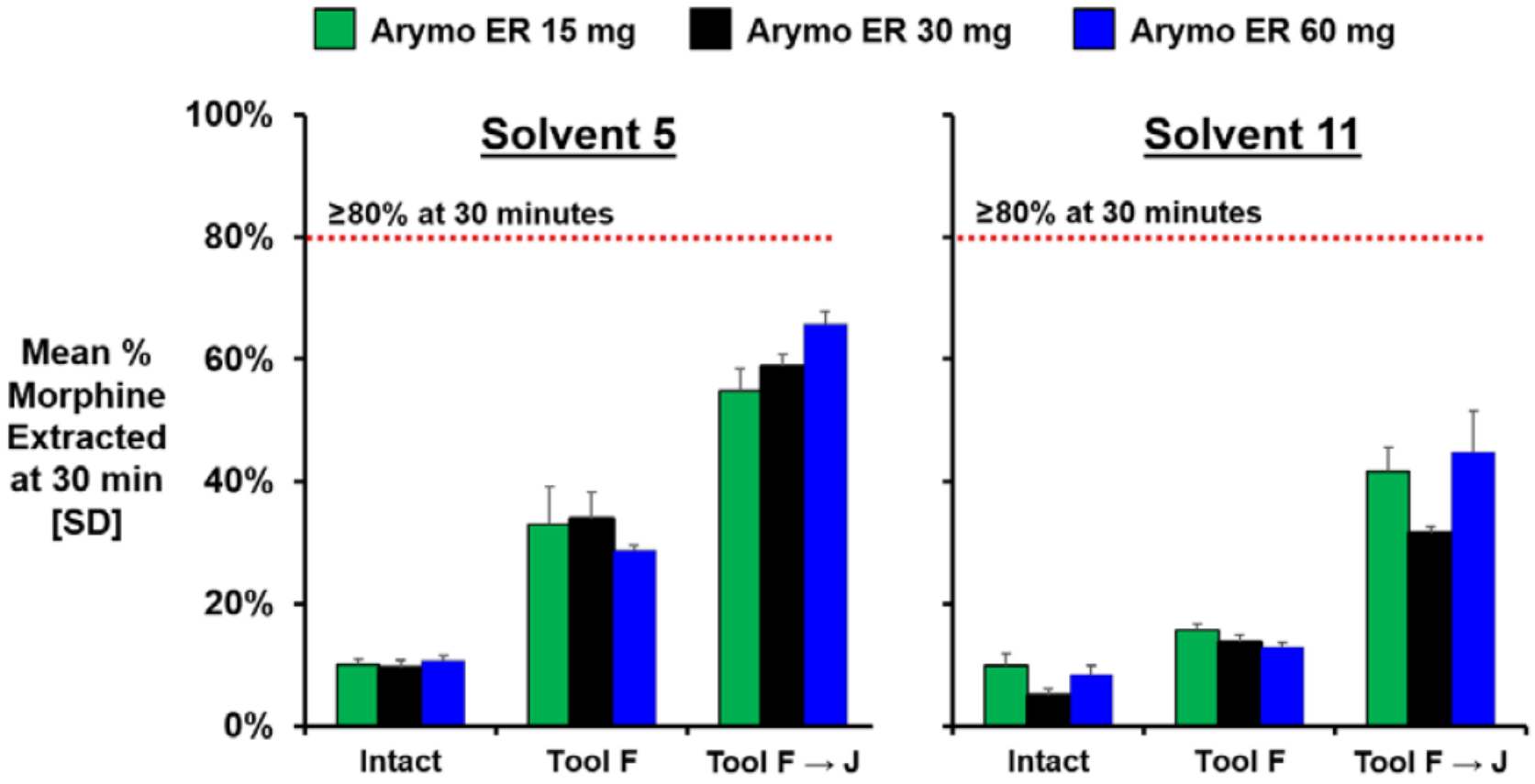
"Highlights from the first quarter include the FDA's **acceptance of our NDA for ARYMO ER, an abuse-deterrent, extended-release morphine product candidate,** and momentum building with the commercialization of our two approved products, SPRIX Nasal Spray and OXAYDO," said Bob Radie, Egalet's president and chief executive officer. **"If approved later this year, we will be able to begin promoting ARYMO ER leveraging our commercial experience over the past 12 months having built relationships with key pain health care professional, pharmacists and payers."**

Arymo ER In Vitro Extraction Studies

"For the large volume extractions, the cumulative percent of morphine released from intact tablets, has decreased with use of solvent 11, when compared to the amount released in [the] presence of solvent 5….The rate of extraction increased with cut tablets in the presence of solvents 1-12 and temperature B. The gelling features of the formulation restricted the extraction into small volumes of a solvent even with particle size reduction and any pre-treatment."

FDA Briefing Document, PDF pages 80-81

Figure 21: *In Vitro* Morphine Release in Solvents 5 and 11 at Temperature A and Agitation B at 30 Minutes



Solvents 5 and 11 are among the group of "Solvents 1, 2, and 4-12 [that] are ingestible", unlike "Solvents 3 and 13-18 [that] are non-ingestible and would be toxic to consume."

Egalet Briefing document: PDF pages 36-37

Oral Human Abuse Likeability Study
MS Contin vs EG001 (Arymo ER)
(from FDA Briefing, PDF p. 84)

Drug Abuse Test	MS Contin	EG 001	p value
Drug liking	73.3	68.3	.0385*
How high now	51.9	38.8	.0175
Would take again	70.1	62.9	.0967
Overall drug liking	69.8	65.1	.226

*FDA “Relevance...to possible abuse deterrent effect is not known.”

Conclusions

- **The 2015 FDA industry Guidance on "Abuse-Deterrent Opioids —Evaluation and Labeling" should be withdrawn and replaced with a regulation safer for patients rather than more flexible for opioid makers.**
- **Current labeling for opioids with potentially abuse deterrent features, as specified in the Guidance, has clearly encouraged companies to insert language that can easily be turned into misleading promotional material increasing, not decreasing, use and abuse.**
- **Arymo ER should not be approved because of serious concerns about increased risk and abuse, with some residual in vitro manipulability and unsatisfactory performance in oral human abuse likeability studies.**