OBSERVATIONS

THE WASHINGTON BRIEF

A morphine-oxycodone combo pill: toward the “holy grail” for opioids or a justifiably rejected drug?

Sidney M Wolfe *founder and senior adviser, Health Research Group at Public Citizen, Washington, DC, USA*

In 1997, the Australian drug company QRx took out a US patent entitled, “Production of analgesic synergy by co-administration of sub-analgesic doses of a mu opioid agonist and a kappa-2 opioid agonist” for MoxDuo, a combination pill containing morphine and oxycodone.¹ Early in its development, according to the FDA, QRx stated that its product “would provide a synergistic effect resulting in the need for lower overall opioid doses and an improved safety profile.”²

In a November 2012 memo referring to the results of a recently completed randomized clinical trial on MoxDuo, the company stated: “The 75 year search for a product having opioid efficacy without the typically associated adverse events has been compared with that for the Holy Grail.”¹ The company was referring to a review of the history of opioid research in the *British Journal of Pharmacology*.³

The QRx memo continued, “To the best of our knowledge, MoxDuo IR [instant release] is the first opioid product to demonstrate a lower risk of respiratory depression in a clinical study comparing morphine equivalent (equianalgesic) doses. These important benefits provide the potential for significant healthcare cost reductions in the treatment of patients receiving opioid therapy and is a significant step toward achieving the Holy Grail of opioid therapy.”¹

The company was referring to Study 022, in 375 patients who had a bunionectomy and were randomized to be treated every six hours with either immediate release MoxDuo or doses of morphine or oxycodone that produced equivalent analgesia.¹ QRx concluded that “episodes of oxygen desaturation were less severe in patients receiving MoxDuo IR compared to those receiving either morphine or oxycodone alone” and that, therefore, “This is an important safety advantage, one we expect will differentiate MoxDuo IR in the acute pain market place.”¹

In case of any doubt that this memo was intended for potential investors, QRx pointed out that the existing US opioid market for acute pain was driven by two products, oxycodone-acetaminophen (such as Percocet) and hydrocodone-acetaminophen (such as Vicodin) with 176 million combined annual US prescriptions. “MoxDuo IR is expected to launch in the US into a dynamically changing acute pain

marketplace in 2013 as a Schedule II opioid.” QRx cited the expected rescheduling of Vicodin and its generics to schedule II (drugs with serious potential for abuse) as one factor that “creates a significant void in the acute pain marketplace” and thus increases the sales potential of MoxDuo. It added, “A modest market share will translate into substantial sales of MoxDuo IR.”¹

If this “significant step toward achieving the holy grail of opioid therapy” sounds too good to be true, it is because it is too good to be true.

The first setback was QRx’s failure to show any synergistic effect on pain with the morphine-oxycodone combination, forcing the company to subsequently stop referring to this theoretically important but non-existent advantage that had been stated in their patent.

In June 2012, well before the glowing holy grail memo in November of that year, the FDA had preliminarily turned down MoxDuo, stating that in order to gain approval the company would have to prove, which it had thus far failed to do, that “MoxDuo either has greater efficacy than comparable doses of oxycodone and morphine, and therefore, could result in the need for a smaller total amount of opioid analgesic or is safer than comparable doses of oxycodone and morphine.”⁴ Given the FDA’s doubts, the overly positive tone of the November memo may have misled potential or actual investors.

After several additional rounds of exchange between the FDA and the company during 2013, including more detailed submissions of safety data from Study 022 and the company’s unsuccessful appeals of unfavorable FDA decisions, the drug was brought to the FDA’s anesthetic and analgesic drug products advisory committee on 22 April 2014. By then, there was no legitimate dispute that MoxDuo was no more effective than individual drugs, and the focus was entirely on the question of greater safety. Despite QRx’s claims of “lower risk of respiratory depression” the FDA concluded that there had been “no respiratory safety advantage” in the original new drug application review and that for the later review of Study 022, there was “no weight of evidence demonstrating advantage for MoxDuo.” On the issue of opioid related adverse events such

as moderate to severe nausea, vomiting, or dizziness, the FDA concluded that there was “No weight of evidence demonstrating advantage for MoxDuo.”⁵

At the end of this meeting, the advisory committee voted on two questions: has the applicant provided evidence that MoxDuo is safer than morphine and oxycodone when these drugs are used individually and at comparable doses and should MoxDuo be approved for the management of moderate to severe acute pain?

For both questions, there was a unanimous no vote.⁶

The *Encyclopaedia Britannica* describes the Holy Grail sought by Arthurian knights as “a wide mouthed or shallow vessel . . . inspired by classical and Celtic mythologies, which abound in horns of plenty, magic life-restoring caldrons, and the like.”⁷ Since the approval of MoxDuo was rejected by an FDA advisory committee and has now been rejected by the agency itself,⁸ QRx’s analogy with the holy grail—intended to boost the stature of its opioid—is misleading. The knights’ legends seem likely to outlast MoxDuo, a drug on its way to extinction.

Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned; not externally peer reviewed.

- 1 QRx Pharma. A non-confidential overview of dual opioid technology and MoxDuo, 25 November, 2012. www.citizen.org/documents/2194a.pdf.
- 2 FDA. Briefing materials for 4/22/14 advisory committee meeting (page 5). www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM393782.pdf.
- 3 Corbett AD, Henderson G, McKnight AT, Paterson SJ. 75 years of opioid research: the exciting but vain quest for the holy grail. *Br J Pharmacol* 2006;147:S153-62.
- 4 FDA briefing materials for 4/22/14 advisory committee meeting, page 20 <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM393782.pdf>
- 5 FDA presentation at 4/22/14 advisory committee meeting, slide 66, PDF page 122: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM396870.pdf
- 6 FDA. Summary minutes of the anesthetic and analgesic drug products advisory committee meeting April 22, 2014. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM397335.pdf.
- 7 Grail. *Encyclopaedia Britannica*. www.britannica.com/EBchecked/topic/240784/Grail.
- 8 QRxPharma receives complete response letter from FDA regarding MoxDuo(R) NDA. Press release, 27 May 2014. <http://online.wsj.com/article/PR-CO-20140527-903404.html>.

Cite this as: *BMJ* 2014;348:g3620

© BMJ Publishing Group Ltd 2014