Theodore F. Shults, MS, JD
Chairman
(919) 489-5407

American Association of Medical Review Officers

MRO Advisory:

6-Acetyl Morphine Reported in DOT Random Urine Test Following High Levels of Prescription Morphine Administration. Issue not Addressed in Rules.

A significant technical issue for MRO verification of 6-AM in DOT and HHS urine tests that is the identification of the 6-AM in urine tests as an artifact or "process impurity" in pharmaceutical morphine. 6-AM is present in very low levels in pharmaceutical morphine preparations. In patients being treated with higher doses of morphine, 6-AM can be detected above the cut-off threshold. This issue is not addressed in the "NEW" October 1, 2010 HHS and DOT rules.

MRO*ALERT* has previously received reports from clinicians who have seen 6-AM in patients who have been prescribed significant levels of pharmaceutical morphine. This observation has, however, never been reported to MRO*ALERT* from an MRO in a DOT or HHS urine test. It was, however, anticipated as a potential problem. (See MRO*ALERT*, Vol. XX, No.8)

Last week, following the implementation of the new laboratory rules for 6-AM reports MRO*ALERT* received a detailed report from an MRO who has observed a 6-AM in DOT random urine from a donor who is taking prescribed morphine for pain. The regulators have been advised. An additional report has also been received in a non-regulated test where the new HHS/DOT laboratory protocol is being followed.

These new observations are due to the increased use of morphine in pain management and the implementation of a new specific and sensitive assay for 6-AM and new laboratory protocols for reporting opiate results, which went into effect October 1, 2010. (Technically this could have happened in the past, but there have been no reports of this to MRO*ALERT*).

6-AM is a low level "process impurity" in morphine sulfate and morphine HCL (oral or parenteral formulations). The urinary concentration of morphine in donors who have prescriptions for morphine in whom 6-AM has been reported is significant. In one case, the morphine concentration is greater than 400,000 ng/mL; in another, it is around 300,000 ng/mL morphine, but the 6-AM was also over the 10 ng/mL cut-off. In the DOT case referenced above, the morphine is reported to be about 200,000 mg/mL.

This 6-AM process impurity is not a new observation; many labs involved in monitoring opiates and medical examiner toxicology post-mortem cases are aware of "process impurities", but many laboratories in workplace drug testing have never had to deal with this, or haven't seen it.

The pharmaceutical industry's Expert Working Group of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines note that the allowable level of impurities in new drug products, that do not have to be listed on the Full Prescribing Information should be below 0.1% (as long as it is not toxic and doesn't change potency significantly). These are voluntary standards. The FDA has a similar threshold and does require the manufacturer to file a list of impurities and concentrations at time of registration. 6-AM is listed as a process impurity of morphine in these registrations.

(A list of other relevant process impurities will appear in the September/October 2010 issue of MRO*ALERT.*)

Although these levels of impurities are quite low and clinically insignificant - these impurities will show up above the urine drug testing cut-offs following higher dosing, where they become critically significant. This is what is purportedly being observed with pain management patients and now with workplace donors. The other most significant process impurity that MROs have run into is the patient on oxycodone who had hydrocodone in the urine.

Unofficial MRO Guidance

The best interim guidance for MROs, until DOT, NRC or HHS issues specific guidance, is for MROs who are verifying a 6-AM and have a high morphine level and a donor who is legally taking morphine would be to strictly follow the existing rules (including addressing any safety concerns over high-level morphine use and safety sensitive performance) and contact the appropriate regulator for additional guidance.

In non-regulated tests where all the facts suggest 6-AM as a process impurity of pharmaceutical morphine, the MRO should contact the DER to discuss the employer's response and policy. Some consideration should be given to having the donor examined for signs of opiate abuse and the appropriateness of a fitness for duty evaluation.

Ethically, the MRO should also discuss the possibility of process impurities as a source of the 6-AM with the donor.

Calling MRO*ALERT* is appreciated and contacting the Lab Director is also good advice.