Pharmacokinetics, ADMET Challenges

1. Study the role of cyclooxygenase isoforms and specificity of COX inhibitors and answer the following questions:

    a. Why were COX-2 specific inhibitors more toxic than traditional NSAIDs?

    b. Why was Vioxx (Rofecoxib) noticeably more dangerous than Celecoxib?

    c. How could Merck have prevented this debacle?

2. Read the paper "On-line Formation, Separation, and Estrogen Receptor Affinity Screening of Cytochrome P450-Derived Metabolites of Selective Estrogen Receptor Modulators" by Sebastiaan Liempd and colleagues. This paper discusses application of bioreactors and modern analytical techniques for the identification of drug metabolites. You may also want to perform independent research about biological activity of Answer the following questions:

    a. What do the authors mean when they that their methodology is based on the *hyphenation* of a bioreactor to solid phase extraction and gradient HPLC?

    b. Outline the sequence of operations that allowed identification of major metabolites of tamoxifen

    c. Tamoxifen is used to treat estrogen receptor positive breast cancers. Antidepressants, such as fluoxetine (Prozac) are slow substrates for CYP2D6, effectively inhibiting the ability of this enzyme to metabolize tamoxifen. Comment on a proposal that women who are diagnosed with estrogen receptor dependent breast cancer should be prescribed Prozac to prevent any possible depression that often accompanies cancer diagnosis.

    d. There are several concerns about side effects of tamoxifen. Two serious issues appear to be (i) induction of heart arrhythmias via inhibiting ion currents in the heart tissue, and (ii) increased risk of uterine cancer.
       1) Why is tamoxifen, which acts as estrogen receptor antagonist in the breast tissue, increasing the risk of uterine cancers?
       2) Would you expect that a more hydrophobic analogue of tamoxifen would display better safety profile? Justify your answer
       3) Would you expect that isosteric replacement of the ether oxygen with the CH_2 linker is a way to produce a safer analogue of tamoxifen?

    e. Tamoxifen and raloxiphene are two of the most widely prescribed selective estrogen receptor antagonists. A third drug, lasoxiphene, is currently approved only in the European Union, partially because FDA is concerned that it may cause cancers in the lining of the uterus. How could you use the methodology outlined in the Liempd paper to identify which metabolites of lasoxiphene bind to the estrogen receptor?