



XenoTech carries an extensive selection of subcellular fractions for drug metabolism-related research.

Subcellular fractions are widely used in drug discovery and preclinical drug development to evaluate species differences, similarities in metabolite formation by various species, metabolic stability, *in vitro* intrinsic clearance, reaction phenotyping (enzyme mapping), inhibition of CYPs and UGTs, and enzyme induction.

Our standard products feature fully-characterized liver subcellular fractions from the following toxicologically-relevant species:

- Human
- Monkey
- Dog
- Rat
- Mouse
- Minipig
- Rabbit
- Guinea pig
- Hamster

Advantages of Using XenoTech's Subcellular Fractions

- Large donor pools minimize lot-to-lot variation and increase the long-term availability of each lot.
- All lots are prepared and characterized according to Standard Operating Procedures.
- The quality of all subcellular fractions is governed by the assigned Study Director, the Study Manager, and XenoTech's Quality Control Unit.
- Preparation procedures allow for the production of matching S9 and microsomal donor pools.
- Characterization assays for human pools are performed under conditions to obtain V_{max} values.
- CYP and UGT activity characterization assays are performed with XenoTech's automated liquid handling and incubation system along with LC-MS/MS analysis. Enzymatic activity assays are end-point assays performed in triplicate with saturating concentrations of the probe substrate.
- Established acceptance criteria and positive controls are to determine the acceptability of lots.

Pooled Human Liver Microsomes

XenoTech features pooled products that approach enzymatic activity rates typically expressed in the general population. These typical rates are determined from individually characterizing hundreds of livers for enzymatic activities prior to pooling. Individual donors that comprise these products are each significantly represented in the pools we prepare. XenoTech offers the 200-donor XTreme pool as well as our standard 50-donor pooled human liver microsome product. The XTreme 200 pool is the largest commercially-available pool of human liver microsomes. Large pool size yields average activities and provides long-term use of the same lot of human liver microsomes over time.



Characterization of Human Liver Microsomes

XenoTech's microsomes have been trusted to provide the most reliable characterization in the industry. Each lot of human liver microsomes comes with the following information:

- Cytochrome P450 content
- Cytochrome b_5 content
- NADPH-cytochrome c reductase activity

Validated LC/MS/MS Methods

| Enzyme | Marker substrate reaction (pmol/mg/min) |
|----------|---|
| CYP1A2 | Phenacetin O-dealkylation |
| CYP2A6 | Coumarin 7-hydroxylation |
| CYP2B6 | Bupropion hydroxylation |
| CYP2C8 | Amodiaquine N-dealkylation |
| CYP2C9 | Diclofenac 4'-hydroxylation |
| CYP2C19 | S-Mephenytoin 4'-hydroxylation |
| CYP2D6 | Dextromethorphan O-demethylation |
| CYP2E1 | Chlorzoxazone 6-hydroxylation |
| CYP3A4/5 | Testosterone 6 β -hydroxylation |
| CYP3A4 | Midazolam 1'-hydroxylation |
| CYP4A11 | Lauric acid 12-hydroxylation |
| FMO | Benzydamine N-Oxidation |
| UGT1A1 | 17 β -estradiol 3-glucuronidation |
| UGT1A4 | Trifluoperazine glucuronidation |
| UGT1A6 | 1-Naphthyl glucuronidation |
| UGT1A9 | Propofol glucuronidation |
| UGT2B7 | Morphine 3-glucuronidation |

Treated Animal Liver Subcellular Fractions

Treatment of animals with various xenobiotics may cause a marked induction of liver microsomal CYP levels, which, in chronic studies, may be associated with liver and/or thyroid tumor formation. XenoTech offers subcellular fractions from Cynomolgus monkeys, Beagle dogs and Sprague-Dawley rats treated with prototypical inducers to serve as positive controls for *ex vivo* enzyme induction studies.

Microsome Kits

Reaction Phenotyping Kit (H0500) (U.S. Patent # 5,478,723)

This kit helps predict pharmacokinetic variability and potential for drug-drug interactions by identifying the human enzymes responsible for metabolizing a drug. Samples in this kit are carefully selected to minimize correlations or outliers that can interfere with reliable results.

Contents:

- 1 vial from each of 16 individuals (4 mg/vial)
- 2 vials of pooled human liver microsomes, mixed gender (10 mg/vial)
- Comprehensive characterization data packet including correlation tables for CYPs, FMO and UGT enzymes

Species Kit (K1500)

CYP-dependent metabolism can vary widely from one species to another. This kit provides liver microsomes from four non-human species to compare their metabolic profiles to the profile of humans to assess the most relevant animal model for pharmacokinetic and toxicity studies.

Contains one vial each of liver microsomes from 5 species:

- Human (male, pool of 10)
- Cynomolgus monkey (male pooled)
- Beagle dog (male pooled)
- IGS Sprague-Dawley rat (male pooled)
- CD-1 mouse (male pooled)

Extrahepatic Subcellular Fractions

Subcellular fractions from small intestine, kidney and lung are often used to evaluate the potential for extrahepatic metabolism of a drug candidate. Our Products Department developed proprietary methods to maintain CYP and other enzymatic activities in these extrahepatic fractions during their preparation. Standard extrahepatic products include intestine, kidney, lung and skin subcellular fractions from human, Cynomolgus monkey, Beagle dog, IGS Sprague-Dawley rat, CD-1 mouse and Gottingen minipig.

Genotyped (Genetically-Defined) Human Liver Microsomes

Genotyped human liver microsomes can be used to investigate the influence of allelic variance on the safety and efficacy of new molecular entities. XenoTech offers microsomes from the following polymorphically-expressed enzymes:

- | | |
|-----------|----------|
| • CYP2C9 | • CYP3A5 |
| • CYP2C19 | • UGT1A1 |
| • CYP2D6 | • UGT1A9 |

Microsomes for each of these enzymes are available in high activity, moderate activity and no activity categories, according to their genotype, characterized for each lot, along with enzymatic activities measured using our validated LC-MS/MS methods.

Custom Products

On average, we prepare more than 50 different customized cellular and subcellular preparations from over 15 different species each year. All of these preparations are made and characterized according to our customers' requests. If you are in need of subcellular fractions that are not commercially available, XenoTech can help.

Examples of Custom Preparations:

- Individual human liver subcellular fractions (including poor and extensive metabolizers)
- Demographically-defined human pools (i.e., ethnicity, age, etc.)
- Customized human liver microsome pools
- Non-standard rodent strains, farm animals
- Non-standard tissue, such as adrenal gland

Safety, Handling and Storage



XenoTech accepts only non-transplantable tissue from human donors who test negative for HIV 1 and 2, HTLV, and Hepatitis B and C. All animal tissue is acquired through AALAC-accredited facilities from healthy animals and in accordance with CITES regulations as they apply to non-human primates, which have tested negative for SBV, SRV and SIV. We strongly recommend that all samples are treated as potential biohazards, and universal precautions are excersized when handling and disposing of these products. Cellular and subcellular fractions are intended for *in vitro* use only. These products are shipped overnight on dry ice and should be stored at or below -70°C.

Order these products online at www.xenotech.com or contact a customer service representative at **913.438.7450**.