

DonorPlex[®] Pooled Donor Suspension Hepatocytes

With 10-, 20-, and 50-donor single and mixed gender pools of hepatocytes and a proprietary prediction algorithm, DonorPlex[®] Hepatocytes go beyond your expectations for a robust and consistent pooled donor hepatocyte product.

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Introduction

Understanding hepatic drug metabolism using primary hepatocytes is important in order to meet stricter regulatory and safety testing requirements for market approval. To fully understand a population-based response for metabolism, researchers must use numerous different hepatocyte donors to get an average response. To address this need, cryopreserved hepatocytes that represent a pool of multiple individual donors are commonly used.

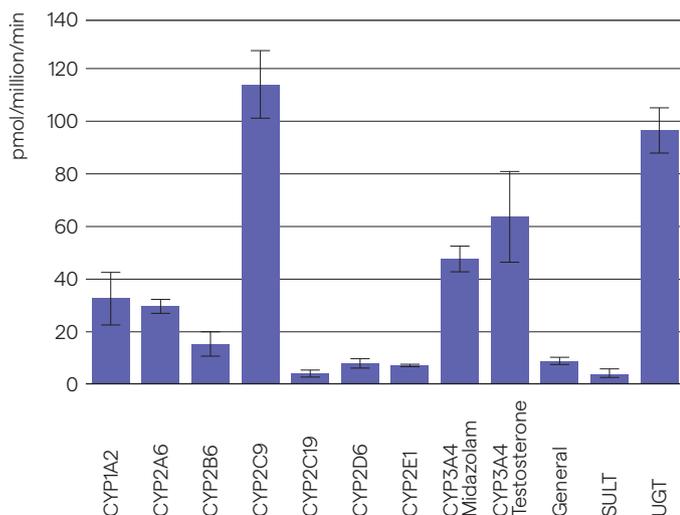


Figure 1. Robustness of pooling process. Three batches of 20 donors with identical donor composition were pooled on three separate dates. Activity values are shown representing our capability to reproduce pooled lots.

Catalog No.	Product Description
HUCS10P, HUCS10F, HUCS10M	10 donor mixed gender or single gender
HUCS20P, HUCS20F, HUCS20M	20 donor mixed gender or single gender
HUCS50P	50 donor mixed gender

Table 1. Portfolio of our current DonorPlex[®] Hepatocyte Products.

We are now producing high quality cryopreserved pooled donor suspension hepatocyte lots. To further improve the utility of pooled donor hepatocytes, we also developed a proprietary algorithm to predict activity phenotype defined by customer specifications. Using our large inventory of single donor human hepatocyte lots and this unique algorithm, we can produce a variety of lots to fit customer's needs (Table 1).

Robust manufacturing

We optimized a robust manufacturing process to produce pooled donor lots with little variability. In Figure 1, we show the ability to reproducibly create a lot with the same phenotype on multiple different dates. The optimized manufacturing process also ensures each lot of pooled suspension hepatocytes meet stringent yield and viability specifications.

Prediction algorithm

Large batches of hepatocytes from pooling donors together can supply research programs for many years. When a new batch is needed, many researchers would like the new batch to be similar to the previous one. We use a proprietary algorithm to predict final activity of a pooled donor batch prior to manufacture. Shown in Figure 2 are the results of the predicted activity of a 20-donor pool compared to the actual activity. This gives us the unique ability to work with customers to create lots with specific CYP activity, or produce lots with CYP levels that represent the average population.

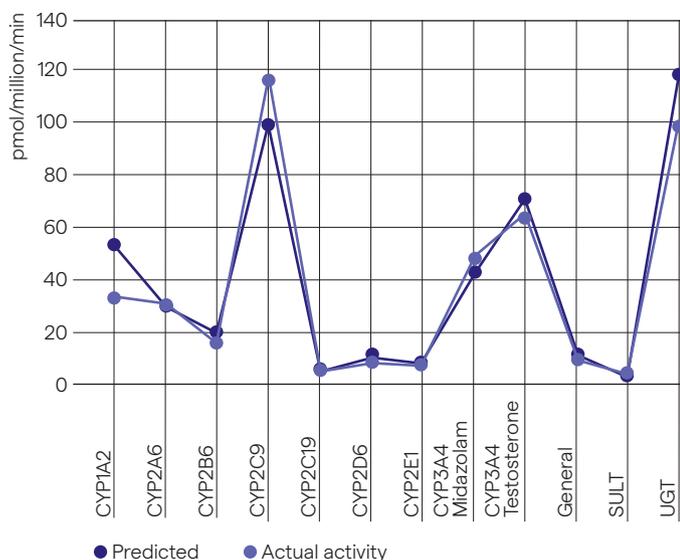


Figure 2. Prediction algorithm. Predicted activities versus measured activities for eight CYP enzymes, general ECOD metabolism and ECOD phase II enzymes (UGT and SULT) when individual donors are pooled together.

Transporter verification

Since pooling requires multiple freeze and thaw steps, transporters which reside on the cell surface can be damaged. To check whether the pooling method preserved transporter activity, we tested pools for OAT1B1/3, OCT1/2, and NCTCP active uptake. Results demonstrated that our pools have active transporters with fold change activity greater than 2-fold when compared to passive uptake (data not shown).

Characteristic	Substrate	Marker Metabolite (pmol/million cells/min) (reported value)
CYP1A2	100 µM Phenacetin	Acetaminophen
CYP2A6	5 µM Coumarin	7-Hydroxycoumarin
CYP2B6	100 µM Bupropion	Hydroxybupropion
CYP2C9	50 µM Diclofenac	4-Hydroxydiclofenac
CYP2C19	30 µM Mephenytoin	4-Hydroxymephenytoin
CYP2D6	10 µM Dextromethorphan	Dextrorphan
CYP2E1	200 µM Chlorzoxazone	Hydroxychlorzoxazone
CYP3A4	100 µM Testosterone	6β-Hydroxytestosterone
CYP3A4	10 µM Midazolam	Hydroxymidazolam
General metabolism	100 µM 7-Ethoxycoumarin	7-Hydroxycoumarin
SULT	5 µM 7-Hydroxycoumarin	7-Hydroxycoumarin Sulfate
UGT	200 µM Hydroxycoumarin	7-Hydroxycoumarin Glucuronide

Table 2. Pooled donor suspension CYP specifications.

Summary

With our optimized pooling procedure, we can provide you with a variety of DonorPlex® Hepatocyte Configurations and sizes for your metabolism testing needs. Moreover, our predictive algorithm, helps to create customizable lots to meet specific CYP activity requirements.

Pooled donor suspension specifications:

Yield $\geq 5 \times 10^6$ viable cells/vial

Customizable CYP, ECOD, and phase II ECOD metabolism activity, as measured by LCMS metabolite formation using model chemicals (Table 2)

OAT1B1/1B3, OCT1, and NCTP transporter activity ratio in a facilitated active uptake study using model chemicals

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