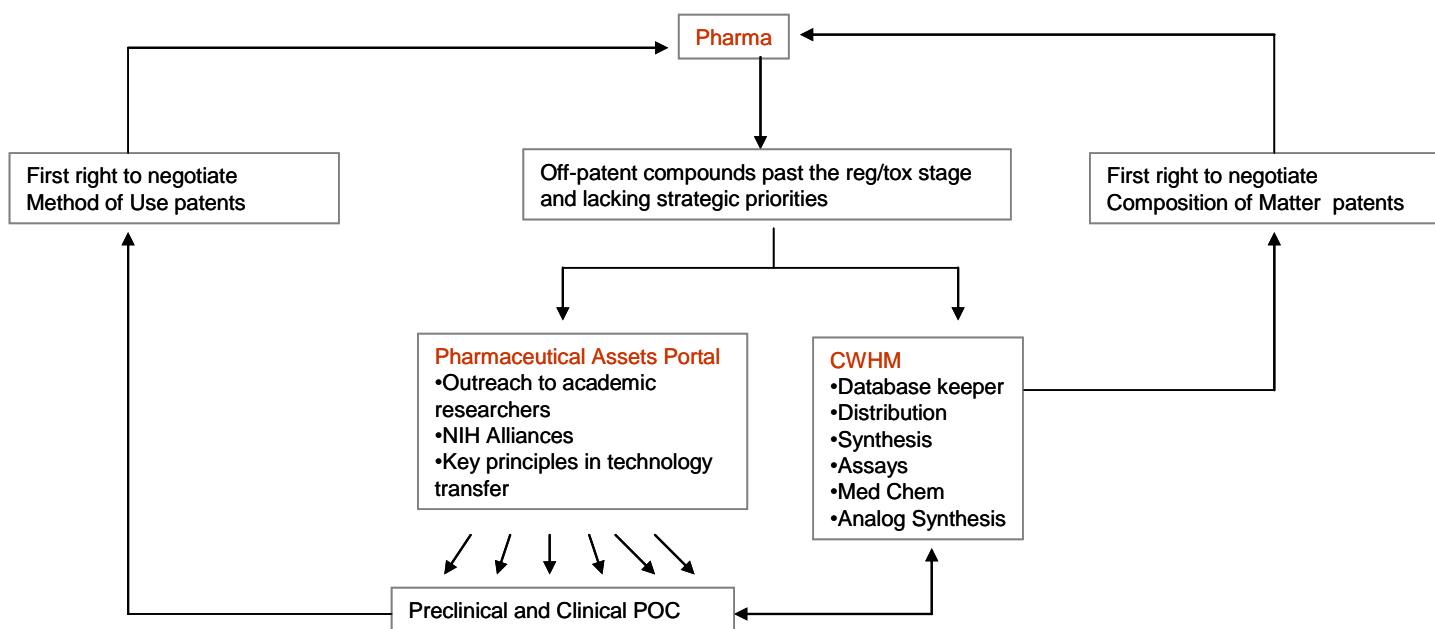


## The CTSA Pharmaceutical Assets Portal and the Center for World Health and Medicine

### Proposal for repurposing of off-patent compounds by the Public-Private Consortium

The CTSA Pharmaceutical Assets Portal ([www.ctsapharmaportal.org](http://www.ctsapharmaportal.org)), the Center for World Health and Medicine (CWHM; [www.cwhm.org](http://www.cwhm.org)) and the pharmaceutical industry will join in the effort to find new uses for discontinued drugs, *specifically focusing on compounds rapidly approaching or having reached their patent expiration terms*. This consortium will contribute to the establishment and development of an Off-Patent Discontinued Drug Library (OPDDL). This is an extension and a significant enhancement of the existing effort of the CTSA Pharmaceutical Assets Portal currently supported jointly by NCCR and Pfizer.

The ultimate goal of this proposal is to leverage existing compounds that are no longer of strategic priority to advance mechanistic understanding of human disease. Integration of academic investigators into collaborative repositioning efforts would substantially increase the knowledge base and the pool of methodologies available for proof-of-concept studies. This research will undoubtedly result in an increased number of approved drugs for new indications and considerable public benefit.



### Background and Significance

The CTSA Pharmaceutical Assets Portal is a project sponsored jointly by Pfizer and the NCCR (National Council for Research Resources). The Portal made significant inroads in establishing collaborations between pharmaceutical companies and CTSA researchers in the area of drug repositioning, which means finding new uses for old drugs. The Portal is managed by the UC Davis Clinical and Translational Science Center on behalf of 46 universities around the US. The Portal also provides a critical link with NIH intramural scientists. The Portal serves as a focal point and a convener for development of the key provisions in the technology transfer.

The Portal members are given an unprecedented opportunity to collaborate with the Pfizer Indications Discovery Unit, a division of Pfizer vested with finding new uses for old drugs. The Compound Portfolio that Pfizer has made available for the CTSA requests contains: marketed compounds, compounds under active investigation, inactive compounds with previous clinical exposure, and preclinical compounds. Information about some of these compounds may be found from publically available sources. But the Portal's unique attribute is providing the path to little or unknown compounds in Pfizer's portfolio. Because companies do not always publish the results of their investigations, information on as many as half of the compounds that enter clinical development remains obscure to the larger research community. Pfizer is encouraging inquiries about the existence/availability of little-known Pfizer compounds that target specific mechanisms of interest through a simple web-based inquiry form.

The ultimate goal is to leverage existing compounds to advance mechanistic understanding of human disease, resulting in novel treatments for patients. Integration of academic investigators into collaborative repositioning efforts with Pfizer would substantially increase the knowledge base and the pool of methodologies available for proof-of-concept studies. These matches will undoubtedly result in an increased number of approved drugs for new indications and considerable public benefit. Membership in the Portal is free for CTSA researchers, and currently over 350 people are registered.

### **Challenges of the Pharma Portal Approach**

There are two main barriers for successful execution of this unique collaborative opportunity.

1) The lack of dedicated funding to the proof-of-concept studies in animals and subsequent proof-of-concept studies in a small number of human subjects. While the Portal's members are encouraged to apply via existing NIH Institute-specific funding routes, these routes are "crowded" and not designed for rapid evaluation and support of small POC studies. The venture will seek new funding sources with *nimble, modern mechanisms* to support the projects that specifically originated from the Portal and from OPDDL. Such pilot funding (in \$50K to \$200K range) combined with the streamlined funding mechanism will *catapult multiple investigations* to find new uses for shelved compounds.

The enthusiasm for such a mechanism is evident from a recent collaborative agreement between Washington University in St. Louis and Pfizer Indications Discovery Unit. The latter agreed to allocate \$3.5M/year towards repositioning POC studies using a selected subset of the Compound Portfolio. However, this funding is not available for other universities interested in participating under the CTSA Pharma Portal path.

2) The fact that the information surrounding industry Compound Portfolios is vigorously protected due to the competitive concerns. In the above example, Pfizer Indications Discovery released some background information, including mechanism of action, to the researchers at Washington University under the master CDA. However, this information is not available for other universities interested in participating under the CTSA Pharma Portal path. Instead, Pfizer is encouraging inquiries about the existence/availability of little-known Pfizer compounds that target specific mechanisms of interest. These "unknown" assets are dubbed "Dream Compounds", meaning those compounds that the researcher always wanted to have but did not know existed. This path solicited only a few requests for Dream Compounds as academic researchers prefer to have at least some information available upfront.

The proposal for creation of an Off-Patent Discontinued Drug Library (OPDDL) will help resolve this issue by refocusing the CTSA Pharma Portal efforts on a specific subset of Compound Portfolios owned by pharmaceutical companies. These are compounds *rapidly approaching or having reached*

*their patent expiration terms and that are no longer of strategic priority to the companies.* With enough incentives, such as external funding, certain IP privileges and data access, we believe that the companies may be persuaded to contribute their otherwise “unused” assets to the PharmaPortal/CWHM consortium.

### **Operational Details**

- The CTSA Pharmaceutical Assets Portal will be a conduit to the global academic research community, intramural NIH scientific community, funding agencies and technology transfer forums.
- The Center for World Health & Medicine (CWHM) will provide a critical mass of highly experienced former pharmaceutical industry scientists. These highly skilled scientists collectively possess expertise seldom found concurrently in academic and government settings. The Center will utilize its expertise in translational pharmacology and medicinal chemistry capabilities to create new molecular entities on the basis of the discontinued off-patent compounds brought into the venture. The CWHM expertise spans each of the critical disciplines required to discover and develop safe and effective drugs, including:
  - Medicinal chemistry
  - Structure-based drug design
  - In vitro and in vivo drug pharmacology and interspecies modeling
  - PK/PD analysis
  - Drug metabolism
  - Cell and molecular biology
  - Protein expression and purification
  - Drug formulation and delivery
  - Toxicology
  - High throughput screening
  - Biomarker development

This legacy pharmaceutical industry expertise uniquely positions the CWHM to become a valuable interface between academic research discoveries and the knowledge of what is required to transform these discoveries into viable clinical entities.

- The CWHM and the Portal will collaborate with a consortium of Pharmaceutical companies to identify and secure discontinued (shelved) drug candidates that have advanced past the pre-clinical reg/tox stage (pre-Phase I to Phase III clinical trials), that no longer have IP protection (patents have expired, are about to expire or have lapsed) and/or no longer have strategic importance to the company.
- Due to the advanced nature of such compounds, ample material most likely resides within the Pharma Company’s compound repository. The request would be to provide a suitable amount of each candidate compound (~10 grams initially, if available) to contribute to this unique Off-Patent Discontinued Drug Library (OPDDL). The material shall be accompanied by the structure and mechanism of action for the original intended indication. Additional information may be provided at the donor’s discretion.
- The CWHM will be the central repository of the OPDDL collection. An identifier will be assigned to each compound deposited into the OPDDL collection that correlates to the compound,

its structure, mechanism of action and the Pharma Company donor. Thus, the compounds could be released without disclosing their structures.

- Researchers or academic institutions registered with the Portal can request access to the OPDDL collection by either requesting compounds that are associated with a particular mechanism of action (renin inhibitors, for example) or by doing an empirical screen of the entire collection against a new target with a developed assay. In the latter case, the collection will be plated out in solution and shipped to the requester. For compounds associated with a particular mechanism of action, individual compounds can be plated out in solution or provided as a small quantity of dry powder. If an assay has been developed, and can be readily adapted, the CWHM can screen the library if so desired.
- If screening identifies a hit, compound scale-up can be requested at the CWHM for additional studies. More likely, however, the hit will provide a high-quality lead molecule that will need to be optimized for the new target. Analogue drug design and analogue synthesis can be carried out by the highly experienced medicinal chemistry team at the CWHM in collaboration with the requesting academic researchers. If successful, the collaboration will then compile a complete pre-clinical data package sufficient to enter human clinical trials. This will be greatly facilitated by the pharmaceutical industry experience of the CWHM scientists, as previously described.
- All data generated by this procedure would be kept confidential to the collaborating entities in order to preserve the potential for new IP and would subsequently be shared with the “donor” pharmaceutical company. The Donor company will have first right to negotiate the exclusive or non-exclusive rights on IP incorporating their compound. The privacy of data streaming from collaborating partners could be protected by utilizing secure data sharing sites such as Collaborative Drug Discovery ([www.cdd.com](http://www.cdd.com)). Afterwards, the data would be made publically available through the typical publication/presentation route.
- If equipment, overhead and FTE’s are funded, costs to the requesting researchers would be for shipping and handling of compounds and plates and incidental supplies and reagents for scale-up or analogue synthesis only.

#### **Advantages for the Pharmaceutical Companies that join the Consortium:**

- Most Pharma companies have publicly expressed their desire to balance commercial viability with social responsibility. This proposal provides a mechanism to facilitate this stated objective by making freely available discontinued drug candidates that are already in the public domain, via expired or lapsed IP, and that no longer have strategic value to the company.
- Pharma Companies would gain access to a vast and diverse number of global researchers with expertise in many varying disease areas. This increases the possibility that the group effort may identify newfound utility for the discontinued drug candidates that would otherwise remain dormant on the shelf. The data for each compound will be tracked. If one of the donated compounds leads to a repositioned opportunity, the parent “donor” company would get the first right to negotiate exclusive or non-exclusive license on the new IP incorporating their compound.
- Pharma Companies get many independent requests from academic researchers for compounds such as the ones proposed. Contributing to the OPDDL collection puts these compounds into a central repository, making the system more efficient and freeing Pharma company employees from processing such requests.
- Public Relations: Being a member of this Consortium would bring high visibility and recognition by contributing assets that have the opportunity to be useful toward neglected diseases.

### **What would be required of the Pharmaceutical Companies?**

- Identification of discontinued (shelved) drug candidates (from late pre-clinical [passed reg/tox] through Phase III human clinical trials) that no longer have IP protection (expired or lapsed), are about to lose IP protection, or are no longer of further interest to the company.
- Provide to the Portal the compound as a dry powder (~10 grams, more if available, less if not), its chemical structure and mechanism of action.

### **Proposed safeguards to the participating Pharmaceutical Companies:**

- All donated compounds to the OPDDL would be coded and structures would not be publically disclosed. The researchers would be able to request compounds based on their disclosed mechanisms of action or screen the entire collection.
- Structure ID, analogue optimization and pre-clinical data generation would be carried out under confidentiality agreements with CWHM.
- The “donor” pharmaceutical company would have the first right to negotiate an exclusive or non-exclusive license for any new IP incorporating their donated compound.
- Public disclosure of data generated through this OPDDL process would occur as soon as determined feasible in order to protect potential new IP generation.
- It is proposed that these and any additional “ground rules” be established and agreed upon collectively by representatives from each of the pharmaceutical companies that make up the OPDDL Consortium.

### **Funding Requirements:**

Off-Patent Discontinued Drug Library (OPDDL) is an extension and a significant enhancement of the existing effort of the CTSA Pharmaceutical Assets Portal. If executed properly, this venture would catapult multiple proof-of-concept studies in animals and human subjects, potentially resulting in numerous new indications and *considerable public benefit*. The path to clinical trials for the compounds from OPDDL is significantly streamlined, as all of them have already undergone toxicity assessment required by the FDA for initiation of human studies. ***Funding of both OPDLL infrastructure and POC studies is necessary*** for lifting these shelved compounds from obscurity to medical use.

This venture will be identifying multiple funding partners within the NIH, foundations, non-profit organizations dedicated to certain diseases, and other less traditional sources to finance this project.