CASE STUDY

Insights to drive preclinical safety programs

EXECUTIVE SUMMARY
This paper discusses a preclinical decision framework around a theoretical drug.

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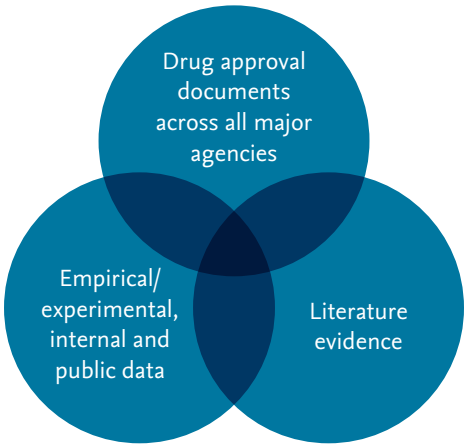
Current Industry Challenge

Figure 1. Evidence-Sources to support preclinical drug development.



The fact that a potentially lethal disease such as HIV can be controlled by drugs speaks to the great potential of pharmaceutical treatment. Examples like this fuel the imagination and passion of biologists, chemists and other scientists who engage in the process of discovering and developing new drugs. The path of drug development is, however, not always easy, and surprises can arise at several steps in the process. Some of the most unwelcome surprises are unforeseen toxicities brought to light in preclinical testing and/or highlighted by regulatory review. Therefore, extensive effort and resources are invested to incorporate pre-existing information into the design of a drug development strategy that anticipates toxicities and addresses regulatory concerns ahead of time.

Seeking to uncover a wide range of potential drug-related toxicities, preclinical safety programs often follow a standard template identified in the ICH guidelines (1,2) to determine primarily "off-target" effects. However, certain drug target and molecule classes may have safety concerns that trigger regulatory concerns and could require modification to the standard safety assessment studies. While information on such class-related toxicities can be found in the medical literature, particularly relevant to the design of a preclinical safety program are concerns raised and documented by regulatory authorities.

Ideally, a well-informed preclinical safety program should collect evidence from multiple sources, including regulatory documents, literature and empirical or experimental data (Fig. 1). Collecting regulatory data is challenging, but also highly informative, because it provides precedent data and a glimpse into the thought process of regulatory agencies during the drug approval process.

An impactful inspection of drug approval information includes the following analyses:

- Examine the landscape of regulatory documents for a given unique drug target.
- Scrutinize preclinical and clinical safety findings for approved drugs that engage that target to identify toxicities or adverse effects noted in regulatory reviews, and to assess if the preclinical safety strategies used adequately anticipated clinical safety findings.
- Explore the landscape of regulatory documents mentioning particular safety concerns for any unique characteristic of the molecule or its class.
- Finally, based on the information gleaned from the investigations above, determine if modifications to a standard safety assessment strategy should be incorporated.

This paper examines the work flow described above on a theoretical drug indicated for metastatic renal cancer.

Renal Cancer Disease

Examining existing drug approval data for mRCC therapeutics may provide insights to strengthen study designs for the theoretical mTOR inhibitor and to address issues confronted by earlier compounds.

Table 1: Renal cancer stages and five-year survival rates

Renal cancer stage
Stage 1: tumors 7 cm or less in diameter and confined to the kidney **Five-year survival rate:** 81%
Stage 2: tumors more than 7 cm in diameter but still confined to the kidney **Five-year survival rate:** 74%
Stage 3: cancer has invaded a nearby lymph node, blood vessel or the fatty tissue surrounding the kidney **Five-year survival rate:** 53%
Stage 4: cancer has spread to lymph nodes in other parts of the body or to another organ **Five-year survival rate:** 8%

Source: American Cancer Society and Cancer.net 2014.

Renal cancer affects approximately 64,000 people in the United States, and mortality rate for 2014 is estimated at 22% (3). Renal cell carcinoma is the most common type of kidney cancer in adults, representing about 80% of cases. Despite recent improvements in therapy, the overall survival for metastatic stage 4 renal cell carcinoma patients remains poor.

Today, the rapamycin-analogues everolimus and temsirolimus are indicated for poor-risk patients (4,5). Importantly, these two drugs engage the mammalian target of rapamycin (mTOR), a protein that has been implicated in several other cancers (6,7). Multiple studies have led to a better understanding of the mTOR pathway and, with this knowledge, to an interest in second-generation mTOR inhibitors that modulate the pathway more specifically (4).

Recent investigations suggest that the mTOR complex 2 (mTORC2) is a promising drug target. The analysis of the mTORC2 illustrated in this paper is based on hypothetical mTOR inhibitor that covalently binds to the target, and may offer advantages over existing therapies.

Whereas in the past such molecules might have been viewed as potentially too toxic, several irreversible inhibitors have recently received FDA approval (8). Examining existing drug approval data for mRCC therapeutics may provide insights to strengthen study designs for the theoretical mTOR inhibitor and to address issues confronted by earlier compounds.

Preclinical and Clinical Safety Concerns for Existing mRCC Drugs

Table 2: Selected adverse effects observed in clinical trials for everolimus and temsirolimus

Adverse Effects	Everolimus Drug Label Nov 8 2013	Temsirolimus Drug Label June 6, 2012
stomatitis	X	
pneumonitis	X	
increased risk of infections	X	X
oral ulceration	X	
renal failure	X	X
elevation of serum creatinine	X	X
elevation of blood glucose	X	X
elevation of lipids	X	X
decrease in hemoglobin	X	
decrease in neutrophils	X	X
decrease in platelets	X	X
interstitial lung disease		X
bowel perforation		X
elevated alkaline phosphatase		X
hypophosphatemia		X

Everolimus and temsirolimus are the only two approved mTOR inhibitors for use in mRCC (4,5). The data on these two drugs is critical in developing a preclinical safety program for new molecules. Only selected aspects of the analysis described earlier, are highlighted in this article.

A. Drug label

The FDA drug label represents the distilled safety assessment of the FDA at both the preclinical and clinical level, and provides insights into potential risks. Analyses of the most recent label for everolimus and temsirolimus are listed in Table 2.

Several questions can be asked. Are these toxicities notable concerns that standard testing, as established by ICH, would not cover? What types of data were collected during the clinical trials to document these adverse events? A look into the approval packages as well as other information sources for the drugs may help uncover answers to these questions.

A key finding for Everolimus, was that cynomolgus monkeys were selected as the non-rodent species due to gastrointestinal intolerability in dogs.

B. Clinical concerns

Examination of the Medical/Clinical Review documents in the drug approval packages provides additional insights. A comprehensive list noted that deaths attributed to everolimus were caused by acute respiratory failure, infection, and renal failure, while adverse reactions (4% or more of patients) included anemia, hyperglycemia, stomatitis and lymphopenia. A similar check with temsirolimus confirmed that, as seen with everolimus, the clinical warnings and adverse events noted in the drug label are reflected in the clinical reviews.

C. Translating clinical findings into preclinical concerns

A picture of the clinical toxicity of these two drugs sets the stage to examine how well clinical effects were indeed anticipated in preclinical studies. Preclinical data show that the toxicities elicited by these two compounds are virtually identical, with immunosuppression being the primary effect, and with toxicities seen in lung, kidney, heart, gastrointestinal tract and pancreas, along with hyperglycemia and hypercholesteremia. These preclinical findings are indeed concordant with the toxicities seen in the clinic. The bottom line is that the preclinical studies for these two mTOR inhibitors appear to anticipate the findings in patients, suggesting that the preclinical testing strategy as defined by ICH is appropriate.

However, the review on everolimus notes that cynomolgus monkeys were selected as the non-rodent species for toxicity studies because gastrointestinal intolerability was observed in dogs. This important observation has a real impact on the design of a preclinical safety assessment program. While standard endpoints would be appropriate for monitoring the toxicities anticipated for an mTOR inhibitor, conducting non-rodent studies in dogs may be risky, i.e., initial studies indicate that the hypothetical mTORC2 inhibitor might be as intolerable in dogs as everolimus. While more expensive, the expedient approach would be to design non-rodent studies in cynomologous monkeys from the start.

An important consideration (even for a drug treating advanced cancer) is whether these toxicities are seen in animals at drug levels concordant with those causing such toxicities in human.

D. Translating exposure data to support preclinical dosing studies

An important consideration (even for a drug treating advanced cancer) is whether these toxicities are seen in animals at drug levels concordant with those causing such toxicities in human. In other words, are animals just as sensitive as humans (if not more so) to the drug's adverse effects? This helps determine if more care is needed in conducting the animal studies, e.g. including additional endpoints.

A head-to-head comparison of preclinical and clinical doses and effects requires extraction of data from regulatory documents, and subsequent analysis in a software tool such as Microsoft® Excel®. Much of this work can be done manually from drug approval packages, but it is tedious and time-consuming. An easier and much faster analysis can be completed by exporting the data from PharmaPendium® (Elsevier) directly into a spreadsheet or other tool.

The goal is to compare the preclinical findings with the human findings on a dose-by-dose basis. Animal doses are often converted to human doses through conversion factors that are specific to each species. The FDA has published a guidance describing these calculations (9). These factors can be used to determine a human equivalent dose, or HED, (see Fig. 2) for preclinical data. The HED at which toxicity is recorded in a preclinical study can then be compared to the minimum human dose at which an adverse event is observed. The highlighted preclinical data can be merged with the clinical data to produce a composite that simultaneously

Figure 2. Calculated human equivalent dose (HED) for preclinical data. Partial data set shown.

Exported PharmaPendium Data								Data Transformation Completed on Exported Data		
Drug Name	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source Document	Year	mg HED or Min Dose	Dose Value	Dose Unit
Everolimus	Blood creatinine increased	R	0.005 mg/kg/day	Repeated	I	FDA approval package document Pharmacology Review. page 49	2009	0.048	0.005	mg/kg/day
Everolimus	Blood glucose increased	R	0.005 mg/kg/day	Repeated	I	FDA approval package document Pharmacology Review. page 49	2009	0.048	0.005	mg/kg/day
Everolimus	Prothrombin time abnormal	R	0.005 mg/kg/day	Repeated	I	FDA approval package document Pharmacology Review. page 49	2009	0.048	0.005	mg/kg/day
Everolimus	Lunz disorder	R	0.01 mg/kg/day	Repeated	I	FDA approval package document Pharmacology Review. page 49	2009	0.096	0.01	mg/kg/day
Temsirolimus	Thymus disorder	R	0.03 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 97	2007	0.288	0.03	mg/kg/day
Everolimus	Azoospermia	R	0.05 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 64	2009	0.48	0.05	mg/kg/day
Everolimus	Biopsy thymus gland abnormal	R	0.05 mg/kg/day	Repeated	I	FDA approval package document Pharmacology Review. page 49	2009	0.48	0.05	mg/kg/day
Everolimus	Blood cholesterol increased	R	0.05 mg/kg/day	Repeated	I	FDA approval package document Pharmacology Review. page 49	2009	0.48	0.05	mg/kg/day
Everolimus	Blood cholesterol increased	R	0.05 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 52	2009	0.48	0.05	mg/kg/day
Everolimus	Blood cholesterol increased	R	0.05 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 64	2009	0.48	0.05	mg/kg/day

H = Human, **R** = Rat, **CM** = Cynomolgus Monkey, **I** = Intravenous, **O** = Oral, **HED** = Human Equivalent Dose

Figure 3. Composite column displaying animal and human doses for rapid examination of relationships. Partial data set shown.

Exported PharmaPendium Data								Data Transformation Completed on Exported Data		
Drug Name	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source Document	Year	mg HED or Min Dose	Dose Value	Raw Value
Everolimus	White blood cell count decreased	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 29	2010	1.5	3 mg/day	1.5-3
Everolimus	White blood cell count decreased	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 36	2010	1.5	3 mg/day	1.5-3
Everolimus	White blood cell count decreased	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 37	2010	1.5	3 mg/day	1.5-3
Everolimus	White blood cell count decreased	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 62	2010	1.5	3 mg/day	1.5-3
Everolimus	White blood cell count decreased	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 68	2010	1.5	3 mg/day	1.5-3
Everolimus	Band neutrophil count increased	CM	0.1 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 47	2009	1.92	0.1 mg/kg/day	
Everolimus	Carditis	CM	0.1 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 47	2009	1.92	0.1 mg/kg/day	
Everolimus	Decreased appetite	CM	0.1 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 72	2009	1.92	0.1 mg/kg/day	
Everolimus	Mepatomegaly	CM	0.1 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 47	2009	1.92	0.1 mg/kg/day	

H = Human, **R** = Rat, **CM** = Cynomolgus Monkey, **I** = Intravenous, **O** = Oral, **HED** = Human Equivalent Dose

An important consideration is that furthermore clinical cardiac adverse events seen with Everolimus, occurred at doses lower than the HED observed to produce cardiotoxicity in preclinical studies.

displays both human and animal findings (see Fig. 3). Data can be sorted from smallest to largest value in the combined column "mg HED (preclinical)/Min Dose (human)" for a closer examination of dose relationships between preclinical and clinical toxicities.

Renal toxicity endpoints confirm that toxicity is indeed seen in preclinical studies at HED consistent with the doses eliciting clinical renal toxicity (Fig 4, see Appendix). Liver toxicity shows a similar result: preclinical findings anticipate clinical findings when comparing HED to human dose level (Fig. 5). Cardiac toxicity, however, follows a different pattern. A large number of clinical toxicity events where observed (113, based on PharmaPendium® extracted data), while only a modest number of preclinical studies reported cardiotoxicity (39). Furthermore, clinical cardiac adverse events occurred at doses lower than the HED observed to produce cardiotoxicity in preclinical studies (see Fig. 6). Given the recent interest in cardiotoxicity caused by protein kinase inhibitors (10), this pattern points to an area of concern for a new drug.

This unique analysis identifies a concern in the preclinical safety assessment program. A safety concern not highlighted in the original regulatory reviews was anticipated for the new program for this drug target. At the very least, particular attention should be paid to the endpoints relevant for cardiotoxicity. Inclusion of a sensitive translational biomarker of cardiotoxicity, such as cardiac troponins (11), might be considered. Such an approach should be discussed with the FDA in a pre-IND meeting to assure that regulatory concerns are addressed.

Figure 6. Cardiac toxicity observed in preclinical studies at HED is not consistent with doses in clinical studies. Partial data set shown.

Exported PharmaPendium Data								Data Transformation Completed on Exported Data			
Drug Name	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source Document	Year	mg HED or Min Dose	Max Dose	Dose Units	Raw Value
Everolimus	Cardiac failure congestive	H	0.75-1.5 mg/twice a day	Repeated	I	FDA approval package document: Label. page 12	2010	0.75	1.5	mg/twice a day	0.75-1.5
Everolimus	Acute myocardial infarction	H	1.5-3 mg/day	Repeated	O	FDA approval package document: Medical/Clinical Review. page 15	2010	1.5	3	mg/day	1.5-3
Everolimus	Acute myocardial infarction	H	1.5 mg/ day	Repeated	O	FDA approval package document: Medical/Clinical Review. page 12	2010	1.5	1.5	mg/day	1.5
Everolimus	Acute myocardial infarction	H	1.5 mg/ day	Repeated	O	FDA approval package document: Medical/Clinical Review. page 12	2010	1.5	1.5	mg/day	1.5
Everolimus	Myocarditis	R	0.5 mg/ kg/day	Repeated	O	FDA approval package document: Pharmacology Review. page 107	2009	4.8	0.5	mg/kg/day	
Temsirolimus	Cardiac disorder	R	0.5 mg/ kg/once a week	Repeated	I	FDA approval package document: Pharmacology Review. page 87	2007	4.8	0.5	mg/kg/ once a week	
Everolimus	Cardiac disorder	CM	0.3 mg/ kg/day	Repeated	I	FDA approval package document: Pharmacology Review. page 52	2009	5.76	0.3	mg/kg/day	
Everolimus	Cardiac disorder	CM	0.3 mg/ kg/day	Repeated	I	FDA approval package document: Pharmacology Review. page 52	2009	5.76	0.3	mg/kg/day	

H = Human, **R** = Rat, **CM** = Cynomolgus Monkey, **I** = Intravenous, **O** = Oral, **HED** = Human Equivalent Dose

Regulatory Concerns for Molecule Class

A unique characteristic of these molecules is that they are irreversible inhibitors of mTORC2. While this type of drug has seen recent regulatory acceptance (5), it would be wise to investigate concerns raised about this molecule class in previous regulatory documents. Such comparative analyses are extremely difficult to conduct, as they require consistent extraction of data from approval documents associated with several drugs that identify mTOR as the primary target, and development of a database.

A search for irreversible inhibitor in PharmaPendium retrieves a small amount of information across all three categories, confirming that relatively few molecules of this class have been approved (Fig. 6). Ibrutinib has summaries of its toxicities in its FDA Approval Package, but no evidence of unique concerns. A number of toxicities are noted to be reversible. Data in the Pharmacology Reviews of the irreversible proteasome inhibitor Carfilzomib indicate that cellular recovery from this drug comes from synthesis of new proteasomes and that the drug is cleared quickly.

In summary, FDA experience with irreversible inhibitors does not seem to cause critical concerns, especially if recovery from toxicities is shown and supported on a mechanistic basis.

Conclusions on Safety Assessment Strategies

The analyses performed revealed a number of toxicities and adverse events associated with mTOR inhibitors that are seen at comparable doses in both clinical and preclinical studies. Two critical findings of the investigation were that (1) dogs did not tolerate current mTOR inhibitors, suggesting the use of cynomologous monkeys as a non-rodent preclinical species for safety assessment, and (2) cardiotoxicity was recorded in more clinical studies and at lower doses than in preclinical studies. The latter suggests that biomarkers such as cardiac troponins should be included in toxicity studies to complement standard endpoints. A pre-IND meeting with the FDA to confirm the safety assessment study strategy is advisable.

Note: Parts of this analysis were performed using PharmaPendium, a database of regulatory information extracted from drug approval, advisory committee and adverse events reports across preclinical and clinical studies and post-market monitoring.

References

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Appendix

Figure 4. Renal toxicity is observed in preclinical studies at HED consistent with doses in clinical studies. Partial data set shown.

Exported PharmaPendium Data								Data Transformation Completed on Exported Data			
Drug Name	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source Document	Year	mg HED or Min Dose	Max Dose	Dose Units	Raw Value
Everolimus	Blood creatinine increased	R	0.005 mg/kg/day	Repeated	I	FDA approval package document Pharmacology Review. page 49		0.048	0.005	mg/kg/day	
Everolimus	Renal disorder	R	0.05 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 64	2009	0.48	0.05	mg/kg/day	
Everolimus	Renal tubular disorder	R	0.05 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 64	2009	0.48	0.05	mg/kg/day	
Everolimus	Blood urea increased	H	0.75-1.5 mg/twice a day	Repeated	O	FDA approval package document Label. page 12	2010	0.75	1.5	mg/twice a day	0.75-1.5
Everolimus	Creatinine renal clearance decreased	H	0.75-1.5 mg/twice a day	Repeated	O	FDA approval package document Clinical Pharmacology and Biopharmaceutics Review. page 26	2009	0.75	1.5	mg/twice a day	0.75-1.5
Everolimus	Glomerular filtration rate decreased	H	0.75 mg/twice a day	Repeated	O	FDA approval package document Label. page 7	2010	0.75	0.75	mg/twice a day	0.75
Everolimus	Nephritis interstitial	H	0.75-1.5 mg/twice a day	Repeated	O	FDA approval package document Label. page 13	2010	0.75	1.5	mg/twice a day	0.75-1.5
Everolimus	Nephropathy toxic	H	0.75 mg/twice a day	Repeated	O	FDA approval package document Label. page 7	2010	0.75	0.75	mg/twice a day	0.75
Everolimus	Nephropathy toxic	H	0.75-1.5 mg/twice a day	Repeated	O	FDA approval package document Clinical Pharmacology and Biopharmaceutics Review. page 35	2009	0.75	1.5	mg/twice a day	0.75-1.5
Everolimus	Renal and urinary disorders	H	0.75 mg/twice a day	Repeated	O	FDA approval package document Label. page 11	2010	0.75	0.75	mg/twice a day	0.75

H = Human, **R** = Rat, **CM** = Cynomolgus Monkey, **I** = Intravenous, **O** = Oral, **HED** = Human Equivalent Dose

Figure 5. Liver toxicity is observed in preclinical studies at HED consistent with doses in clinical studies. Partial data set shown.

Exported PharmaPendium Data								Data Transformation Completed on Exported Data			
Drug Name	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source Document	Year	mg HED or Min Dose	Max Dose	Dose Units	Raw Value
Everolimus	Prothrombin time abnormal	R	0.005 mg/kg/day	Repeated	I	FDA approval package document Pharmacology Review. page 49	2009	0.048	0.005	mg/kg/day	
Temsirolimus	Hepatic necrosis	R	0.1 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 99	2007	0.96	0.1	mg/kg/day	
Everolimus	Hepatomegaly	R	0.15 mg/kg/day	Repeated	O	FDA approval package document Pharmacology Review. page 49	2009	1.44	0.15	mg/kg/day	
Everolimus	Blood bilirubin increased	H	0.75-1.5 mg/twice a day	Repeated	O	FDA approval package document Label. page 12	2010	0.75	1.5	mg/twice a day	0.75-1.5
Everolimus	Hepatic enzyme increased	H	0.75-1.5 mg/twice a day	Repeated	O	FDA approval package document Label. page 12	2010	0.75	1.5	mg/twice a day	0.75-1.5
Everolimus	Alanine aminotransiferase increased	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 9	2010	1.5	3	mg/day	1.5-3
Everolimus	Alanine aminotransiferase increased	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 8	2010	1.5	3	mg/day	1.5-3
Everolimus	Biliary tract disorder	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 13	2010	1.5	3	mg/day	1.5-3
Everolimus	Biliary tract disorder	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 11	2010	1.5	3	mg/day	1.5-3
Everolimus	Biliary tract disorder	H	1.5-3 mg/day	Repeated	O	FDA approval package document Medical/Clinical Review. page 9	2010	1.5	3	mg/day	1.5-3

H = Human, **R** = Rat, **CM** = Cynomolgus Monkey, **I** = Intravenous, **O** = Oral, **HED** = Human Equivalent Dose

PharmaPendium's searchable databases of extracted information from FDA /EMA approval documents, Adverse Events (FAERS), and FDA Advisory Committee documents provides the comprehensive content for critical drug development decisions including, accessing drug safety of lead candidates, prioritizing their selection, and developing risk mitigation and management strategies for clinical trials. In addition, all FDA/EMA Drug Approval documents are text searchable enabling fast retrieval of critical information.

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