



TITANIUM

Software to Anticipate Adverse Events and Reduce Project Failures

Titanium adverse event models help you anticipate adverse events you will encounter in clinical trials, minimizing project failures

Pharmatropé Titanium™ models are based on *human* data gathered by the United States Food and Drug Administration (FDA) under its Adverse Events Reporting System (AERS). The AERS is a collection of over 80 million adverse events reported over the last decade.

Titanium uses a proven fragment-based approach to model connections between drugs and adverse events based on chemical substructures contained in each drug. The resultant models *predict adverse events of your drugs based on fragment fingerprints*.

The model-making process probed over 11,000 defined adverse event types to identify 650 events with significant associations with known drugs. These events span a wide range of toxicities and include cardiovascular and hepatic events. All are reported using the MeDRA controlled vocabulary.

Predictive models require only compound structure files in standard formats as input and can assess thousands of compounds in minutes.

Key Advantages

- Prioritize compounds for development
- Reduce the chances of failed clinical trials
- Evaluate compounds for in-licensing
- Identify chemical classes to avoid
- Based on Human Data, not Animal Models

Robust Statistical Evaluations

The models are evaluated by computing recall, precision, and specificity. In addition, each model is compared to randomized models with the same proportion of true positives as the real model to compare the true ability of the model to make predictions better than random selection.

Example statistics from the Long QT Syndrome model:

		COUNTS		total
		Predicted		
Observed	TRUE	35	42	77
	FALSE	12	1220	
total		47	1262	1232
Recall =	35 / 77 =	45%		
Precision =	35 / 47 =	74%		
Specificity =	1220 / 1232 =	99%		

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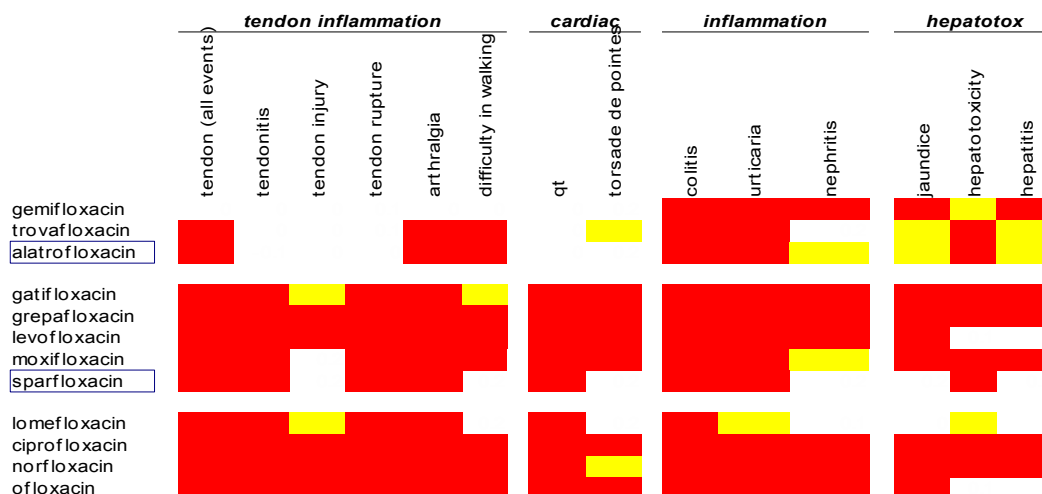
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Fluoroquinolone Antibiotics – An Illustrative Case Study

Prediction of Tendon Rupture – An event difficult to anticipate with in-vitro assays

Adverse events associated with tendon damage are common and significant adverse events for the fluoroquinolone drugs. The adverse event “tendonitis” is almost universally observed for drugs in this class, while the more severe event “tendon injury” is interesting because it shows variation among the drugs reported in the AERS database. We therefore chose these two events as a test of the error rates for the adverse event QSAR model.

Adverse events are by nature relatively rare events and reporting of adverse events may be sporadic, inconsistent, and dependent on the length of time a drug is prescribed. The absence of statistically significant reports in the AERS does not necessarily mean, therefore, that a drug is free from liability. As an indication of the predictive ability of the models, the model for combined tendon-associated events implicates sparfloxacin and alatrofloxacin in tendon damage even though significant numbers of events for these drugs have not been reported in the AERS database itself. This prediction is confirmed for sparfloxacin by reports of tendon injury at high doses in preclinical studies.² Similarly, alatrofloxacin is a prodrug of trovafloxacin and so can be expected to have similar liabilities as trovafloxacin for tendon injury. The model is therefore suggesting a liability that could not be gleaned from the AERS.



Red blocks indicate strong predicted association of drug and event, yellow blocks moderate association.

System Requirements

- Sun JAVA run-time system (JRE), which is available for Linux, Solaris, Windows (2000/2003/2008/XP/Vista) Mac OS X
- Reads SD file format for input, writes tagged SD files as output

The system is delivered as a self-contained “jar” file with all software, models, and configuration files packaged into a single file. This mechanism makes installation very easy and flexible. The use of the JAVA language allows you to get exactly the same result on any type of computer.

2 Kashida, Y. Kato, M. Characterization of Fluoroquinolone-Induced Achilles Tendon Toxicity in Rats: Comparison of Toxicities of 10 Fluoroquinolones and Effects of Anti-Inflammatory Compounds *Antimicrobial Agents and Chemotherapy* **1997**, 41, 2389–2393.