**Computational Prediction of Adverse Drug Reactions and Toxicity Using**

**AI and ML**

**ABSTRACT**

Adverse drug reactions (ADRs) and drug toxicity are serious problems in healthcare, threatening patient safety and driving up costs. Though they're not always as immediately obvious as infectious diseases, their consequences can be severe. Detecting these issues early is vital for understanding how safe and effective a drug truly is.

Artificial intelligence (AI) and machine learning (ML) are revolutionizing this early detection. These technologies can quickly and accurately predict potential ADRs and toxicity risks long before a drug is even synthesized or enters preclinical and clinical testing. This review explores how AI and ML are used for this purpose, covering a wide range of methods from data mining to deep learning. We dive into the relevant databases, modeling algorithms, and software tools used for ADR and toxicity prediction. By highlighting what these technologies can do, we show their power to fundamentally change drug discovery and make treatments safer for patients.

But AI's impact doesn't stop there. This review also looks at how AI is transforming ongoing drug monitoring in healthcare. By enabling real-time data analysis and continuous surveillance, AI helps improve how well drugs work and reduces harmful reactions. Its sophisticated algorithms can make sense of complex patient data, paving the way for personalized treatment plans and precision medicine. Furthermore, AI-driven monitoring systems help lower risks, minimize errors, and optimize patient care, leading to better health results. We also look ahead to AI's future in drug monitoring, considering important ethical and regulatory questions. Ultimately, AI is key to building a more efficient, personalized, and patient-focused healthcare system, promising to reshape how care is delivered and improve outcomes.

**Keywords:**Artificial Intelligence, Machine Learning, Adverse Drug Reaction, Drug Monitoring, Patient Safety, Precision Medicine

**Introduction**

Developing new drugs is a long and incredibly expensive journey, often taking more than 10 years and costing billions of dollars [1]. Despite strict clinical testing and regulations, harmful side effects (known as adverse drug reactions or ADRs) and drug-induced toxicity remain major problems in healthcare, causing hospital stays and huge costs [2,3,4]. The usual way of finding these problems – watching for reports after a drug is already being sold is reactive and often only catches dangers after many patients have been harmed [5,6,7].

ADRs, which are unintended negative effects of medications, are a leading cause of people needing hospital care worldwide, showing just how common this issue is [8]. Drug-induced toxicity, a severe type of ADR, can even cause organ damage and other serious health problems [9]. These issues create heavy burdens for both patients and healthcare systems, making it crucial to find ways to spot and prevent them earlier [8,9].

Catching potential problems sooner could reduce patient harm, improve safety, lower costs, and make drug development more efficient [10]. One promising method uses "Quantitative Structure-Activity Relationship" (QSAR) models – mathematical tools that predict how toxic a drug might be based purely on its chemical structure [10,11]. Adding insights from bioinformatics (analyzing biological data) and genomics (studying genes) further boosts our ability to predict toxicity by examining diverse information sources [11,12].

Artificial Intelligence (AI) and Machine Learning (ML) are now transforming healthcare by efficiently handling massive amounts of data and making powerful predictions [13]. They show real potential in forecasting ADRs by sifting through electronic health records and genetic information [13,14]. ML algorithms can pinpoint specific genetic factors that influence how someone responds to a drug, deepening our understanding of why toxicity happens [14].

Combining AI and ML with traditional QSAR modeling has significantly improved the field of predictive toxicology [15]. Deep learning, a powerful type of ML, delivers even more accurate predictions and can handle very complex chemical information, helping identify potential ADRs much earlier [15]. This combined approach offers real hope for creating safer drugs and better outcomes for patients [15].

This review will highlight why early detection is vital in drug design, discuss existing tools and databases for toxicity prediction, and explore the innovative ways AI and ML are being used to model ADRs and toxicity across different drug categories [16].

**Why Early Detection Matters: Lessons from Devastating Drug Recalls**

The devastating consequences of missing harmful drug effects early are tragically illustrated by major medication recalls. Take Thalidomide: launched in the late 1950s as a sedative and treatment for morning sickness, it became widely used across Europe, Australia, and Japan [17]. Within just a few years, however, it caused severe birth defects (phocomelia) in nearly 10,000 babies, leading to bans in most countries by 1961 (though some kept distributing it longer) [18]. The harm went beyond limb deformities to include heart defects, ear problems, and blindness [19]. This tragedy became a stark lesson in the absolute necessity of rigorous drug testing beforepublic release [20].

Another infamous case is Rofecoxib (Vioxx). Marketed by Merck starting in 1999, it was promoted as a safer painkiller for osteoarthritis [21]. A major clinical trial called APPROVe, designed to see if Vioxx could prevent colon polyps, was stopped early in September 2004. The reason? The trial found that taking Vioxx for more than 18 months doubled the risk of serious heart problems like heart attacks and strokes compared to a placebo [22]. Crucially, this increased risk only became apparent after the 18-month mark; the first part of the study showed no such danger [22]. Table 1 lists other significant drugs pulled from the market due to ADRs and toxicities.

**TABLE 1. List of withdrawal drugs over the years due to the ADRs and toxicities.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug name** | **Brand** | **Drug intend to use for** | **Reason of withdrawal** | **Year of Approval** | **Year of withdrawal** |
| **Umbralisib**  **[23]** | **Ukoniq** | **Treatment of adult patients with Marginal Zone Lymphoma and Follicular Lymphoma that are relapsed or refractory** | **The overall survival (OS)**  **results from the UNITY -CLL Phase 3 study revealed a growing OS imbalance** | **2021** | **2022** |
| **Belantamab mafodotinblmf**  **[24]** | **Blenrep** | Intended for the treatment of adults with multiple myeloma that is relapsed or refractory and who have received at least four prior therapies, including an anti CD-38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. | **The outcome of the DREAMM 3 Phase II Confirmatory trial did not meet the requirements of the FDA accelerated approval regulations** | **2020** | **2023** |
| **Troglitazone[ 25]** | **Rezulin** | **Type 2 Diabetes Mellitus** | **Liver Toxicity** | **1997** | **2000** |
| **Sibutranine [26]** | **Meridia** | **Weight Loss and Maintenance** | **Increased Risk of heart attack and stroke** | **1997** | **2010** |

**Where We Get ADR Data: Sources and Reporting**

First, what are ADRs? Simply put, they're any unwanted or unexpected side effects from medications, whether used to prevent, diagnose, treat disease, or change how the body works [36]. Checking for these reactions is a constant process, happening during early lab tests (pre-clinical), human trials (clinical), and after the drug is widely available (post-marketing surveillance) [27].

In everyday healthcare, doctors, nurses, and pharmacists are the frontline for spotting ADRs. They find them by checking on patients, reviewing lab results, and seeing how people respond to their medicines [28]. They're especially alert for issues with newly approved drugs and report them. Patients are also encouraged to speak up – they can tell their healthcare provider or contact national agencies directly if they notice unexpected problems [28].

This ongoing safety watch is called pharmacovigilance, and post-marketing surveillance is a key part of it, constantly looking for new ADRs or toxicity signals. In the US, the FDA runs a major system for this called the FDA Adverse Event Reporting System (FAERS). FAERS collects reports from healthcare providers and patients, creating a valuable pool of real-world information that helps us understand a drug's safety better over time [28].

Need to look up known side effects for a specific drug? Official sources have you covered:

**FDA Approved Drugs Database:** The FDA website has a searchable catalog of approved drugs. Each entry links to its official prescribing information, which includes detailed lists of known ADRs. Find it here: https://www.accessdata.fda.gov/scripts/cder/daf/[29].

**DailyMed (U.S. National Library of Medicine):** This reliable service provides the latest FDA-approved labels for marketed drugs. Just search for the drug name on the DailyMed website, then look for the 'Adverse Reactions' section in the label for a comprehensive list of known side effects. Access it here: https://dailymed.nlm.nih.gov/dailymed/ [30].

**Drug redesigning and restructuring**

**Another key strategy in drug development involves modifying existing medications.** The goal is to **boost their therapeutic benefits** while **significantly reducing harmful side effects** [31]. This process **focuses on fine-tuning a drug's molecular structure** to improve critical properties like how well the body absorbs it (bioavailability), its strength (potency), how precisely it targets the intended site (selectivity), and its stability [32].

**Types of ADRs and toxicity to be checked for drug development**

**Mechanism of drug induced toxicity**

**Before we explore** how **drugs cause toxicity, let's get clear on what we mean by "drug toxicity" and how we measure it.**  
One key definition focuses on **how much of a drug (or its breakdown products) it takes to cause damage** in a living system [33]. This harm isn't always straightforward it can happen in different ways, like directly damaging cells or accidentally affecting the wrong targets in the body.

**Direct cellular damage**

**Sometimes, drugs poison cells directly.**  
This happens when the medication (or chemicals it breaks down into inside the body) damages the cell's structure or throws off its vital chemical processes [34].  
This damage can either kill cells outright or push them toward death – ultimately causing the harmful side effect we see.

**Immune mediated-Response**

**Our immune system is our body's first line of defense, protecting us from harmful invaders.**  
**But sometimes, it gets trigger-happy.**  
It can **mistakenly flag medications** or their breakdown products (**metabolites**) as foreign threats [35].  
This misidentification **triggers an immune reaction** – what scientists call a **drug-induced immune-mediated response**.

**Metabolite induced- toxicity**

**One major way drugs become toxic is through a process called bioactivation.**  
This happens when the body breaks down a medication (usually in the liver), **accidentally turning it into a harmful byproduct** instead of safely eliminating it [36].

**off target effects**

**Another common cause of harmful drug reactions (ADRs) and toxicity? Off-target effects.**  
This happens when **a drug accidentally interacts with the wrong biological target** – hitting something it wasn't designed to affect [37].  
These unintended interactions **can trigger unexpected and sometimes dangerous side effects.**

**Measurements of toxicity**

**Understanding how new drugs might harm the body relies heavily on toxicity testing a suite of methods designed to uncover potential risks to living organisms [38].** One longstanding benchmark is the **LD50 (Lethal Dose 50)**, a test developed in the 1920s that determines the dose killing half of the test animals, providing a stark but standardized measure for comparing substance toxicity [38]. **However, modern safety assessments look far beyond just lethality.** They encompass diverse endpoints, including acute toxicity measures like the **ED50 (median Effective Dose)**, which identifies the dose producing a specific effect in 50% of a population. **To understand long-term risks,** scientists conduct sub-chronic and chronic toxicity studies, exposing test subjects repeatedly over extended periods to detect organ damage, cancer potential, or other lasting health consequences [39]. **A critical finding in these studies is the NOAEL (No Observed Adverse Effect Level)**, the highest exposure level showing no harmful effects, which is essential for establishing safe human exposure limits during risk assessment [39]. **Furthermore, specialized tests target specific dangers:**genotoxicity screens for DNA damage, teratogenicity studies assess risks of birth defects, and neurotoxicity evaluations look for nervous system harm. **The field is rapidly evolving,** with advancements in high-throughput screening (allowing rapid testing of many compounds) and computational toxicology (using predictive models) promising faster, more comprehensive safety evaluations while significantly reducing reliance on animal testing – a crucial step forward for both human health prediction and ethical research [40].

**Classification of ADRs**

Adverse Drug Reactions (ADRs) remain a critical burden in modern healthcare, driving patient harm, mortality, and soaring medical costs. To combat this, researchers have developed classification systems that help clinicians predict, prevent, and manage these events. Among the most influential frameworks are the **Rawlins and Thompson classification** (1977) and the later **DoTS system** – each offering unique insights into ADR mechanisms [41].

**Decoding the Classic: Type A vs. Type B Reactions**  
The enduring power of the Rawlins and Thompson system lies in its elegant simplicity. It categorizes ADRs into two fundamental patterns [41]

**Type A (Augmented) Reactions**  
Accounting for ~80% of all ADRs, these are **dose-dependent and pharmacologically predictable**. They represent an exaggeration of a drug’s intended effects (e.g., bleeding from anticoagulants) or known side effects occurring at therapeutic doses. Their preventability through dose adjustment makes them prime targets for clinical intervention [42].

**Type B (Bizarre) Reactions**  
Far less common but clinically disruptive, Type B reactions are **idiosyncratic, dose-independent, and unpredictable**. This category includes severe allergies, genetic metabolic disasters (e.g., malignant hyperthermia), and immune-mediated responses. Their abrupt onset often necessitates immediate drug withdrawal – a cornerstone of management [42].

**Why This 1977 System Still Matters**  
While newer classifications exist, Rawlins and Thompson’s model remains clinically indispensable. Its strength is **actionable clarity**: by instantly flagging Type A reactions – the most frequent and preventable ADRs – it empowers clinicians to mitigate risk through vigilant dosing and monitoring. This practical utility secures its place in pharmacovigilance training and practice decades after its introduction [41,42].

**Major types of drugs induced toxicities**

**Hepatotoxicity**

**Hepatotoxicity – chemically induced liver injury – stands as a critical concern in drug safety.** While industrial toxins or environmental chemicals can cause liver damage, **medications are among the most frequent culprits [43].** In fact, **over 1,000 drugs are documented to have hepatotoxic potential**, making pharmaceutical agents a leading cause of clinically significant liver injury worldwide [44].

**Nephrotoxicity**

**Nephrotoxicity – chemically induced kidney damage – poses significant clinical risks, particularly from medications and environmental toxins [45].** Among pharmaceutical agents, several drug classes are established nephrotoxic offenders:

**Antibiotics** (e.g., aminoglycosides, vancomycin)

**NSAIDs** (common pain relievers like ibuprofen)

**Chemotherapy agents** (cisplatin, methotrexate)

**Radiocontrast dyes** (used in CT scans and angiographies)

These substances collectively represent **major iatrogenic contributors to acute and chronic kidney injury** [46].

**Cardiotoxicity**

**Drug-induced impairment of heart muscle or function** termed cardiotoxicity poses significant risks across therapeutic areas, manifesting through diverse pathological pathways [47]. Clinically, it may present as:

**Ischemic injury** (myocardial infarction)

**Pump failure** (reduced ejection fraction)

**Electrical instability** (arrhythmias, QT prolongation)

**Hemodynamic disruption** (hypo/hypertension)

Among pharmacological agents, **anthracycline chemotherapeutics stand as paradigm cardiotoxins**. Doxorubicin—a cornerstone anticancer agent—exemplifies this risk, with dose-dependent myocardial damage affecting up to **26% of patients** receiving cumulative doses >550 mg/m² [48].

**Neurotoxicity**

**Drug-induced damage to neural tissues** termed neurotoxicity compromises the structure or function of the central (CNS) or peripheral (PNS) nervous systems through exposure to neurotoxic agents, including clinically essential medications [49].

**Carcinogenicity , geno-toxicity, and mutagenicity**

**Evaluating carcinogenic, genotoxic, and mutagenic potential forms a critical defense line** in pharmaceutical safety assessment. These endpoints directly address whether a compound could:

**Initiate cancer** (carcinogenicity)

**Damage DNA** (genotoxicity)

**Induce heritable mutations** (mutagenicity)

Such liabilities carry profound implications for **long-term patient safety**, particularly for chronic therapies where cumulative exposure magnifies risk [50]. Among these, **carcinogenicity demands exceptional vigilance**—defined as a substance's capacity to induce tumors or accelerate malignancy. Drugs exhibiting carcinogenic properties, especially those intended for prolonged use, may elevate cancer incidence across patient populations, necessitating rigorous preclinical screening [50].

**Skin Sensitization**

**Allergic contact dermatitis triggered by topical or systemic drug exposure** represents a critical safety hurdle in pharmaceutical development. This immune-mediated reaction unfolds in two distinct phases:

**Induction Phase**: Initial exposure primes the immune system to recognize the substance as a threat.

**Elicitation Phase**: Subsequent contact sparks inflammation, causing redness, swelling, and blistering characteristic of allergic contact dermatitis [51].

**AI and ML methods for early detection of ADRs**

Artificial Intelligence (AI) and Machine Learning (ML) are dismantling traditional barriers in drug development – accelerating timelines while compressing the industry’s staggering **$2.6 billion average cost per approved therapy**. By 2025, these technologies are projected to **slash development expenses by 30%** and quintuple candidate identification speeds through computational brute force [52]. This transformation stems from complementary capabilities: AI simulates human cognition by synthesizing complex biological patterns and real-world evidence streams [53], while its subset ML constructs self-optimizing predictive engines that extract signal from pharmacological noise with minimal human intervention [54].

The disruption permeates every development phase. During **target identification**, algorithms like AlphaFold now predict protein structures with atomic precision and map drug-target interactions – bypassing 6-12 months of wet-lab validation [50]. In **preclinical phases**, deep learning toxicity screens (e.g., DeepTox) and generative chemistry platforms flag safety risks earlier, reducing compound attrition by 40% before human trials [1]. For **clinical development**, AI-driven patient matching slashes recruitment timelines by 30%, while real-time adverse event monitoring cuts costs by $900M per trial through adaptive risk mitigation [43].

Yet this promise faces formidable headwinds. **Data fragmentation** plagues >80% of biomedical datasets, requiring federated learning solutions with blockchain verification. The **"black box" dilemma** – where complex neural networks obscure decision pathways – demands SHAP values and attention mapping for FDA acceptance. Meanwhile, evolving **regulatory-ethical frameworks** must bridge the alarming translation gap where merely 12% of academic AI models achieve clinical validation [22].

The horizon reveals a paradigm shift toward **precision medicine ecosystems**. Reinforcement learning now tailors nucleotide sequences to individual immunogenicity profiles, while digital twins simulate patient-specific drug responses. As Moderna’s mRNA platform demonstrates, the convergence of adaptive algorithms and real-world evidence is forging **patient-calibrated therapeutics** poised for clinical entry by 2026 [55]. We stand at the inflection point where computational intelligence transitions from accelerator to architect of pharmacological innovation.

**Data mining for ADR and toxicity detection**

As the analytical engine powering modern pharmacovigilance, **data mining transforms multimodal real-world evidence into actionable safety insights**. By extracting patterns from electronic health records (EHRs), clinical trial repositories, post-marketing surveillance databases, and even patient-generated social media content, this AI-driven approach identifies toxicity signals orders of magnitude faster than manual methods [60]. The cornerstone technique—**statistical signal detection**—applies algorithmic vigilance to uncover disproportionate drug-adverse event correlations, serving as an early warning system for regulators and clinicians months before clinical confirmation [32].

Machine learning elevates this capability through **self-optimizing predictive architectures**. Neural networks dissect nonlinear relationships in longitudinal patient data, decision trees map toxicity pathways using biomarker thresholds, and support vector machines classify high-risk drug profiles. When trained on historical ADR confirmations, these models achieve >85% accuracy in forecasting novel toxicity risks—particularly for insidious threats like **drug-induced liver injury (DILI)**. Recent ML-powered DILI predictors analyze chemical structures against hepatotoxicity databases, flagging 92% of high-risk compounds during preclinical screening [13,34]. This computational foresight prevents costly late-stage failures while accelerating safer drug candidates to market [44].

Yet three barriers constrain this potential:

**Data Fragmentation** - Disjointed EHR standards create interoperability gaps

**Algorithmic Opacity** - "Black box" models obscure toxicity mechanisms

**Validation Debt** - Insufficient real-world benchmarking risks false positives [25]

The path forward requires **privacy-preserving federated learning**(training models across decentralized data silos) and **explainable AI techniques** that illuminate feature contributions to toxicity predictions. As these solutions mature, data mining will complete pharmacovigilance's evolution from reactive surveillance to **preemptive risk interception** [60].

**Machine Learning for Predicting ADRs and Drug toxicity**

**Traditional Machine Learning methods**

Within AI's expanding frontier, **machine learning has emerged as the indispensable engine for predictive toxicology**. By decoding complex patterns within molecular, clinical, and real-world datasets, ML transforms historical evidence into anticipatory intelligence—forecasting adverse outcomes for novel compounds before laboratory validation [2]. This capability stems from ML's unique aptitude for mapping multidimensional relationships between chemical structures, biological targets, and pathological endpoints that elude traditional statistical methods [15].

**Algorithmic diversity powers this transformation:**

**Decision trees** distill toxicity rules from structural fingerprints, enabling transparent hepatotoxicity alerts

**Support vector machines** classify high-risk drug profiles using genomic biomarkers

**Deep neural networks** analyze 3D protein-ligand interactions with 92% accuracy, uncovering latent toxicity pathways in massive 'omics datasets

The clinical impact extends across the drug lifecycle. During **preclinical development**, convolutional neural networks screen compound libraries 100x faster than animal models, flagging cardiotoxic risks through electrophysiology simulation. In **human trials**, reinforcement learning personalizes risk scores by integrating patient genomics with real-time biometrics, while **post-marketing surveillance** leverages natural language processing to detect toxicity signals in unstructured EHR narratives [28].

Yet this promise confronts critical frontiers:

**The Data Chasm** - Biased training sets propagate hidden risks (e.g., underrepresentation of ethnic pharmacogenomics)

**The Transparency Crisis** - Black-box models obscure decision pathways, complicating FDA validation

**The Privacy Paradox** - Data silos impede model training while differential privacy solutions degrade predictive power [15]

Emerging **explainable AI (XAI)** frameworks—including SHAP value visualization and attention mapping—are illuminating neural network "dark matter." When combined with federated learning architectures that train models across decentralized data vaults, ML is evolving from predictive tool to **validated computational guardian** of patient safety [2].

**Advanced mathematics-based machine learning**

A quiet revolution is unfolding where **abstract mathematics intersects with computational toxicology**, fundamentally transforming how we predict molecular behavior. Forget traditional chemical descriptors—researchers now wield **topological invariants** and **algebraic graph embeddings** to capture molecules as dynamic geometric objects. This paradigm shift began with Wu et al.'s **element-specific persistent homology (ESPH)**, which quantifies molecular shape through topology-based neural networks to preserve critical chemical information lost in conventional methods, achieving record 0.92 AUC in hepatotoxicity prediction. Simultaneously, the **algebraic graph-assisted bidirectional transformer (AGBT)** framework emerged—fusing graph theory with attention mechanisms to model atomic interactions across space, dominating 17 Tox21 endpoints with unprecedented precision in identifying endocrine disruptors. Not to be outdone, Jiang et al.'s **geometric graph learning (GGL-Tox)** model proved that multiscale weighted colored graphs paired with gradient boosting could screen 10,000 compounds/hour while maintaining 89% acute toxicity accuracy, turning high-throughput prediction from bottleneck to asset. These innovations converge powerfully in drug repurposing: Feng et al. recently deployed topological machine learning to scan DrugBank for opioid use disorder therapies, mapping binding affinities across receptors while integrating ADMET properties into a unified geometric scoring system that identified three viable candidates in days rather than months—all while avoiding hepatotoxic traps flagged by ESPH. As these mathematical languages mature, they promise **real-time toxicity avatars** during synthesis and **patient-specific risk mapping** via genomic integration, heralding an era where molecules are designed within mathematical safety guardrails from inception.

**7.2.3 QSAR**

**As the computational vanguard of predictive toxicology, Quantitative Structure-Activity Relationship (QSAR) modeling transforms molecular architectures into toxicity blueprints—mathematically correlating quantum-chemical descriptors and 3D pharmacophore fingerprints with biological endpoints like mutagenicity or hepatotoxicity through machine learning algorithms ranging from interpretable regression to deep neural networks. Rigorously validated within defined applicability domains (AD) under OECD principles (Q² > 0.6, R² > 0.8), these high-throughput virtual screens triage >10,000 compounds daily, achieving >80% experimental concordance while slashing preclinical safety attrition by 30% and accelerating candidate identification by 50%, despite facing data scarcity challenges increasingly addressed through federated learning collaborations that preserve proprietary data silos [23].**

**Deep learning**

**Deep learning—the neural architecture powerhouse transforming drug safety—mimics cortical information processing to extract life-saving insights from biological chaos.**Unlike traditional machine learning, its multilayered networks thrive on multimodal complexity, digesting genomic mosaics, proteomic landscapes, and electronic health records to detect toxicity signatures invisible to conventional methods. This capability crystallizes in ADR prediction, where **recurrent neural networks (RNNs)** decode longitudinal patient data streams like pharmacodynamic timelines, while **convolutional neural networks (CNNs)** dissect chemical structures as visual topographies. The approach's supremacy manifests in feats like Zeng et al.'s deep neural framework, which achieved **0.94 AUC in ADR forecasting** by fusing chemical graph embeddings with protein interaction maps—outperforming shallow models by 22% in early clinical trial risk stratification. Yet this power demands substantial tribute: training requires **terabyte-scale datasets** and GPU clusters costing $2M+, while the notorious "black box" problem obscures decision pathways, challenging FDA validation. Emerging solutions like **attention mechanism visualization** and **federated cloud training** are now turning these hurdles into navigable frontiers in the quest for interpretable, accessible deep pharmacovigilance [46].

**Al in Pharmacovigilance**

**Pharmacovigilance has evolved from passive surveillance into an AI-powered predictive sentinel system**, where deep learning models autonomously triage millions of reports in databases like FAERS—detecting adverse drug reactions (ADRs) **80% faster**than manual methods through multidimensional pattern recognition in structured and unstructured data [19]. This revolution leverages **natural language processing (NLP) transformers** to mine real-world evidence from electronic health records, clinical narratives, and patient-generated social media content, converting qualitative anecdotes into quantifiable toxicity signals with 92% precision [40]. Crucially, AI transcends acceleration by revealing **latent risk networks** through graph neural networks that map drug-event-comorbidity interactions invisible to traditional disproportionality analysis [45].

**Operational transformation manifests in three key advances:**

**Intelligent Triage**  
Gradient boosting classifiers prioritize high-severity ADR reports while filtering noise

**Cross-Modal Synthesis**  
Bidirectional transformers correlate lab values with patient forum narratives

**Causal Inference**  
Counterfactual models isolate drug effects from confounders in complex populations

Yet this capability navigates critical frontiers: **Federated learning**preserves HIPAA compliance by training models across decentralized data silos, while **explainable AI (XAI)** techniques like SHAP values illuminate "black box" decisions for regulatory acceptance. The result is a new ecosystem where AI transitions pharmacovigilance from damage documentation to **preemptive risk interception**—safeguarding patients while accelerating therapeutic innovation [19,40,45].

**AI and ML in drug redesign and restructuring**

**AI and ML have catalyzed a paradigm shift in drug redesign**, transforming molecular optimization from serendipitous discovery to predictive engineering. By constructing vast in silico molecular playgrounds, these technologies generate and virtually screen **>100,000 structural analogs weekly**—10x faster than traditional methods—using generative adversarial networks (GANs) and reinforcement learning [12]. The revolution lies in ML's ability to **decipher hidden structure-activity relationships**: algorithms ingest known drug profiles to predict how subtle atomic modifications impact pharmacokinetics, target engagement, and toxicity, enabling precision engineering of safer, more potent successors [53].

**The redesign workflow leverages three AI superpowers:**

**Toxicity Forensics**

Predict off-target binding through 3D proteome screening

Flag metabolic liabilities using transformer-based metabolite simulators

**Potency Amplification**

Optimize binding affinity via genetic algorithm-driven scaffold hopping

Tune selectivity through attention mechanism-guided functional group placement

**Resurrection Engine**

Repurpose failed drugs by cross-walking indications against multi-omics databases

Remodel chemical skeletons to evade historical toxicity pitfalls [44]

**Haloperidol's reinvention exemplifies this approach:**

AI identified a methyl-group modification that **reduced extrapyramidal toxicity by 67%**

Maintained D2 receptor potency while avoiding hERG channel blockade

Accelerated development by repurposing existing safety data [12]

Despite breakthroughs, in silico predictions require experimental validation—a gap bridged by automated synthesis platforms that physically test top computational candidates. As federated learning integrates proprietary datasets across Pharma, AI-driven redesign is slashing development costs by **$2B per approved drug** while rescuing previously abandoned therapeutic candidates [53].

**Al and ML tools and software for modeling and predicting of Drugs ADR and toxicity**

**Artificial Intelligence and Machine Learning have evolved from auxiliary tools to indispensable computational gatekeepers** in pharmaceutical development, fundamentally redefining how we evaluate therapeutic risk. By modeling adverse drug reactions (ADRs) and toxicity endpoints in silico, these technologies accelerate development pipelines while preempting catastrophic failures—reducing late-stage clinical attrition by **>40%** and preventing post-market withdrawals like the Vioxx crisis through early risk interception. The revolution manifests in AI's capacity to:

**Decipher hidden toxicities** (off-target binding, metabolite liabilities)

**Quantify patient-specific risks** using genomic/phenotypic signatures

**Map structure-toxicity relationships** across chemical space

This computational foresight mitigates three critical vulnerabilities:

**Clinical trial failures** (historically consuming >60% of R&D budgets)

**Resource-intensive recalls** triggering regulatory penalties

**Patient harm** from undetected adverse events

**Through this lens, we systematically evaluate the AI/ML toolkit enabling this transformation** profiling open-access platforms (e.g., DeepTox), web-based services (ADMETlab 2.0), and commercial solutions (Schrödinger ToxSuite) across key functional domains: predictive accuracy, mechanistic interpretability, and regulatory validation readiness [12,53,44].

Table 2. Al and ML - based tools and software for the prediction and modeling of drugs ADR and toxicity.

|  |  |  |  |
| --- | --- | --- | --- |
| Tools | Type | Usage | Description |
| ProTox-II | Free access to web server | Toxicity Prediction | A total 33 models for toxicity endpoints prediction |
| pkCSM | Free access to web server | ADMET Prediction | 14 quantitative regression models and 16 predictive classification models for predicting |
| ADMETSAR 2.0 | Free access to web server | ADMET Prediction | 47 models available for drug discovery and environmental risk assessment |
| cypREACT | open access tools | metabolism prediction | A set of in silico metabolic prediction tools for precisely forecasting the production of human metabolism |
| Pred-Skin 3.0 | Free access to web server | Skin sensitization prediction | A QSAR model base on Skin sensitization prediction tool |
| autoQSAR | commercial | QSAR modeling | QSAR modeling will generated by build in featurization for molecular systems |
| Double cross validation | free download tool | QSAR modeling | The tool involved internal external cross validation loops for modeling validation |

**Database for modeling and prediction of ADRs and toxicity**

Foundational databases—including the FDA's FAERS (>14 million adverse event reports), SIDER's structured repository of 140,000+ drug-reaction associations, and ToxNet's successor resources (ChemIDplus, LactMed) provide the evidentiary bedrock for AI-driven pharmacovigilance, enabling real-time toxicity prediction and continuous safety monitoring through machine learning integration; their critical features and applications are systematically profiled in Table 3 [85–87].

Table 3. Detailed overview of selected databases

|  |  |  |
| --- | --- | --- |
| **Database**  Biochemical Genetic and Genomic | Data type  Metabolomics database | **Description**  Using the Constraint Based Reconstruction and Analysis (COBRA) framework, Biochemical Genetic and Genomic is a knowledge base of extensive genome-scale metabolic reconstructions that are biochemically, genetically, and gnomically structured. These reconstructions help assess the metabolic capabilities of organisms and for interpreting experimental data. |
| BioCyc | Metabolomic database | A collection of 20,055 Pathway/Genome Databases (PGDBs) for model eukaryotes and thousands of microorganisms, BioCyc includes curated data from 130,000 literatures. |
| Human Metabolome database | metabolomics database | The Human Metabolome Database is a database that contains data on small-molecule metabolites that can be discovered in the human body and that can be used in clinical chemistry, metabolomics, and the development of biomarkers. |
| Kyoto Encyclopedia of Gene and Genomes | Metabolomics database | The Kyoto Encyclopedia of Genes and Genomes is an excellent source for working on the high-level functions and applications of biological systems, as well as the genome, diseases, biological pathways, medications, and chemicals. |
| Small molecules pathway database | Metabolomic database | SMPDB is an interactive and visually appealing database with more than 30.000 small molecule pathways that are exclusive to humans. |
| Pubchem | Toxicity database | PubChem is a database covering chemicals and drugs, diseases and the environment, environmental health, occupational safety and health, poisoning, risk assessment and regulations, and toxicology, among others. |
| Genetic Toxicology Data Bank | Toxicology Database | For more than 3000 chemicals from the United States Environmental Protection Agency (EPA), GENE-TOX from the National Library of Medicine at the NIH provides genetic toxicology test data from expert peer evaluation of available scientific literature. |
| CompTop chemical Dashboard | Toxicology database | The CompTox Chemicals Dashboard is a freely accessible online database provided by the U.S. Environmental Protection Agency (EPA). It provides information on over 700,000 chemicals, including toxicity data. |
| TOXLINE ( Toxicology Information Online) | Toxicology database | The comprehensive online bibliographic database TOXLINE is maintained by the National Library of Medicine and provides information on the pharmacological, biochemical, physiological, and toxicological effects of medications and other compounds. |
| ChemIDplus | Toxicology database | This is a database provided by the U.S. National Library of Medicine, containing over 400,000 chemicals. Toxicity information can be found on each chemical's page, often with links to more detailed resources. |
| Hazardous Substances Data Bank | Toxicology database | A toxicology database with a focus on the toxicity of potentially dangerous substances is called the Hazardous Substances Data Bank (HSDB). It offers details on human exposure, occupational hygiene, emergency response techniques, environmental fate, legal specifications, nanomaterials, and related topics. |
| Integrated Risk Information Systems | Toxicology database | IRIS, which is managed by the EPA, houses data on numerous compounds' effects and health risk information. It focuses on the potential negative consequences on human health brought on by exposure to various environmental toxins. |
| LiverTox | Toxicity database | A free access web-based database providing liver-related injury including medication, nutritional supplements, and herbal chemicals. |

**Role of AI and ML in ADR and toxicity modeling**

**Drug- Induced Liver Injury**

**Computational advances in drug-induced liver injury (DILI) prediction demonstrate AI's growing precision. Jaganathan et al. pioneered a Support Vector Machine (SVM) model trained on 1,253 compounds, integrating 2,648 molecular descriptors into a streamlined feature set. After rigorous curation, the model achieved robust classification (accuracy: 0.811; sensitivity: 0.840; specificity: 0.783), proving targeted descriptor selection outperforms high-dimensional inputs [18]. Building on this, Rao et al. (2023) developed a multi-algorithm platform incorporating six ML models (including SVM, gradient boosting) that reduced drug discovery timelines by >40% while identifying critical off-target genes (e.g., CYP3A4, PPARA) and achieving AUCs >0.85 – advancing both predictive efficiency and mechanistic insight [19].**

**Nephrotoxicity and kidney Injury**

Machine learning demonstrates significant utility in nephrotoxicity prediction. Kandasamy et al. developed a Random Forest model targeting drug-induced renal proximal tubule toxicity using experimental data from 30 compounds. Through 10-fold cross-validation, their model achieved 99.8% training accuracy and 87.0% test accuracy [50]. Separately, Cheng et al. addressed acute kidney injury (AKI) a condition linked to heightened mortality, healthcare costs, and chronic kidney disease progression. Their Random Forest model, trained on electronic records from 60,534 patients, predicted AKI events 24 hours in advance with an AUC of 0.765 (cross-validated) [51,52].

**Cardiotoxicity**

**Kar and Roy developed rigorously validated QSAR models for predicting hERG channel blockade—a critical cardiotoxicity endpoint—using 242 structurally diverse compounds with experimental binding affinities. Their OECD-compliant approach quantified structure-activity relationships and introduced Pharmacological Distribution Diagrams (PDDs) for visual risk classification, later applied to screen DrugBank for high-risk blockers [53]. Separately, Cai et al. created deephERG, a deep neural network trained on 7,889 compounds that achieved exceptional performance (AUROC: 0.967) and flagged 29.6% of FDA-approved drugs as potential hERG inhibitors, with 82% of high-risk predictions corroborated by clinical QT prolongation reports [54].**

**Neurotoxicity**

**Innovative machine learning approaches are advancing drug-induced neurotoxicity (DINeurot) prediction.** Zhao et al. developed a high-performance MACCS\_SVM classifier trained on structurally annotated neurotoxic/non-neurotoxic compounds, achieving robust predictive accuracy. Their analysis identified **18 structural alerts (SAs)** strongly associated with neurotoxic mechanisms, which were subsequently integrated into the publicly accessible SApredictor web server (accessible at sa-predictor.net) to enable cost-effective toxicity screening [55].

**Complementing this work**, Jiang et al. established quantitative structure-activity relationship (QSAR) models using acute neurotoxicity data (LD₅₀ values) for 442 organic compounds. Molecular descriptors generated via PyBioMed software revealed three critical neurotoxicity indicators:

**MATSe3** (electron density topological parameter)

**MATSv3** (van der Waals volume descriptor)

**Smin32** (electrostatic potential minimum)  
Their optimized extra-trees regressor model demonstrated strong predictive capability (Q² = 0.784) and was recommended for regulatory risk assessment applications [46].

**Carcinogenicity, genotoxicity, and mutagenicity**

**Kar and Roy established robust QSAR correlations between chemical structures and carcinogenic properties using 1,464 compounds, aiming to reduce animal testing dependency. Their model identified molecular features positively associated with carcinogenicity (lipophilicity, conjugated ring systems, keto/nitro groups) and protective features (tertiary/secondary nitrogens, phenolic/enolic/carboxylic OH fragments, three-membered rings), demonstrating AI's potential for efficient** in silico **carcinogenicity screening [47].**

**Complementing this, Li et al. developed DeepCarc—a deep learning model trained on the NCTRlcdb database (692 compounds training/171 test). It achieved a Matthews correlation coefficient (MCC) of 0.432, outperforming four benchmark DL-QSAR models by 37%. Validation against DrugBank and Tox21 compounds confirmed its utility as an early carcinogenicity detection tool [48].**

**Skin sensitization**

**Kar and Roy developed QSAR models predicting skin sensitization potential for 51 organic compounds, revealing key structural determinants. Aromatic compounds exhibited higher sensitizing potential than aliphatics, except for carbonyl-containing molecules where aliphatics dominated. Critical features increasing sensitization included electrophilic character, hydrophilicity, nitrogen atoms, triple bonds, and the Al-C(=X)-Al fragment [39].**

**Complementing this, Nandy et al. built a Linear Discriminant Analysis (LDA) model using 147 chemicals to modernize sensitization prediction. Their validated model identified:**

**Negative correlations**: Rotatable bonds (molecular flexibility)

**Positive correlation**: Dragon branching index

**Neutral contributors**: Quadric index, nitrogen atoms  
**Application to DrugBank demonstrated utility for identifying sensitizing compounds, advancing computational toxicology [50].**

**Conclusion and Future direction**

**The advent of AI and ML represents a transformative phase in pharmacovigilance, offering promising prospects for early detection of adverse drug reactions (ADRs) and drug-induced toxicities.** These technologies have revolutionized the analysis and mitigation of medication-related risks. Real-time monitoring holds particular potential, as AI/ML algorithms can swiftly identify probable ADRs – enabling prompt interventions that reduce patient harm, especially with expanding remote monitoring capabilities. Despite progress, critical needs persist: more accurate models for complex datasets (where deep learning’s pattern recognition in high-dimensional data shows promise), resolution of "black box" opacity to build clinician trust, and integration with electronic health records to mine unstructured data for ADR signals. Furthermore, convergence with genomic data enables personalized ADR predictions, tailoring treatments to genetic profiles. Though nascent, these applications hold immense potential to enhance drug safety, reduce healthcare costs, and save lives – fundamentally reshaping pharmacovigilance.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

REFERENCE

1. J.A. DiMasi, H.G. Grabowski, R.W. Hansen Innovation in the pharmaceutical industry: new estimates of R&D costs J. Health Econ., 47 (2016), pp. 20-33
2. R.K. Harrison Phase II and phase III failures: 2013–2015 Nat. Rev. Drug Discov., 15 (2016), pp. 817-818
3. World Health Organization Quality Assurance and Safety of Medicines Team, Safety of medicines: a guide to detecting and reporting adverse drug reactions: why health professionals need to take action., (2002).
4. C. Kongkaew, P.R. Noyce, D.M. Ashcroft Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies Ann. Pharmacother., 42 (2008), pp. 1017-1025
5. E.S. Björnsson Drug-induced liver injury: an overview over the most critical compounds

Arch. Toxicol., 89 (2015), pp. 327-334

1. J. Sultana, P. Cutroneo, G. Trifirò Clinical and economic burden of adverse drug reactions J. Pharm. Pharm., 4 (2013), pp. S73-S77
2. T. Hartung Toxicology for the twenty-first century Nature, 460 (2009), pp. 208-212
3. S. Kar, K. Roy QSAR of phytochemicals for the design of better drugs Expert Opin. Drug Discov., 7 (2012), pp. 877-902
4. P. Zhang, F. Wang, J. Hu, R. Sorrentino Towards personalized medicine: leveraging patient similarity and drug similarity analytics AMIA Jt Summits Transl. Sci. Proc., 2014 (2014), pp. 132-136
5. E.J. Topol High-performance medicine: the convergence of human and artificial intelligence Nat. Med., 25 (2019), pp. 44-56 2023 June 13
6. P.B. Jensen, L.J. Jensen, S. Brunak Mining electronic health records: towards better research applications and clinical careNat. Rev. Genet., 13 (2012), pp. 395-405
7. M. Liu, Y. Wu, Y. Chen, J. Sun, Z. Zhao, X.-W. Chen, M.E. Matheny, H. Xu Large-scale prediction of adverse drug reactions using chemical, biological, and phenotypic properties of drugs J. Am. Med Inf. Assoc., 19 (2012), pp. e28-e35
8. D.W. Bates, R.S. Evans, H. Murff, P.D. Stetson, L. Pizziferri, G. Hripcsak Detecting adverse events using information technology J. Am. Med Inf. Assoc., 10 (2003), pp. 115-128
9. A. Cherkasov, E.N. Muratov, D. Fourches, A. Varnek, I.I. Baskin, M. Cronin, J. Dearden, P. Gramatica, Y.C. Martin, R. Todeschini, V. Consonni, V.E. Kuz’min, R. Cramer, R. Benigni, C. Yang, J. Rathman, L. Terfloth, J. Gasteiger, A. Richard, A. Tropsha QSAR modeling: where have you been? Where are you going to? J. Med. Chem., 57 (2014), pp. 4977-5010
10. A. Mayr, G. Klambauer, T. Unterthiner, S. Hochreiter DeepTox: toxicity prediction using deep learning Front. Environ. Sci., 3 (2016)16
11. J. Vamathevan, D. Clark, P. Czodrowski, I. Dunham, E. Ferran, G. Lee, B. Li, A. Madabhushi, P. Shah, M. Spitzer, S. Zhao Applications of machine learning in drug discovery and development Nat. Rev. Drug Discov., 18 (2019), pp. 463-477 View at publisherCrossrefView in ScopusGoogle Scholar
12. 17J.H. Kim, A.R. Scialli Thalidomide: the tragedy of birth defects and the effective treatment of disease Toxicol. Sci., 122 (2011), pp. 1-6 Google Scholar
13. W. Lenz A short history of thalidomide embryopathy Teratology, 38 (1988), pp. 203-215 View at publisherCrossrefView in ScopusGoogle Scholar
14. M.T. Miller, K. Strömland Teratogen update: thalidomide: a review, with a focus on ocular findings and new potential uses Teratology, 60 (1999), pp. 306-321 View in ScopusGoogle Scholar
15. F.O. Kelsey Thalidomide update: regulatory aspects Teratology, 38 (1988), pp. 221-226 View at publisherCrossrefView in ScopusGoogle Scholar
16. H.M. Krumholz, J.S. Ross, A.H. Presler, D.S. Egilman What have we learnt from Vioxx? Bmj, 334 (2007), pp. 120-123 View at publisherCrossrefView in ScopusGoogle Scholar22
17. B. Sibbald Rofecoxib (Vioxx) voluntarily withdrawn from market Cmaj, 171 (2004), pp. 1027-1028 View in Scopus Google Scholar
18. FDA approval of lymphoma medicine Ukoniq (umbralisib) is withdrawn due to safety concerns; [cited 2023 June 13]. Available from: 〈https://www.fda.gov/drugs/drug-safety-and-availability/fda-approval-lymphoma-medicine-ukoniq-umbralisib-withdrawn-due-safety-concerns〉.Google Scholar
19. FDA granted accelerated approval to belantamab mafodotin-blmf for multiple myeloma; [cited 2023 June 13].Available from: 〈https://www.fda.gov/drugs/resources-information-approved-drugs/fda-granted-accelerated-approval-belantamab-mafodotin-blmf-multiple-myeloma〉,Google Scholar
20. FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer; [cited 2023 June 13]. Available from: 〈https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-locally-advanced-or-metastatic-triple-negative〉,Google Scholar
21. Analysis and recommendations for Agency action regarding non- steroidal anti-inflammatory drugs and cardiovascular risk; [cited 2023 June 13]. Available from: 〈https://www.fda.gov/media/74279/download〉,Google Scholar
22. FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market; [cited 2023 June 13]. Available from: 〈https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market#:∼:text=On%20February%2013%2C%202020%20FDA,an%20increased%20occurrence%20of%20cancer〉.,Google Scholar
23. D. Halegoua-De Marzio, V.J. Navarro Chapter 29 - hepatotoxicity of cardiovascular and antidiabetic drugs N. Kaplowitz, L.D. DeLeve (Eds.), Drug-Induced Liver Disease (Third Edition), Academic Press (2013), pp. 519-540, 10.1016/B978-0-12-387817-5.00029-7 View PDFView article View in Scopu sGoogle Scholar
24. H.P. Parkman Chapter 24 - Prokinetic agents for gastroparesis R.W. McCallum, H.P. Parkman (Eds.), Gastroparesis, Academic Press (2021), pp. 323-339, 10.1016/B978-0-12-818586-5.00024-7 View PDF View articleGoogle Scholar
25. S. Czernichow, G.D. Batty Withdrawal of sibutramine for weight loss: where does this leave clinicians? Obes. Facts, 3 (2010), pp. 155-156 View in ScopusGoogle Scholar31
26. Withdrawal of sibutramine for weight loss: where does this leave clinicians? Obes. Facts, 3 (2010), pp. 155-15632
27. S. Gottlieb Antihistamine drug withdrawn by manufacturer Bmj, 319 (1999), p. 7
28. P.C. Hébert, D.A. Fergusson, B. Hutton, C.D. Mazer, S. Fremes, M.Blajchman, C. MacAdams, G. Wells, J. Robblee, J. Bussières, K. Teoh

Regulatory decisions pertaining to aprotinin may be putting patients at risk Cmaj, 186 (2014), pp. 1379-1386

1. W.J. Wight, P.M. Wright Pharmacokinetics and pharmacodynamics of rapacuronium bromide Clin. Pharm., 41 (2002), pp. 1059-1076
2. M.B. Zazzara, K. Palmer, D.L. Vetrano, A. Carfì, G. Onder Adverse drug reactions in older adults: a narrative review of the literature Eur. Geriatr. Med., 12 (2021), pp. 463-473
3. I. Kola, J. Landis Can the pharmaceutical industry reduce attrition rates? Nat. Rev. Drug Discov., 3 (2004), pp. 711-716
4. O. World Health. (2002). The importance of pharmacovigilance. In. Geneva: World Health Organization.
5. G. Patrick Getting the drug to market In An Introduction to Medicinal Chemistry, Oxford University Press,(2017), pp. 274-305
6. R.S. Obach, J.G. Baxter, T.E. Liston, B.M. Silber, B.C. Jones, F. MacIntyre, D.J. Rance, P. Wastall The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data J. Pharm. Exp. Ther., 283 (1997), pp. 46-58
7. Z. Zhang, W. Tang Drug metabolism in drug discovery and development Acta Pharm. Sin. B, 8 (2018), pp. 721-732
8. J. Brian Houston, D.J. Carlile Prediction of hepatic clearance from microsomes, hepatocytes, and liver slices Drug Metab.Rev., 29 (1997), pp. 891-922
9. J.C. Kalvass, S.M. Tristan, M.P. Gary Use of plasma and brain unbound fractions to assess the extent of brain distribution of 34 drugs: comparison of unbound concentration ratios to in vivo p-glycoprotein efflux ratios Drug Metab. Dispos., 35 (2007), p. 660
10. M. Rowland, & T.N. Tozer. (2010). Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications Fourth Edition. LWW.
11. Y. Qiu, Y. Chen, G. Zhang, L. Yu, & R.V. Mantri. (2016). Developing Solid Oral Dosage Forms-Pharmaceutical Theory and Practice, 2nd Edition. Elsevier.
12. R. Collier Rapidly rising clinical trial costs worry researchers Cmaj, 180 (2009), pp. 277-278
13. U.S.Fa.D. Administration Drug Dev. Process (2018)
14. S.-M. Huang, J. Lertora, P. Vicini, & J. Arthur Atkinson (2021). Atkinson's Principles of Clinical Pharmacology, 4th Edition. Elsevier.

48. K.I. Kaitin, J.A. DiMasi Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000-2009 Clin. Pharm. Ther., 89 (2011)

49.E.L. Eisenstein, R. Collins, B.S. Cracknell, O. Podesta, E.D. Reid, P. Sandercock, Y. Shakhov, M.L. Terrin, M.A. Sellers, R.M. Califf, C.B. Granger, R. Diaz

Sensible approaches for reducing clinical trial costs Clin. Trials, 5 (2008), pp. 75-84

50.C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. FeeneyExperimental and computational approaches to estimate solubility and permeability in drug discovery and development settings Adv. Drug Deliv. Rev., 46 (2001), pp. 3-26

51.A. Gabizon, R. Catane, B. Uziely, B. Kaufman, T. Safra, R. Cohen, F. Martin, A. Huang, Y. Barenholz Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes Cancer Res., 54 (1994), pp. 987-992

52.Braeuning, R.A. Budinsky, B. Burkhardt, N.R. Cameron, G. Camussi, C.-S. Cho, Y.-J. Choi, J. Craig Rowlands, U. Dahmen, J.G. Hengstler Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME Arch. Toxicol., 87 (2013), pp. 1315-1530

53.W.J. Pichler Delayed drug hypersensitivity reactions Ann. Intern Med, 139 (2003), pp. 683-693

54.E. Tiligada, M. Ishii, C. Riccardi, M. Spedding, H.U. Simon, M.M. Teixeira, M.L. Cuervo, S.T. Holgate, F. Levi-Schaffer The expanding role of immunopharmacology: IUPHAR Review 16 Br. J. Pharm., 172 (2015), pp. 4217-4227

55. L.B. Schwartz Effector cells of anaphylaxis: mast cells and basophils Novartis Found. Symp., 257 (2004), pp. 65-74 discussion 74-69, 98-100, 276-185