The AAPS Journal (2023) 25:67
https://doi.org/10.1208/s12248-023-00826-1

RESEARCH ARTICLE

Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict *In Vivo* Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study

Gopal Pawar[1] · Fang Wu[2] · Liang Zhao[2] · Lanyan Fang[2] · Gilbert J. Burckart[3] · Kairui Feng[2] · Youssef M. Mousa[2] · Abdullah Al Shoyaib[2] · Marie-Christine Jones[1] · Hannah K. Batchelor[4]

Received: 5 January 2023 / Accepted: 25 May 2023 / Published online: 29 June 2023

Abstract

This study investigated the impact of gastro-intestinal fluid volume and bile salt (BS) concentration on the dissolution of carbamazepine (CBZ) immediate release (IR) 100 mg tablets and to integrate these *in vitro* biorelevant dissolution profiles into physiologically based pharmacokinetic modelling (PBPK) in pediatric and adult populations to determine the biopredictive dissolution profile. Dissolution profiles of CBZ IR tablets (100 mg) were generated in 50–900 mL biorelevant adult fasted state simulated gastric and intestinal fluid (Ad-FaSSGF and Ad-FaSSIF), also in three alternative compositions of biorelevant pediatric FaSSGF and FaSSIF medias at 200 mL. This study found that CBZ dissolution was poorly sensitive to changes in the composition of the biorelevant media, where dissimilar dissolution (F2 = 46.2) was only observed when the BS concentration was changed from 3000 to 89 µM (Ad-FaSSIF *vs* Ped-FaSSIF 50% 14 BS). PBPK modeling demonstrated the most predictive dissolution volume and media composition to forecast the PK was 500 mL of Ad-FaSSGF/Ad-FaSSIF media for adults and 200 mL Ped-FaSSGF/FaSSIF media for pediatrics. A virtual bioequivalence simulation was conducted by using Ad-FaSSGF and/or Ad-FaSSIF 500 mL or Ped-FaSSGF and/or Ped-FaSSIF 200 mL dissolution data for CBZ 100 mg (reference and generic test) IR product. The CBZ PBPK models showed bioequivalence of the product. This study demonstrates that the integration of biorelevant dissolution data can predict the PK profile of a poorly soluble drug in both populations. Further work using more pediatric drug products is needed to verify biorelevant dissolution data to predict the *in vivo* performance in pediatrics.

Keywords carbamazepine tablets · *in vitro* dissolution · PBPK · pediatric biorelevant dissolution media · virtual bioequivalence

Introduction

Dissolution is commonly used as an *in vitro* testing method for orally administered drug products, such as tablets. Typically, biopredictive dissolution methods can use biorelevant media that is designed to simulate the composition of gastrointestinal (GI) fluids, such as fasted state simulated gastric fluid (FaSSGF) and fasted state simulated intestinal fluid (FaSSIF) which are both derived from the characterization of healthy adults GI media

✉ Gopal Pawar
G.Pawar@bham.ac.uk

✉ Fang Wu
Fang.Wu@fda.hhs.gov

✉ Hannah K. Batchelor
Hannah.batchelor@strath.ac.uk

[1] School of Pharmacy, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

[2] Division of Quantitative Methods and Modelling, Office of Research and Standard, Office of Generic Drug Products, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland 20993, USA

[3] Office of Clinical Pharmacology, Office of Translational Science, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland 20993, USA

[4] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, UK

composition (1, 2). However, the solubility of drug substances (and hence dissolution profiles of oral drug products) in pediatric GI fluid may be different from those in adults due to inherent differences in GI fluid volume (3) and composition, for example in terms of bile salt (BS) concentrations (4).

Biorelevant pediatric Ped-FaSSGF media has been proposed previously, based on literature-reported BS concentration (5, 6), where values were lower in neonates (20 μM) and infants (60 μM) in comparison to adults (80 μM). Moreover, due to the lack of accurate data on pediatric BS concentrations, simulated Ped-FaSSIF media with BS concentrations corresponding to 50 and 150% (1.5 and 4.5 mM) of adult content (3 mM) were proposed as an alternative media for exploratory studies (5). Recent studies that characterized pediatric gastric and intestinal fluids measured a lower BS concentration in pediatric fasted state intestinal fluids compared to adults (0.18 mM *vs* 3 mM) (4, 7–9) providing new data on which pediatric simulated media can be developed.

The volume of dissolution media is a critical factor in designing the *in vitro* dissolution method for poorly soluble drug substances. Generally, the recommended dissolution volume in USP I/II apparatus is 500 mL, which more closely resembles the GI volume in adults (10). The volume of fluids in pediatric populations has been reported in two recent studies where the fasted gastric volume was reported to be a maximum of 8 mL in a population from 0 to 16 years ($n=32$) (3) although an alternative study suggested a median volume of 5.0 mL in infants and 26.6 mL in adolescents (11). The corresponding fasted state intestinal fluids were reported to reach a maximum of 51 mL in a population from 0 to 16 years ($n=32$) (3) or have a median volume of 23.9 mL in infants and 62.9 mL in adolescents (11). When considering the dissolution volume to use, an important consideration is the fluid volume administered with a tablet which is typically 240 mL in adults whereas previous data on relative bioavailability studies suggest a volume of 120 mL in children (12, 13).

Physiologically based pharmacokinetics (PBPK) modeling uses mathematical models and simulations to combine animal or human physiological data with drug characteristics to mechanistically describe the PK behaviors of a drug (14). PBPK has been particularly useful in pediatric drug development as it can factor ontogeny into relevant predictions (15–17), making quantitative predictions in pregnancy and in the fetus (18, 19), and in examining pediatric predictions in drug absorption in varying age groups (20). PBPK models can also incorporate *in vitro* dissolution data to predict the *in vivo* performance of oral formulations and to verify the clinical relevance of *in vitro* dissolution data (21–23). The identification of a biopredictive dissolution method for pediatric populations and subsequent integration of the generated dissolution data into PBPK modeling would aid in de-risking pediatric clinical programs, specifically with reference to relative bioavailability studies or bioequivalence (BE) studies for generic drug products. Furthermore, virtual bioequivalence (VBE) trials using PBPK modeling could provide a powerful tool to predict and compare the *in vivo* performance of test drug products and reference listed drug (RLD) products by integrating the dissolution data generated by using the biorelevant medias and the inclusion of inter-subject variabilities.

Carbamazepine (CBZ) is an anti-convulsant drug used in adults/pediatric populations to control seizures and as a mood-stabilizing drug in patients suffering from bipolar disorder (trigeminal neuralgia), attention-deficit hyperactivity disorder (ADHD) and schizophrenia (24, 25). The solubility of CBZ in water was measured to range from 0.14 to 0.27 mg/L at 25°C (26) According to the Biopharmaceutics Classification System (BCS), CBZ is a BCS class II (poorly soluble; highly permeable) compound where dissolution is the rate limiting factor for its absorption (27). Due to its high pKa (11.8 or 14), no ionization of CBZ is expected within the physiological pH range (28). A previous study (5) showed that CBZ solubility in neonatal or infant FaSSGF, where the BS concentration was, respectively, 25% (20 μM) or 75% (60 μM) of adult values (80 μM), was significantly reduced at the lower BS concentrations. However, the impact on solubility of CBZ upon varying the BS concentration in FaSSIF media from 50 to 150% (1.5–4.5 mM) was not significant (29). The impact of gastric fluid volume (135 mL in neonates, 120 mL in infants) on the dissolution of the reference product, Tegretol© (carbamazepine) 200 mg tablets, was reported using the USP4 Flow-through-apparatus and media volumes selected to match those in neonates and infants. In all cases, dissolution was incomplete due to volume-limited dissolution (29). No data is available on dissolution of CBZ pediatric suspensions which may be the more commonly used dosage form for such young patients.

To better understand the impact of biorelevant dissolution conditions on the release of CBZ from a tablet formulation and to integrate these dissolution profiles into PBPK software to evaluate the impact on the predicted PK profile in pediatric and adult populations, this work seeks to explore the following objectives:

- To compare *in vitro* dissolution profiles of CBZ IR tablets using industry recommended USP media as well as biorelevant simulated adult and pediatric medias.
- To explore the impact of dissolution media volume on the dissolution profiles of CBZ tablet.
- To compare the dissolution profiles of the RLD and generic CBZ 100 mg IR tablets using USP media, adult biorelevant, and our new proposed pediatric biorelevant media for PBPK-based virtual BE testing.

- PBPK model development and validation for CBZ to identify the absorption factors that could result in bioinequivalence between pediatric and adult populations or between branded or generic CBZ product by integrating the biorelevant dissolution data into a CBZ PBPK model.

Materials and Methods

Chemicals

Bile Salts Cholic acid (CA); glycocholic acid (GC); glycochenodeoxycholic acid (GCDC); glycodeoxycholic acid (GDC); glycoursodeoxycholic acid (GUDC); taurocholic acid (TC); taurochenodeoxycholic acid (TCDC); taurodeoxycholic acid (TDC); tauroursodeoxycholic acid (TUDC); taurolithocholic acid (TLC); deoxycholic acid (DC), lithocholic acid (LC), and ursodeoxycholic acid (UDC) were purchased from either Sigma Aldrich (Gillingham, UK) or Acros Organics (Fisher Scientific, Loughborough, UK).

CBZ powder, sodium-lauryl-sulfate (SLS), lecithin, pepsin, acetonitrile HPLC grade, sodium hydroxide (NaOH), and hydrochloric acid (HCL) were purchased from Sigma Aldrich (Gillingham, UK). Biorelevant powder (Ad-FaSSGF/Ad-FaSSIF) was purchased from Biorelevant (https://biorelevant.com/; London, UK).

Tegretol© 100 mg tablets (Novartis Pharmaceuticals UK Limited, Batch No-B00964; Exp-07/2023) were used as RLD and Carbamazepine Medreich 100 mg tablets (Medreich PLC, Feltham, UK) as a generic product. Tegretol© was purchased from Queen Elizabeth Hospital Pharmacy (Birmingham, UK) and generic product from New Castle Healthcare NHS pharmacy.

Preparation of Dissolution Media

USP Media SLS (1% w/v) was added to Milli-Q Type-1 (18.2 MΩ cm^{-1}) water and stirred at 40°C for 2 h. The pH was adjusted to enable comparison with biorelevant dissolution media. The pH of the USP media was adjusted (but not buffered) to either 1.2 (to mimic gastric pH) by adding 0.1 N HCl or to 6.5 (to mimic intestinal pH) by adding 0.1 M NaOH before use. All pH-adjusted USP dissolution media were prepared on the day of the experiment and used within 4 h of preparation (30, 31).

Adult Biorelevant Media Ad-FaSSGF.V2 (pH 1.2) and Ad-FaSSIF.V2 (pH 6.5) (9, 32) were prepared according to the protocol provided by the supplier, Biorelevant (London, UK). The pH of the media Ad-FaSSGF.V2 was adjusted (but not buffered) to either 1.2 by adding 0.1 N HCl or to 6.5 by adding 0.1 M NaOH before use. Media was used within 48 h of preparation. FaSSIF V2 media is the most widely used simulated intestinal fluid despite more recent versions and reviews of further characterization of adult intestinal fluids (8, 32, 33).

In the literature, FaSSGF-V2 has a pH value of 1.6, but we modified it to pH 1.2 for this study as described above. The traditional medium to simulate gastric conditions in the fasted state was USP simulated gastric fluid (SGF) which has a pH of 1.2. Note that due to the pH independent solubility of CBZ, this slight difference in pH would not have a significant impact on this study (34). In addition to this, a range of ~ 1 to 3 has been reported for gastric pH in fasted healthy humans after they have ingested a glass of water (35).

In this study, Ad-FaSSGF contained taurocholate to represent the bile salt concentration (0.08 mM), phospholipids (0.02 mM), sodium (34 mM), and chloride (59 mM). The Ad-FaSSIF media contained taurocholate (3 mM), phospholipids (0.75 mM), sodium (148 mM), chloride (106 mM), and phosphate (29 mM).

Pediatric Biorelevant Media

Ped-FaSSGF/FaSSIF (14BS) Media Ped-FaSSGF containing 14 bile salts (14BS) and Ped-FaSSIF (14BS) were prepared based on the median concentrations (mM) (0.016 mM for Ped-FaSSGF and 0.178 mM for Ped-FaSSIF) of bile acids present in the gastric or intestinal fluid samples aspirated from children reported previously (4). All the ingredients listed in Supplementary Table S1 were added to Milli-Q Type-1 (18.2 MΩ cm^{-1}) water and stirred for 2 h until completely dissolved; the pH of each media was then adjusted to either 1.2 by adding 0.1 N HCL or to 6.5 by adding NaOH before use. Ped-FaSSGF and Ped-FaSSIF were stored at 8°C and used within 48 h of preparation.

Ped-FaSSGF/FaSSIF (50% 14BS) Media This media was prepared to contain 50% of the concentration of each BS reported previously (4) by diluting the Ped-FaSSGF/FaSSIF media containing the 14 BS with Milli-Q Type-1 water. As a result of dilution, the concentration of other components such as sodium chloride, lecithin, and pepsin was also reduced to 50% of the originally reported concentration. Finally, the pH of the prepared 50% 14BS media was adjusted to either pH 1.2 or 6.5 by adding 0.1 N HCL or NaOH, respectively. This 50% version was included to provide a "worst-case" scenario as there was large variability in the measured bile salt concentrations from the GI fluids of pediatric participants (4).

Ped-FaSSGF/FaSSIF (Na TCA) Media Ad-FaSSGF and Ad-FaSSIF contained only a single bile salt, Na TCA (3 mM in Ad-FaSSIF; 0.08 mM in Ad-FaSSGF); therefore,

Ped-FaSSGF/FaSSIF media containing only Na TCA were also prepared. Na TCA concentrations mimicked the total bile acid concentration found in the 14 BS pediatric media.

High Performance Liquid Chromatography (HPLC) Method Development

HPLC methodology was based on previous methods (36, 37) where the accuracy and specificity were previously reported. In brief, HPLC analysis of CBZ was carried out using an Agilent (1260 infinity 2) HPLC equipped with binary pump, DAD detector UV at 285 nm, and C18 column (Ascentis: 25 cm, 5 µm, 4.6 mm). The mobile phase was water and acetonitrile at a ratio of 6:4 (v/v) which ran in isocratic mode at a flow rate of 1.0 mL/min. The injection volume was 5 µL, and the run time was 10 min (min), followed by 1-min post run to avoid any co-elution or carry-over of the analyte.

Calibration Standards CBZ Calibration standards (0.002–1 mg/mL) were prepared in all the different adult/pediatric FaSSGF/FaSSIF media to exclude any interference or matrix effect (CBZ HPLC peak and calibration standards provided in Supplementary Figures S1A to S1K).

In Vitro Dissolution Study

Dissolution studies were conducted in accordance with USP dissolution (General chapter 711) guidelines (38) using USP apparatus 2 (Copley Scientific, Nottingham, UK). The temperature of dissolution medium in vessels was maintained at 37.0°C ± 0.5°C. Six replicates/units were used for each experiment. The size of the dissolution vessel was changed for smaller volumes (200 mL, 100 mL, and 50 mL) to match the hydrodynamics of the standard vessels. To scale down the volumes, low-volume conversion kits (Copley, UK) comprising vessels of either 100- or 200-mL capacity with appropriate mini-paddles, vessel cover, and centering ring assemblies were used. One mL of dissolution medium was withdrawn without replacement at each pre-specified time point (15, 30, 60, 90, 120, and 150 min) and filtered using Agilent's 13-mm syringe filters (polypropylene 0.45 µm pore size) before analysis using the validated HPLC method. A summary of the dissolution conditions is presented in Supplementary Table S2. The dissolution studies were all conducted using a 100 mg CBZ tablet. This tablet strength is not available in the USA but is available in the UK (25). This strength was selected to use the lowest dose to be applicable to pediatric populations and also to minimize the solubility effects when evaluating the dissolution conditions (30); the lower strength enabled the maximum discrimination between the dissolution conditions and also accounts for the high permeability of CBZ to best enable integration into the PBPK modeling software.

Dissolution Data Analysis

Similarity between two dissolution profiles was determined by the difference factor (F1) and similarity factor (F2) (39) calculated as follows:

$$F1 = \frac{\sum_{t=1}^{t=n} |R_t - T_t|}{\sum_{t=1}^{t=n} R_t} \times 100 \quad (1)$$

$$F2 = 50 \times \log\left[\frac{100}{\sqrt{1 + \sum_{t=1}^{t=n} (R_t - T_{t)2}}}\right] \quad (2)$$

where R_t = Dissolution (% label claim) for reference (R) formulation at time t

T_t Dissolution (% label claim) for test (T) formulation at time t.

n number of time points

Generally, three or more dissolution sampling timepoints with one measurement after 85% dissolution are required to calculate F1 and F2. The compared dissolution profiles are considered similar when F1 ≤ 15 and F2 ≥ than 50.

CBZ PBPK Model

A PBPK model for CBZ was developed using SimCyp® Simulator (Version 21, Release 1; Certara UK Limited, Sheffield, UK) that incorporated drug-dependent and system-related input parameters obtained from SimCyp's internal compound library (Supplementary Table S4). The *in vitro* dissolution datasets generated in the "In Vitro Dissolution Study" section were incorporated into SimCyp® Simulator Advanced Dissolution, Absorption and Metabolism (ADAM) model; full details of the dissolution data that was integrated are provided in Supplementary Table S3.

The dissolution profiles using various BS concentrations and dissolution volumes were integrated into SimCYP according to the methods previously described by Guimaraes (2002) (40). In brief, a single-stage fasted intestinal profile (FaSSIF dissolution conditions as an intestinal profile) was integrated as the "intestinal profile." Using this approach, the software considers the same dissolution profile for the stomach and intestinal compartments (FaSSIF dissolution conditions). A second scenario was also included where both the single-stage fasted gastric and intestinal profiles (input of the CBZ single-stage dissolution profile in fasted state simulated gastric fluids (FaSSGF) entered as "stomach profile" and single-stage dissolution profile in fasted state simulated intestinal fluids entered as "intestinal profile" thus incorporating both FaSSGF + FaSSIF dissolution conditions.

Model prediction was validated using published clinical PK studies with CBZ (Tegretol© IR 100 or 200 mg) conducted in an adult population (41–44). Note that, here, the term validation is used as defined by Kuemmel 2019, "Process of determining the degree to which a model or simulation is an accurate representation of the real world." In other terms, "validation relates to model (model form, model inputs), comparator (test samples, test conditions), and assessment (equivalency of input parameters, output comparisons)" (45).

SimCyp Pediatric Version 21 (Release 1) was used as the pediatric PBPK (ped-PBPK) modeling platform. CBZ specific properties (including its metabolic clearance) used in the adult PBPK model (Supplementary Table S4) were transferred into the pediatric model (Supplementary Table S5). The metabolic clearance of CBZ is mediated by CYP3A4, CYP 3A5, and CYP2C8; hence, the ontogeny of CBZ-metabolizing enzymes in pediatric populations was expressed according to the following sigmoidal function (Eq. 3) which is a default equation used in SimCyp (46, 47).

$$\text{Fraction of adult} = F_{\text{Birth}} + (F_{\max} - F_{\text{Birth}}) \times \text{Age}^n / (\text{Age}_{50}{}^n + \text{Age}^n) \quad (3)$$

where $F_{\max}$ is the maximum adult relative expression, F_{birth} is the relative expression of enzyme at birth, Age_{50} is the age at which the fractional expression (/activity) is in the middle of the birth and adult values, and n is the exponent related to the sigmoidicity of the developmental curve or analogous to the Hill coefficient.

In order to incorporate the age-dependent expression pattern of CYP3A4, CYP3A5, and CYP2C8 in the pediatric PBPK model, the time to reach 50% maturation (Age_{50}) for each enzyme was used. The Age_{50} of hepatic and intestinal CYP3A4 maturation was 0.64 and 2.36 years, respectively (47–49). For CYP3A5, since no age-dependent change in hepatic expression was noted (50), no ontogeny for hepatic CYP3A5 was assumed in this study but for intestinal ontogeny, similar Age_{50} value (i.e., 2.36) of CYP3A4 was considered. For CYP2C8 ontogeny, Age_{50} of hepatic maturation was 0.366 years (51). A zero value was used for intestinal CYP2C8 ontogeny due to lack of abundance data (52).

Generally, young children have lower volume of distribution (Vss) for lipophilic drugs due to reduced body fat compared to adults. Due to lack of a volume of distribution (Vd) values in children, a Vd of 0.3 L/kg in young children (compared to 0.78–1.9 L/kg in adults) was estimated by our visual trial and error simulations in order to fit the pediatric PBPK model to the observed data (53). Moreover, the volume of fluid intake with CBZ tablet was changed to 120 mL for pediatric populations compared to 240 mL for adult populations in line with reported clinical protocols (13).

The CBZ model was validated in adults by calculating the prediction error percentage (PE%) fold error (FE), average fold error (AFE), and absolute average fold error (AAFE) for Cmax and AUC. The adult model was subsequently updated and applied to children (6–15 years) and further verified and validated using clinical PK data conducted in children on 20 mg/kg dose ($n=12$) by Hartley (1991) (54) and 9.3 mg/kg dose ($n=6$) by Bano (1986) (55) (Table III).

This PBPK model was also used to predict the plasma concentration profile of CBZ in pediatric populations younger than 6 years to better understand the potential differences in CBZ exposure between children younger and older than 6 years old when CBZ was administered as an IR suspension (prepared from crushed Tegretol© tablets) (56). CBZ doses of 17 and 19 mg/kg suspension were tested in 20.9 days newborn ($n=7$; 3.2 kg; 25 mL water) and 5.1-year-old children (1.25–8 years; $n=5$; 120 mL water), respectively (56). Based on the fraction absorbed (66%) from the IR suspension (42), the 66% was assumed to be dissolved for an IR suspension to run the simulations in younger (< 6 years) pediatric population. This assumption would be a limitation of model simulations, and any future dissolution work would help to further improve the model prediction.

Due to higher clearance values in younger children (57), a clearance value of 3.18 L/h (42) was used to run the model; the volume of distribution (Vss) was fitted (by visual observation of the superimposed predicted and observed datasets) (2.6 L/kg for 20.9 days new-born and or 2.850 L/kg for 5.1 years child) to capture the observed clinical datasets published in Rey (1979) study (56).

Virtual Bioequivalence (VBE) Studies

Preliminary exposure simulations were performed using the dissolution data generated in Ad-FaSSGF and Ad-FaSSIF 500 mL media for Tegretol© 100 mg IR tablets and the predicted PK profile was validated using literature data (Kohlman study (42); 200 mg IR tablet). Although the dissolution data was generated using 100 mg tablet, previous literature has reported that the dissolution of these IR tablets is similar to the 200 mg product used in the clinical study (54). So, the assumption of similar dissolution profiles for both 100 mg and 200 mg tablets was used for the simulation purposes.

VBE simulations were performed in a fully replicated, two treatment, multiple trials ($N=10$) in a cross-over design with a sample size of $n=12$,16, 24, 36, and 48 in healthy adults (18–45 years) (58). The number trials ($N=10$) were fixed as per the SimCyp VBE protocol (23, 58). A single dose of CBZ IR tablets 100 mg was administered with 240 mL of fluids. For VBE simulation, the dissolution profiles for Tegretol© 100 mg and generic product 100 mg (Medreich) generated in Ad-FaSSGF and FaSSIF 500 mL were incorporated into the adult PBPK model. The default coefficients of variation (%CV) for accounting the inter-subject variability of the physiological parameters provided in the SimCyp database

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.