

Reusable and Disposable Insulin Pens for the Treatment of Diabetes: Understanding the Global Differences in User Preference and an Evaluation of Inpatient Insulin Pen Use

Riccardo Perfetti, M.D., Ph.D.

Abstract

Insulin is essential for the management of type 1 diabetes and is more commonly being used for the treatment of type 2 diabetes. Insulin pen devices were first introduced over 20 years ago and have evolved to provide significant practical advantages compared with the vial and syringe. Pen devices are now used by patients with diabetes worldwide, but there are marked geographical variations in the use of reusable and disposable pens. In some countries the vial and syringe is still the most popular method of administering insulin, whereas in other countries the use of reusable or disposable pens is more prevalent. Therefore, the aim of this review is to discuss the factors that seem to be involved in these differences, which include patient access to insulin, cost, and physician/patient awareness and preference. Inpatient use of insulin is also common, and the use of insulin pens could offer substantial benefits in this patient population, not only during the admission period but also after discharge from the hospital. However, the evidence base for inpatient use is still weak, and more studies are needed to investigate the use of insulin pens in this patient population.

Introduction

THE PREVALENCE OF DIABETES worldwide was estimated to be in excess of 170 million patients in 2000¹ and is expected to increase to over 440 million among individuals 20–79 years of age by 2030.² Most of the cases will have type 2 diabetes, as type 1 diabetes represents less than 10% of all cases of diabetes. In type 2 diabetes, standard first-line therapy consists of metformin in combination with lifestyle modifications.³ However, ongoing intensification is usually necessary to achieve blood glucose control, and the American Diabetes Association/European Association for the Study of Diabetes³ advocate the introduction of insulin as second-line therapy or third-line therapy after metformin plus sulfonylurea, with further insulin intensification, as needed, to maintain A1c within an acceptable range (i.e., <7.0%). The Centers for Disease Control and Prevention estimated that, in the United States in 2007, 15.1% of patients with diabetes (any type) were using insulin alone, 11.5% were using insulin in combination with oral medications, and 50.6% were using oral medications, while the remainder were not using any treatment.⁴

Many approaches to insulin administration have been investigated in order to circumvent the common fear of injection, such as oral and inhaled insulin, in addition to needle-free

devices. However, injectable insulin is the mainstay approach and can be administered in three ways: vial and syringe, insulin pen devices, and insulin pump.

Since the first insulin pen was introduced in 1985, insulin pens have significantly influenced the treatment of diabetes. Other articles in this supplement will provide an overview of the options available in terms of insulin administration and the advantages and disadvantages of each approach. Therefore, this information will not be repeated here. In brief, insulin pens offer several advantages over the vial and syringe method, such as discretion of use, portability, reduced dose variability, and reduced risk of hypoglycemia.^{5–8} The reluctance of patients to initiate insulin therapy in a timely manner is an important factor to consider when developing new methods of insulin administration to address the common concerns regarding insulin therapy, such as social embarrassment or stigma and needle anxiety.⁹

These concerns, as well as constant improvements in existing technologies, have led to important developments in insulin pen technology.^{5,10} Some of the targets include ease of use and training, injection force, differentiating features, dose accuracy, maximum dose per injection, memory of the dose, and easier cartridge change, as well as improvements in needle technology with smaller/narrower needles and

sanofi-aventis, Paris, France.

portant when considering that, overall, the use of pens for insulin administration, particularly in the disposable form, is increasing.⁵

There are geographical variations in the methods used for injecting insulin worldwide (Fig. 1).¹⁷ The first aim of this review is to investigate potential reasons for these differences. As hospitalization is frequent for patients with diabetes and because, in some cases, it is an opportunity to initiate insulin in patients with type 2 diabetes with suboptimal glycemic control, the different methods of insulin administration within an inpatient setting should also be examined.

Global Patterns of Insulin Pen Use

Worldwide, insulin pens are used by just over 60% of insulin users; there are, however, marked differences between regions (Fig. 1).¹⁷ For example, in Japan, China, and Australia, approximately 95% of patients on insulin use insulin pens rather than other methods (e.g., vial and syringe or insulin pump).¹⁷ In contrast, insulin pens are only used by approximately 20% of insulin users in the United States and India.¹⁷ Furthermore, there are substantial differences in the use of reusable and disposable insulin pens among patients taking insulin. In France, Italy, Spain, Sweden, Turkey, Japan, and China, patients use a greater percentage of disposable pens. Patients taking insulin in Brazil, Canada, China, Germany, India, The Netherlands, and Poland use a greater percentage of reusable pens, whereas patients in Australia and the United Kingdom use reusable and disposable pens almost equally (Fig. 1).¹⁷

terms of insulin analogs, SoloSTAR[®] and ClikSTAR[®] (both Sanofi-aventis, Paris, France) are used for administration of insulin glargine and insulin glulisine, FlexPen[®] and NovoPen[®] 4 (Novo Nordisk, Bagsværd, Denmark) are used for administration of insulin detemir, insulin aspart, and premixed insulin aspart, and the Luxura[®] pen and KwikPen[™] and Humalog[®] prefilled pens (Eli Lilly and Co., Indianapolis, IN) (hereafter, the Humalog prefilled pen, also known as the “original prefilled pen,” is referred to as the Lilly prefilled pen) are available for insulin lispro and premixed insulin lispro formulations. Several insulin devices are also produced by third parties, such as Becton-Dickinson and Co. (Franklin Lakes, NJ), Owen Mumford (Woodstock, UK), and Ypsomed (Burgdorf, Switzerland). Many of these pens are also available in disposable form or can be fitted with cartridges to deliver manufacturer-specific human/neutral protamine Hagedorn (NPH) insulin-based products.

Although the restrictions relating to manufacturer and product specificity may affect the variations in pen use observed between regions, other factors, such as access to funding, local treatment guidelines, physician awareness, and patient preference, must also be considered.

Clinical Factors

Access

Perhaps one of the most important drivers for the use of a specific product by patients is the funding status and whether the product is reimbursed by the local/national health service

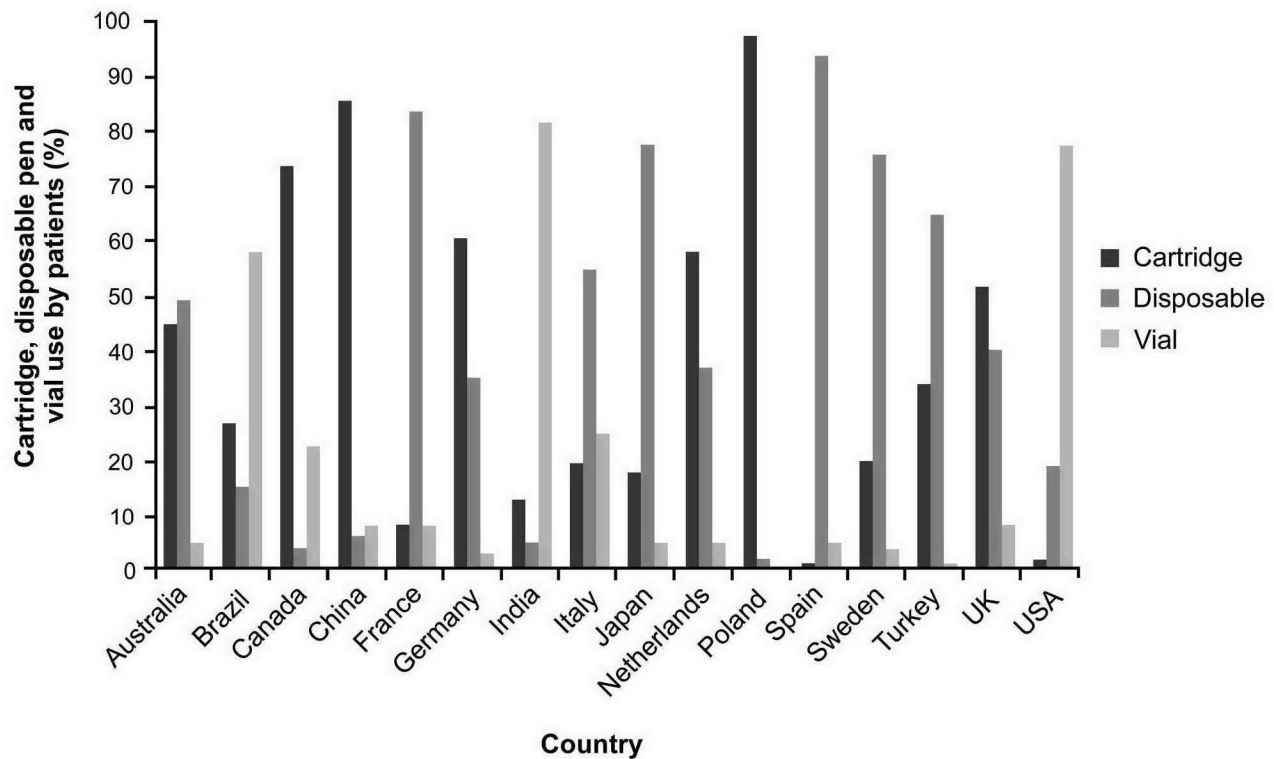


FIG. 1. Geographical variations in the use of pens versus vial and syringe to administer insulin worldwide (as of June 2009). Data are percentages of patients using reusable cartridge pens, disposable pens, and insulin vials. Data source: IMS Health.¹⁷

are dependent on the products approved for funding by the insurance provider. However, many insurance providers currently have a limited list of approved products. Similarly, for those individuals without health insurance who rely on Medicaid, a further reduced list of approved products may apply. Modern insulin analogs and their respective devices are widely available on the approved lists, but overall access for insulin administration with pens is lower than for the vial and syringe. Therefore, many patients may use the vial and syringe to inject their insulin regimen, and others have access only to early-era insulin such as NPH insulin and human insulin.

Thus, many insulin users in the United States and in other countries are unable to reap the benefits of pairing the most modern insulin analogs with devices that have been designed and engineered to facilitate their injection. It is important to try to change this situation. Recently published data have shown that using pen devices is cost-effective because it reduces the overall cost of the management of diabetes compared with syringe and needles. In a study of U.S. patient records,⁸ switching from the vial and syringe to insulin pens was associated with improved medication adherence and reduced the all-cause annual treatment costs by \$1,590 per patient (from \$16,359 to \$14,769; $P < 0.01$) after taking into account the greater device costs associated with insulin pens versus the vial and syringe. These lower costs were mainly the result of reduced healthcare costs attributable to hypoglycemia (\$1,415 vs. \$627; $P < 0.01$). This significant decrease was reflected in significant annualized mean savings, particularly for hospitalization (\$857 vs. \$288; $P < 0.01$) and pharmacy (\$254 vs. \$176; $P < 0.01$) costs.⁸ Decreases in costs of emergency visits and hospitalizations associated with hypoglycemia were largely driven by decreases in the mean annual number of emergency room visits and hospital length of stay.

A retrospective analysis of patients with type 2 diabetes on a Medicaid program in North Carolina¹⁸ showed that those who switched from oral antidiabetes agents to an insulin pen incurred significantly reduced total annualized healthcare costs compared with those who switched from oral antidiabetes agents to vial and syringe (\$14,857.42 vs. \$31,764.78, respectively; $P < 0.05$). These reduced costs were attributable to lower hospital costs (\$1,195.93 vs. \$4,965.31, respectively; $P < 0.05$), reduced diabetes-related costs (\$7,324.37 vs. \$13,762.21, respectively; $P < 0.05$), and reduced outpatient costs (\$7,795.98 vs. \$13,103.51, respectively; $P < 0.05$).

In the same study,¹⁸ total healthcare costs, excluding prescriptions for oral antidiabetes agents, insulin, or devices, were comparable for patients who switched from a syringe to a pen device ($n = 560$) (\$11,476.42) and for those who remained on syringe therapy ($n = 560$) (\$10,755.31). A cost reduction was observed in syringe-related resource use after switching to a pen (from \$670.52 to \$535.70). The overall medication adherence rate was significantly higher—although numerically only slightly higher—for patients who switched from syringe to pen than for those who remained on syringe therapy (92% vs. 90%, respectively; $P < 0.05$). However, the diabetes-related medication adherence rate for patients who switched from syringe to pen was significantly lower than for those who remained on syringe therapy (45%

lower adherence in patients who switched from syringe to pen devices. Added treatment costs could be one of the reasons for this observation. Alternatively, a change in insulin regimen could account for some of the differences; because NovoPen and FlexPen were the only pen devices included in this study, any changes to an insulin produced by a company other than Novo Nordisk were not considered in the analysis.

Based on these findings, the use of an insulin pen can reduce total treatment costs and should be more actively considered for reimbursement by health insurance schemes. Actual annual savings may range from \$1,600 to \$15,000.

Local treatment guidelines and insulin availability

A factor related to patient access is local clinical guidance. For example, in the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) develops its own recommendations, not only for a disease setting but also for specific treatments. In the NICE updated CG87 guidelines (available since May 2009) covering newer agents for type 2 diabetes,¹⁹ NICE recommends adding insulin when control of blood glucose remains or becomes inadequate ($HbA_{1c} \geq 7.5\%$ or other higher level agreed with the individual) with other measures. Thus, insulin is likely to have been underused in the United Kingdom as a result of previous guidelines. However, the new guidelines advocate its use for the treatment of type 2 diabetes and provide evidence to suggest that the new insulin analogs offer advantages over NPH insulin in terms of reduced rates of hypoglycemia. Following the publication of these new guidelines, the use of insulin analogs is expected to increase, which may also increase the use of pen devices.

Meanwhile, in Germany, there is no such support in terms of treatment guidelines for the use of insulin analogs.²⁰ As a consequence, a lower use of pen devices may be anticipated. However, as shown in Figure 1, pen devices, particularly reusable/cartridge pens, are more commonly used in Germany than the vial and syringe.

Physician Awareness

A survey of primary care physicians and endocrinologists²¹ in the United States indicates that the physicians' preferences in terms of pen use were a function of their personal and practice characteristics, as well as their perceptions of the pens themselves. Physician characteristics (specialty, therapeutic philosophy, and practices) play an important role in their decision regarding which treatment to give to their patients. The presentation of pens as an option to patients, by physicians, is strongly associated with perceived pen convenience and ease of use. However, physicians' pen recommendations and the estimated pen use/initiation of pen use by their patients are most strongly associated with the perception that pen use is better at facilitating self-care and blood glucose monitoring.

A survey of residents from Ontario, Canada, 66 years of age or older, who received a first prescription for insulin between 1998 and 2006 indicated that the proportion of patients using insulin pen devices increased from 46% in 1998 to 86% in 2006.²² Patients who started insulin under the guidance of a specialist were statistically more likely to use an insulin pen (odds ratio [OR], 2.24; 95% confidence interval [CI],

long-term care residences, where staff are more likely to administer insulin than patients, were less likely to use an insulin pen (OR, 0.51; 95% CI, 0.49–0.54). Initiation of insulin during hospitalization was also less likely to be with an insulin pen (OR, 0.74; 95% CI, 0.71–0.78).²²

Collectively, these surveys indicate profound variations in physician awareness of the advantages of insulin pens versus the vial and syringe, particularly for populations who may benefit most from these advantages. Another factor that should be considered is that the preference for using insulin pens rather than a vial and syringe may also be driven by the nursing staff and certified diabetes educators who are usually involved in delivering patient training. In one survey²³ of 112 pediatric diabetes specialist nurses across the United Kingdom, the patient's doctor was more commonly responsible for selecting the diabetes regimen (always, 20.5%; sometimes, 59%; never, 20.5%) than the pediatric diabetes nurse (always, 9%; sometimes, 67%; never, 24%); the patient's age was considered the most important criterion (always, 57%; sometimes, 31%; never, 12%). Similarly, the final decision on starting dose was more frequently made by the doctor than the diabetes nurse (25% vs. 9%). Interestingly, reusable pens were more commonly prescribed in this patient population than either disposable pens or syringe (86% vs. 27% vs. 17%), whereas pumps were not used as initial therapy. Similar findings were reported in a related survey²⁴ for patients with type 2 diabetes in the United Kingdom, which reported that the consultant physicians had the greatest influence for most decision-making, while nursing groups held varying perceptions of who made clinical decisions. Unfortunately, the findings of these two surveys may not be representative of other countries.

An additional aspect that should be taken into account is nurses' perception of insulin pens because of their role in treatment administration. To our knowledge, one study has assessed nurse satisfaction using insulin pens. That study surveyed 54 registered nurses in a community hospital after implementation of insulin pen devices.⁶ Overall, the study reported that nurses believed that insulin pens were more convenient, simple, and easy to use and provided an overall improvement compared with conventional vials/syringes.

Clearly, this is an area that warrants further research to determine how involved nurse practitioners and certified diabetes educators are in guiding the treatment of diabetes.

Patient Factors

Although access to treatment is an important factor, patient factors, such as patient preference, should also be considered. Some patients may prefer one method of administration over another; notably, studies have demonstrated patient preference for insulin pens versus the vial and syringe.^{25–27} Moreover, it seems feasible that cultural factors, such as the decision to use sustainable technologies, may also influence the patient's decision to use a specific device, although this has yet to be formally evaluated.

In a study conducted in Australia, 2,674 patients with diabetes who were provided with LANTUS[®] (insulin glargine; sanofi-aventis) SoloSTAR as part of their routine clinical practice participated in a telephone survey after 6–10 weeks of

majority (95.4%) reported that they were satisfied or very satisfied with using the device.²⁸ This was consistent with findings reported by the healthcare practitioners involved in the study.²⁹ However, the distinction between the preference for reusable and disposable insulin pens seems less clear. Therefore, using a reusable or disposable pen may reflect a combination of patient preference, devices available for specific insulin formulations, differences in costs, physician preference, and local availability of specific devices. Unfortunately, no study has yet investigated the reasons for the geographical differences in the use of reusable versus disposable pens.

From a patient's perspective, switching from the vial and syringe to insulin pens was associated with a reduced risk of experiencing a hypoglycemic event (OR, 0.50; 95% CI, 0.37–0.68; $P < 0.05$) based on the rates of hypoglycemia recorded during the over 6-month pre-index and over 2-year post-index periods.⁸ This in itself should provide a compelling reason to use insulin pen devices rather than the vial and syringe. This is supported by findings from a recent study³⁰ in which pen device-naïve patients reported greater preference for the KwikPen and FlexPen compared with the vial and syringe, which was particularly true for ease of use and ease of operation.

Interestingly, patients may prefer the specific pen features of one brand of pen versus another. For example, in a study by Haak et al.,³¹ 510 people with diabetes from the United States, France, Germany, and Japan were provided with three marketed prefilled insulin pens and a prototype pen. The participants were asked to rank their pens based on order of preference and then to rank their preferred features. In this study, significantly more participants expressed overall preference for SoloSTAR (53%) versus FlexPen (31%) and the Lilly prefilled pen (15%) ($P < 0.05$), and there were significant differences in terms of specific pen features. Of note is that more people preferred the reduced effort required to inject 40 U, ease of setting the dose, and ease/intuitiveness of using SoloSTAR versus the other pens, whereas the Lilly prefilled pen was preferred for the distance at which the dose button sticks out for 40 U and how well the cap fits the pen. Meanwhile, in a study by Ignaut et al.,³⁰ KwikPen and FlexPen were preferred over the vial and syringe by pen-naïve patients, but the KwikPen was significantly preferred over the FlexPen, suggesting that the KwikPen may be easier to use than the Lilly prefilled pen. As yet, no studies have compared KwikPen with SoloSTAR.

In terms of reusable pens, a study of 654 patients with diabetes from the United States, Canada, the United Kingdom, France, and Germany assessed the performance of ClikSTAR compared with NovoPen 3, NovoPen 4, and Luxura.³² For each pen type, a face-to-face questionnaire assessed the following features: fixing and replacing the cartridge, hearing and feeling the clicks, dialing and delivering a 40-U dose, and overall usability. In this study, ease of use and overall performance of ClikSTAR were equal to or better than those of NovoPen 3, NovoPen 4, and Luxura (Table 1).

It must be acknowledged that insulin pens may not be suitable for all patients. In particular, a large number of overweight and obese patients with type 2 diabetes are still likely to have insulin requirements exceeding the greatest dose per injection of the current insulin pens. For individuals who regularly inject more than 80 U per dose, a pen or

	Luxura	NovoPen 3	NovoPen 4	ClikSTAR
Overall score (%)				
Ease of use	79	50	83	86
Ease of completing task ^a				
Ease of use ^b	5.7*	4.5	5.7*	6.1 [†]
Cartridge replacement	6.0*	4.6	5.9*	6.2 [†]
Hearing/feeling clicks	6.0*/5.5	5.7/5.5	6.0*/5.8 [‡]	6.1*/5.9 [†]
Overall rating	3.4*	2.6	3.6 [‡]	3.7 [‡]
Difficulty completing task ^c				
Dialing 40 U	1.1	1.3 [§]	1.3 [§]	1.1
Delivering 40 U	1.2	1.2	1.1	1.1
Fixing cartridge	1.2	1.6 [†]	1.4 [§]	1.2
Safety	1.2	1.3 [§]	1.3 [§]	1.2

Reproduced with permission from Penformis.³²

^aOn a scale of 1–7, where 1 = not at all easy and 7 = extremely easy.

^bPercentage of patients rating pens as good/very good/excellent.

^cOn a scale of 1–5, where 1 = no difficulty and 5 = got stuck.

**P* = 0.05 versus NovoPen 3; [†]*P* = 0.05 versus all pens; [‡]*P* = 0.05 versus NovoPen 3 and Luxura; [§]*P* = 0.05 versus ClikSTAR and Lilly Luxura; ^{||}*P* = 0.05 versus ClikSTAR and NovoPen 4.

cartridge containing 300 U can only be used for three full injections; the subsequent dose would need to be split with a second pen or cartridge. Clearly, this also has cost and waste implications, such that disposable pens should be avoided in these patients. For these patients, although split-dose injections are possible, the use of a vial and syringe may be more appropriate because vials are available with greater volumes (e.g., 10 mL, 1,000 U) or in greater concentrations (e.g., 300 or 500 U/mL).

To date, except for the studies described above, we are unaware of any others that have included more than 100–200 subjects, and no study has included all six of these pens or other third-party devices. Meanwhile, almost all of the studies published to date have been sponsored or conducted by the manufacturers of the pen devices, raising the potential for bias towards their own pens. Of note is that several studies^{33–35} have only compared the patient preference and ease of use of two devices, commonly a prefilled pen and a reusable pen. Consistently, these studies showed greater preference and greater ease of use for the prefilled pen than the reusable pen. However, this is unsurprising because prefilled pens do not require cartridge insertion, a step that may be considered quite complex without adequate training.

It seems that larger independent studies with a representative population of patients with type 1 and type 2 diabetes and with a greater range of devices will be needed to gain further insight into the preferred features of each device and the suitability of each pen for specific patient populations, such as children and elderly patients.

Taken together, on insulin initiation, the patient should be given an opportunity to evaluate the devices for each insulin. Indeed, patients may find a specific device to be easier to use, which should be considered in the final decision on which insulin should be used.

Inpatient Insulin Use

Inpatient insulin use is a commonly overlooked aspect of clinical care. Insulin is often administered as part of overall

patient care, particularly in patients undergoing surgery, to manage blood glucose levels, thus avoiding unnecessary hyperglycemia. The use of insulin pens has been reported to extend to the inpatient setting, which may be the result of the increasing use of basal–bolus regimens instead of the more traditional sliding-scale approach. Accordingly, within a clinical setting, patients may require different types of insulin, and approaches that simplify insulin treatment appear to be well received. As previously described, a study evaluating nurse satisfaction with insulin pens versus the vial and syringe within an inpatient setting demonstrated that the nurses believed insulin pens to be more convenient, simple, and easy to use than the vial and syringe.⁶ Patients often continue insulin therapy in the outpatient setting; therefore, patient preference and treatment costs are factors that should also be considered when using insulin pen devices in this setting. Davis et al.³⁶ undertook a telephone survey of 94 patients randomized to receive insulin administered either via a pen device (*n* = 49) or a vial and syringe (*n* = 45). Patients in the pen group who self-injected at least one dose of insulin during hospitalization were more likely to use the pen device on discharge than those in the vial and syringe group. Furthermore, the authors estimated that using insulin pens during the hospital stay was associated with a cost saving of \$36 per patient (*P* < 0.05).

As a result, familiarization of patients with insulin pens within an inpatient setting may encourage the use of pens in the outpatient setting. This, in turn, could reduce the costs incurred as a result of using the device and the need for training within an outpatient setting. However, prospective studies are needed to investigate these factors.

Insulin pens carry several disadvantages that are appropriate in an inpatient setting, similar to an outpatient setting, for example, incorrect insulin administration, the risk of needlestick injury,³⁷ and the potential risk of infection if insulin pens are used against Food and Drug Administration recommendations and shared between patients.³⁸ However, these factors are also evident for the vial and syringe and other injectable drugs, and the use of safety needles should reduce

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.