Comparison of Breath-Enhanced to Breath-Actuated Nebulizers for Rate, Consistency, and Efficiency*

Kitty Leung, BSc; Emily Louca, BSc, RRT; and Allan L. Coates, B Eng(Elect), MDCM

Objectives: **To evaluate differences between three new-generation nebulizers—Pari LC Star (Pari Respiratory Equipment; Mississauga, ON, Canada), AeroEclipse (Trudell Medical International, London, ON, Canada), and Halolite (Medic-Aid Limited, West Sussex, UK)—in terms of rate and amount of expected deposition as well as the consistency of the doses delivered.**
Methods: **The *in vitro* performance characteristics were determined and then coupled to the respiratory pattern of seven patients with cystic fibrosis (age range, 4 to 18 years) in order to calculate expected deposition. The Pari LC Star and AeroEclipse were characterized while being driven by the Pari ProNeb Ultra compressor (Pari Respiratory Equipment) for home use, and by a 50-psi medical air hospital source. The Halolite has its own self-contained compressor. Algorithms for the rate of output for the inspiratory flow were developed for each device. Patient flow patterns were divided into 5-ms epochs, and the expected deposition for each epoch was calculated from the algorithms. Summed over a breath, this allowed the calculation of the estimated deposition for each patient's particular pattern of breathing.**
Results: **The rate of deposition was highest for the Pari LC Star and lowest for the Halolite. Rate of deposition was independent of respiratory pattern for the Pari LC Star and AeroEclipse, but proportional to respiratory rate for the Halolite. The differences between the Pari LC Star and AeroEclipse were less when driven by the 50-psi source. The AeroEclipse had the least amount of drug wastage. As designed, the Halolite delivered a predetermined amount of drug very accurately, whereas expected deposition when run to dryness of the other two devices had significant variations.**
Conclusions: **To minimize treatment time, the Pari LC Star would be best. To minimize drug wastage, the AeroEclipse would be best. To accurately deliver a specific drug dose, the Halolite would be best.** ***(CHEST 2004; 126:1619–1627)***

Key words: aerosols; asthma; breath-actuated nebulizers; breath-enhanced nebulizers; cystic fibrosis; pediatrics

Abbreviations: CF = cystic fibrosis; CI = confidence index; O_T = total drug output; RF = respirable fraction; UV = ultraviolet; V_R = residual volume

Jet nebulization is one of the mainstays of treatment for cystic fibrosis (CF), where it is used to deliver medications ranging from antibiotics[1] to mucolytics,[2,3] and is also commonly used to deliver bronchodilators for the emergency department treatment of asthma.[4] From previous studies,[5–7]

*From the Division of Respiratory Medicine and Lung Biology Research, Hospital for Sick Children, Research Institute, Toronto, ON, Canada.
The nebulizers studied were provided through the generosity of PARI Respiratory Equipment Inc., Trudell Medical International Inc., and Medic-Aid Limited.
Supported from a grant from the Hospital for Sick Children's Foundation, made possible by a generous donation from Arnold and Lynn Irwin for cystic fibrosis research.

Manuscript received September 5, 2003; revision accepted May 28, 2004.

Correspondence to: Allan L. Coates, B Eng(Elect), MDCM, Division of Respiratory Medicine, The Hospital for Sick Children, 555 University Ave, Toronto, ON, Canada, M5G 1X8; allan.coates@sickkids.ca

breath-enhanced nebulizers are more efficient than unvented nebulizers, but not all breath-enhanced nebulizers have the same efficiency,[8] with differences in residual volume (VR) and particle size resulting in significant differences in expected pulmonary deposition. There is a new generation of jet nebulizers that are breath actuated, producing medication only during inspiration, which makes them potentially even more efficient than the breath-enhanced devices. At present, there are little comparative data available to help the clinician choose between devices for specific applications.

All jet nebulizers have a nebulizing chamber containing liquid medication and a high-pressure, high-velocity jet of gas that creates a partial vacuum at the exit orifice of the jet, resulting in the medication being drawn up toward the high-velocity orifice, where shear forces fragment the liquid into a polydisperse aerosol. The aerosol passes around a series of baffles, where larger particles are removed by inertial impaction and fall back into the reservoir for renebulization. Particles that escape the baffles either leave the nebulizer, or "rain out" and fall back into the medication chamber under the influence of gravity. Simplistically, the major difference between unvented and breath-enhanced nebulizers is that the patient's inspiratory flow is entrained into the device, and particles that would otherwise rain out are swept along into the patient during inspiration.[5,9] Hence, the rate of output of breath-enhanced nebulizers increases with increasing inspiratory flow and falls back to baseline during expiration when no flow is entrained. Furthermore, since inertial impaction of droplets on the baffles is in part dependent on velocity of the particle, increases in entrained flow increases the likelihood that larger particles will impact on the baffles. This may give rise to a smaller particle size distribution during inspiration as the inspiratory flow increases.[8] Particles between 1 μm and 5 μm in diameter are ideal for pulmonary drug delivery, in that they are small enough so as not to be removed by inertial impaction at the posterior pharynx, but large enough to carry a significant amount of drug. Given that particle volume is proportional to the third power of the radius, particles < 1 μm carry little drug. The fraction of the volume of the nebulizer output carried in particles with a diameter ≤ 5 μm is defined as the respirable fraction (RF).[10–13]

In terms of the appropriate choice of device, a number of factors come into play. Clearly, the ability to produce a high-density aerosol with a large RF during the inspiratory phase is the basic principle, but other factors such as VR at end nebulization are an issue, especially if the medication is very expensive.[14] Since one of the challenges in the treatment of CF is patient adherence to recommended treatment regimens, devices that reduce treatment time would be expected to offer advantages to the already very time-consuming daily multifaceted treatment activities of these patients.[15–17] The devices should therefore be evaluated on the expected pulmonary deposition of a specific dose, and the delivery time required. The breath-enhanced nebulizer, the Pari LC Star (Pari Respiratory Equipment; Mississauga, ON, Canada) [Fig 1], has been shown to be one of the more efficient breath-enhanced nebulizers.[8] Breath-actuated nebulizers, such as the AeroEclipse (Trudell Medical International, London, ON, Canada) [Fig 2] and Halolite (Medic-Aid Limited, West Sussex, UK) [Fig 3] have recently been developed. The Halolite uses an adaptive aerosol delivery system that can adapt the drug delivery to each patient's breathing pattern. Table 1 provides a functional comparison of all three devices.

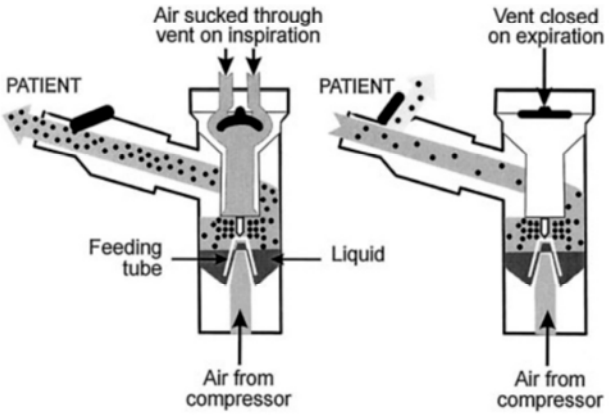

FIGURE 1. A schematic of the breath-enhanced nebulizer Pari LC Star.

The purpose of this study was to compare the three devices in terms of *in vitro* performance, expected *in vivo* rate of deposition, and *in vivo* efficiency using the respiratory pattern of patients with CF breathing through a nebulizer. Significant end points are considered to be the percentage of the initial dose that would be delivered to the lungs, the time required to deliver a "target" dose, and the ability to deliver a precise pulmonary dose. It is recognized that the importance of these variables depends on the expense of the drug being delivered, the value in terms of possible greater adherence to recommended therapy from rapid delivery, and the therapeutic safety profile of the drug in terms of accurately delivering a specific amount.

METHODS AND MATERIALS

Device Operation

The nebulizers and compressors used in this study were the Pari LC Star nebulizer driven by the Pari Proneb Ultra compres-

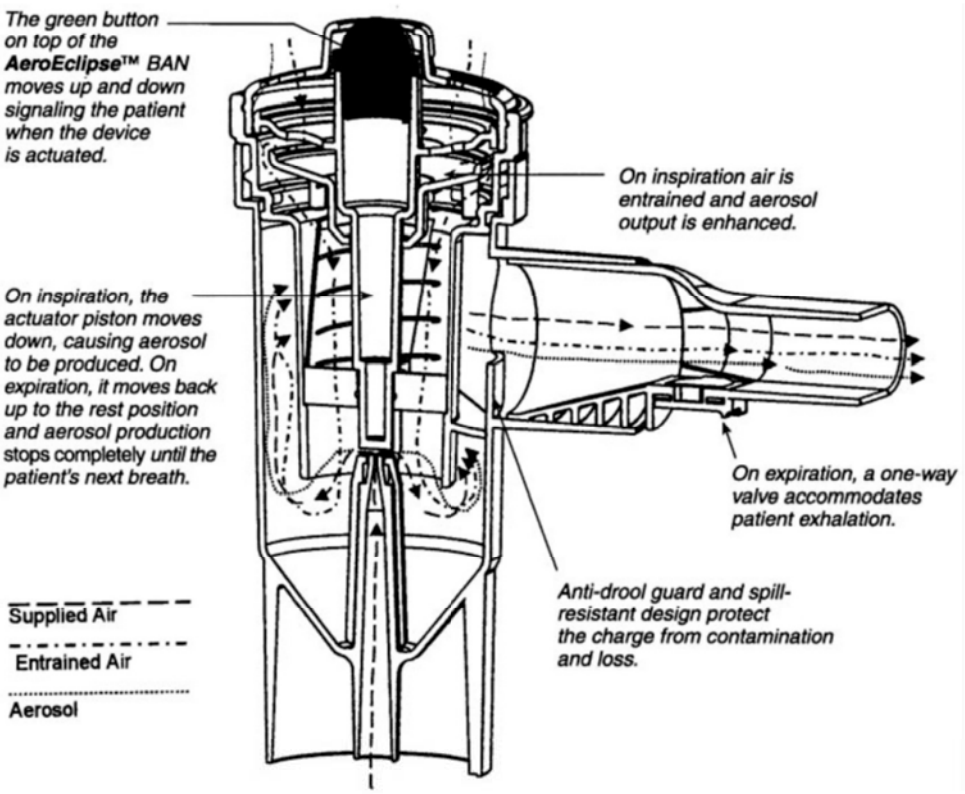

FIGURE 2. A schematic of the breath-enhanced, breath-actuated nebulizer (BAN) AeroEclipse.

sor (Pari Respiratory Equipment); the AeroEclipse nebulizer, which was also driven by the Pari compressor, as no specific compressor was recommended; and the Halolite nebulizer with a built-in compressor. The Halolite is a microprocessor-controlled device that activates the compressor on each inspiration. Three examples of both the Pari LC Star and the AeroEclipse were studied, but only a single Halolite device was available. The test drug was 2.5 mg (0.5 mL) of albuterol (Ventolin Respirator Solution; GlaxoSmithKline; Mississauga, ON, Canada) diluted with 3.5 mL of saline solution. This was chosen because it lends itself to ultraviolet (UV) spectrophotometry for quantification of output.[8] The Pari LC Star and the AeroEclipse were also evaluated using compressed dry air (hospital air, 50-psi source) at 8 L/min, which is the same flow recommended by the manufacturer for the AeroEclipse. Flow from the compressor was measured by a flow calibration instrument (Timeter RT200; Allied Health Care Products, St. Louis, MO), and the flowmeters on the hospital air line were calibrated to adjust for "back pressure,"[12] so as to deliver the expected driving nebulizing flow. When driving either the AeroEclipse or the Pari LC Star, the output of the ProNeb Ultra compressor was 4.9 L/min.

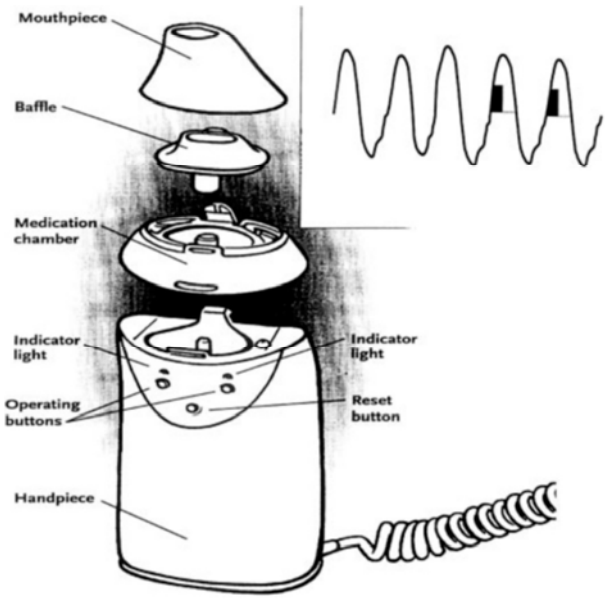

FIGURE 3. A schematic of the breath-actuated nebulizer Halolite, which uses adaptive aerosol delivery technology. Insert shows breath tracing; dark areas represent device activation.

Particle Size Distribution and Determining Nebulizer Output

Both the Pari LC Star and the AeroEclipse were characterized in terms of particle size distribution and rate of output during steady-state conditions. Briefly, the device was mounted to allow aerosol to pass through the laser beam of a Malvern Mastersizer X (Malvern Instruments; Worcestershire, UK), and particle size was measured using the Mie theory for transparent droplets. Care was taken to avoid vignetting.[18] This method has been described in detail elsewhere.[19] Measurements were made after 2 min of nebulization, which allowed the nebulizer to attain a steady-state temperature,[19] after which particle size distribution and RF were calculated. In order to mimic entrained flow, air at 40% relative humidity was added at the point of the inspiratory valve in flow increments of 5 L/min up to a maximum of 35

Table 1—*A Functional Comparison of the Pari LC Star, AeroEclipse, and Halolite*

Pari LC Star	AeroEclipse	Halolite
Breath enhanced	Breath enhanced Breath actuated	Breath actuated Uses adaptive aerosol delivery system, which adapts drug delivery to each individual patient's breathing pattern Device has two operating buttons; each is designed to deliver the manufacturer's preset volume
Inspiratory valve allows air to entrain into the chamber during inspiration when the flow of patient is greater than nebulizing flow	When entrained flow is > 8 L/m, a unique spring-loaded mechanism allows the actuator piston to be pulled down onto the jet and nebulization commences Aerosol is only produced during the inspiratory phase, making it potentially very efficient	Aerosolization begins when the patient pushes the appropriate button (albuterol for this study) and begins breathing Halolite analyses the first three breaths of the patient to determine the breathing pattern A pulse of drug is delivered every subsequent breath only during the first 50% of inspiration No entrainment of flow on inspiration Output is constant for each pulse and independent of the inspiratory flow
Expiratory valve on mouthpiece prevents exhaled gases from entering the nebulizer	Expiratory valve on mouthpiece prevents exhaled gases from entering the nebulizer	Valves divert ventilation around nebulizing chamber
Treatment complete when device sputters	Treatment complete when device sputters	Treatment is complete when the preset dose has been delivered

L/min, and particle size distributions were measured in each situation. For the AeroEclipse, the first level of entrained flow was 8 L/min because the spring-loaded valve only opens when entrained flow reaches this level. The microprocessor control of the Halolite makes conventional particle sizing difficult since the device is not designed to run continuously. This intermittent operation results in differences in temperature of the aerosol when nebulized continuously vs pulsed. The increased accuracy of 2,000 sweeps during data gathering by the Malvern Mastersizer X for particle size distribution calculations in "continuous" mode offsets the limited data achieved from a "pulse," even with differences in temperature of the aerosol being particle sized. To create a continuous mode, the device was dismantled and the back pressure created by the compressor when driving the Halolite handset, which contains the nebulizing device and microprocessor, was measured as 28 to 30 psi. The compressor uses an elastic reservoir that allows pressure to increase during expiration, and contributes to the compressor output during the pulse of aerosol. This resulted in a driving pressure that is considerably higher than that which would have occur if the compressor were driving the nebulizer continuously. The microprocessor within the Halolite handset was dismantled, and the nebulizer was driven by a dry air gas source at a flow matching the back pressure previously measured from the Halolite compressor, which resulted in an output flow of 5.4 L/min. The mouthpiece of the handset was positioned to send a continuous stream of aerosol across the laser beam. Since there is no entrained flow, only one measurement condition was necessary.

Prior to the particle size measurements, devices were weighed empty (for the Halolite, this was only the medication chamber), filled, and reweighed using an electronic balance (BL150; Sartorius Corporation; Edgewood, NY). After 4 min of steady-state output, the devices were reweighed. Changes in drug concentration due to evaporative losses were assessed initially by changes in UV spectrophotometry and water vapor pressure osmolarity (Advanced Micro-Osmometer 3300; Advanced Instruments; Norwood, MA). Eventually, only osmolarity was used since the simpler technique gives identical results to the more complex UV spectrophotometry. The drug output over the nebulization period was calculated from the VR and the changes in concentration, as seen in Appendix 1.

For each 4-min run under each condition of entrained flow, the total rate of output and that in the RF was calculated, and the mean taken for the three examples of both the Pari LC Star and the AeroEclipse. Polynomial curve-fitting techniques were used to create the algorithm for the rate of output—total and within the RF—over the range of entrained flow. Finally, both the Pari LC Star and the AeroEclipse were run to dryness, defined as the absence of mist for at least 10 s,[8,12] to allow the calculation of the total output of the device. The details of these techniques have been described.[8,19,20] Output data for the Halolite were collected by connecting it to a modified Harvard pump (Model 613; Harvard Apparatus; Holliston, MA) that delivered two half-sine waves, with an inspiratory time/total time of respiratory cycle (TI/TTOT) of 0.4, a tidal volume of 500 mL, and a respiratory rate of 20 breaths/min. These settings approximate the tidal volumes and timing of actual patient flow traces (see below). The Harvard pump was run until the Halolite sensed that the preset volume had been delivered. The output was calculated from the drug remaining in the nebulizer cup via gravimetric techniques and changes in osmolarity, which had complete agreement with UV spectrophotometry. When the output multiplied by the RF is divided by the number of breaths, the result is the expected deposition per breath.

Calculation of Estimated Pulmonary Deposition

From a previous study,[21] digitized breath tracings of seven patients with CF (age range, 4 to 18 years) breathing through a nebulizer (Table 2) were used. Patients with FEV_1 values > 60%

Table 2—*Demographic Information on the Seven Patients Whose Breathing Patterns Were Used To Calculate Estimated Pulmonary Deposition and In Vivo Efficiency

Patient No.	Age, yr	Height, cm	Weight, kg	FEV_1, % Predicted	Respiratory Rate, Breaths/min
1	11	138	28	84	17.1
2	11	141	34	76	18.7
3	7	122	22	68	31.4
4	18	174	55	113	18.9
5	7	122	23	78	41.6
6	14	142	31	26	40.7
7	4	159	42	55	24.6

*From Coates et al.[21]

predicted had essentially normal patterns of breathing, although the younger ones tended to be a bit tachypneic when breathing on the nebulizer. The child with the worse lung function (FEV_1 < 30% predicted) was tachypneic at rest. The respiratory waveforms were broken into 5-ms epochs and were used to calculate the expected deposition. Three breaths were chosen from a pattern that showed regular respiration, and the same three breaths were used to calculate expected deposition for each apparatus. Entrained flow was calculated by subtracting the nebulizer driving flow from the inspiratory flow. When this resulted in a negative number it was defined as zero, since the one-way inspiratory valve would be closed. The spring-loaded valve on the AeroEclipse does not open until the entrained flow reaches 8 L/min; output was considered zero until this occurred. From the algorithms of the total rate of output and that in the RF for the Pari LC Star and the AeroEclipse, the output in each 5 ms-epoch for the specific entrained flow of the epoch was calculated and summed over the entire breath. These calculations are illustrated in Appendix 2. The results are reported as the mean of three breaths for each patient. This allows the *in vivo* efficiency, defined as the output during inspiration in the RF divided by total output over the entire respiratory cycle,[8] to be calculated. For the Halolite, *in vivo* efficiency was equal to the output in the RF during inspiration since there is no expiratory drug loss.

Validation of Assumptions

To test the assumption that the output of the Pari LC Star and the AeroEclipse that was determined under steady-state conditions were valid under dynamic conditions, they were connected to the Harvard pump with the settings described above and run for 3 min. Total drug output (OT) was calculated as described above. The two half waves from the Harvard pump were known mathematically and were entered as the "patient's" breathing pattern. Using the algorithm for rate of drug output, the output over 3 min was calculated and compared to the measured output.

Device evaluation and comparison included the expected pulmonary drug deposition per breath and per minute, *in vivo* efficiency, overall efficiency in terms of expected deposition in relation to the initial charge in the nebulizer, and for the Halolite the accuracy of the device to deliver a preset amount of drug. The calculated output and expected pulmonary deposition of the Pari LC Star and AeroEclipse, as well as the length of time to run to dryness were compared to the Halolite. To have comparable data, the time to deliver a selected predetermined dose was calculated for each device. The predetermined dose was defined as the dose delivered by the Halolite after four button presses, which was found to be essentially equivalent to its point of dryness. The time difference between the devices for each of the seven patients was calculated. The results are expressed as means ± 95% confidence limits. Differences in patient size and device performance were explored by regression analysis.

RESULTS

The steady-state *in vitro* assessment of both the total rate of output and that in the RF for the Pari LC Star and AeroEclipse is shown in Figure 4. With increasing entrained flow, the Pari LC Star increases both the OT and that in the RF. The AeroEclipse begins producing aerosol when the entrained flow reaches 8 L/min (patient inspiratory flow is 13 L/min when the compressor driving flow is taken into consideration), and there is a slight fall off in OT with increasing entrained flow, but there is an initial small increase in the RF, indicating a smaller particle size distribution with increasing flows. Given the design, the Halolite provides a constant output of 0.0029 mg per breath when it is activated.

When the mathematically predicted output of the Pari LC Star and the AeroEclipse for the two half sinusoidal waveforms for the Harvard ventilator are compared to the actual output, there is no difference between the two (0.0089 ± 0.0001 mg per breath vs 0.0090 ± 0.0000 mg per breath, and 0.0046 ± 0.0001 mg per breath vs 0.0045 ± 0.0002 mg per breath for the Pari LC Star and the AeroEclipse, respectively [mean ± 95% confidence index (CI)].

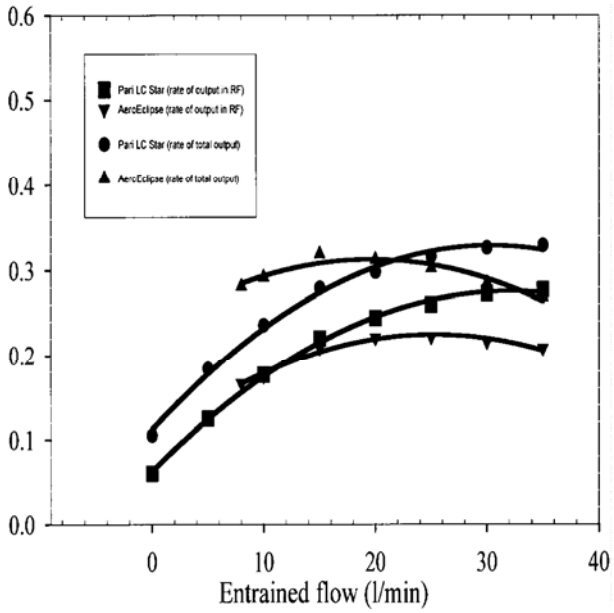

FIGURE 4. Rate of output (total and in RF) in relation to entrained flow for the Pari LC Star and AeroEclipse while being driven by the compressor.

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.