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Expansion of a Cheminformatic Database of Spectral Data for Forensic Chemists and Toxicologists

Final Report

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Abstract

The emergence of designer drugs as abused substances has seen a dramatic increase over the past few years. Forensic laboratories are faced with a challenge in identifying these compounds because reference standards for many of the compounds do not exist. In addition, some current cheminformatic databases are static and updated periodically, thereby requiring users to re-download or purchase an upgrade to access the additional spectra. ForensicDB addresses this need by providing the forensic community with a peer-reviewed, Web-accessible, continuously updated database of multiple spectral methods that is provided at no cost to the user.

The goal of this project was to expand ForensicDB capacity for user traffic and database queries, increase participation of associate curators to manage the review of records, and further develop software automation to improve management of submitted records. Inclusion of nuclear magnetic resonance data in the database was originally proposed, but with the increased presence of designer drugs, it became evident that the focus should be on the inclusion of more relevant compounds and spectral data to assist the forensic practitioner.

The project resulted in an increase in database traffic and community submissions to ForensicDB, as well as an increase in volunteers willing to review spectral data. This project also resulted in the development of a Web-portal for user submissions that is in its final stages of testing.

Executive Summary

Research Purpose

Forensic laboratories are faced with a challenge when attempting to identify an unknown compound in a sample substance. A useful tool to aid in identification is a cheminformatic database populated with reference spectra. Although many laboratories create internal databases of these spectra, such databases are generally small, contain limited records, and are not useful to the broader forensics community.

Widely available spectral and cheminformatic databases are provided through both private and commercial organizations. One of the most popular private databases is the American Academy of Forensic Sciences (AAFS) mass spectrometry database (http://www.ualberta.ca/~gjones/mslib.htm). Although commercial databases contain more compounds, they can be expensive to access and often require proprietary software that is designed to be installed on a single computer. In addition, many commercial databases are static, and for those that are updated periodically, users must download the updates to a local computer. If updates are not downloaded regularly, users may not have the most reliable data and may not realize that they are using outdated information. This is a significant problem in a time when new designer drugs are being discovered at a rapid rate.

In the past year, the rise in prevalence of the synthetic cannabinoid, or "Spice," materials and other "legal high" compounds (i.e., legal products that have a similar structure and produce similar pharmacological effects as their illegal counterparts) has challenged the laboratory system's ability to reliably handle and identify these compounds. Although approximately 20 primary compounds have been seen in available materials, the series of cannabimimetic compounds includes hundreds if not thousands of potential compounds. This is further complicated with inclusion of the synthetic cathinone analogs, tryptamines, and, potentially, cocaine analogs, all compounds that are challenging to regulate. In addition, clandestine chemists rapidly move from one compound to another as they are regulated, thereby creating an ongoing identification challenge. This challenge is evident from monitoring the clandestine laboratory investigating chemists' mailing list (CLIC List) and the "unknowns" forum on Forendex, where users are reaching out to the community for assistance in determining unknowns by uploading PDF files of their spectra and asking if other professionals recognize a compound.

ForensicDB (www.forensicDB.org), the cheminformatic database developed at RTI International (RTI) as part of this collaborative agreement, is designed to help users objectively determine their unknown compound by performing a spectral similarity search between their raw data and the spectra of reference standards in the database. Because most of the currently available spectral databases are static or may only be updated on an annual basis, there is a need in the community for assistance to laboratory personnel attempting to identify unknowns. ForensicDB addresses this need by providing the forensics community with a free, Web-accessible, centrally curated database that is updated continuously.

Research Design and Methods

The Project as Originally Proposed

Created under a previous National Institutes of Justice (NIJ) cooperative agreement (2008-DN-BX-K180), ForensicDB was originally intended to be a spectral database for only Direct

Analysis in Real Time, time-of-flight (DART-TOF) spectra. However, in the early stages of the project, multiple changes occurred that required adjusting the project to a much more widely applicable database that included multiple spectral methods. Thus, it was proposed to continue and extend the capabilities of ForensicDB. Currently, ForensicDB is a fully functional database, where registered users have access to nominal mass, accurate mass and Fourier transform infrared (FTIR) spectra. Users have submitted nominal mass electron ionization mass spectrometry (EI-MS) spectra and accurate mass data from DART-TOF and electrospray ionization quadrupole time-of-flight mass spectrometry (ESI-QTOF). ForensicDB has the capacity to include different instrumental techniques and is not limited to EI-MS, DART-TOF, or ESI-QTOF data.

There current project set out to accomplish four specific goals:

1. Expand the database capacity for user traffic and database queries.
2. Increase the participation of associate curators to manage the review of records submitted by the user population.
3. Extend the spectral information to include nuclear magnetic resonance (NMR) data in the database, along with routine calculation of pKa data for all records with determined structures.
4. Further develop software automation for improving the management of submitted records.

It was proposed to accomplish these goals through collaboration with several agencies and organizations:

- The Virginia Department of Forensic Science (VDFS), a public forensic laboratory that is currently a collaborator in the existing database program.
- NMS Laboratories, a well-recognized commercial private laboratory that has the unique position of providing analytical services to clients all around the world, which at times provides access to unusual compound reference materials (such as new drug metabolites) that many public laboratories have difficulty obtaining.
- Two universities, the University of Colorado and Albany Medical Center Hospital and College. The University of Colorado brings a strong background in NMR data to complement RTI's strength in this technology.
- The Southern Association of Forensic Scientists (SAFS), a professional organization working to create a database of scheduled compounds.
- Advanced Chemistry Development (ACD/Labs), a software developer that worked with RTI on the development of ForensicDB. ACD/Labs sells and supports a unique set of software that enables ForensicDB to incorporate multiple different spectral methods from almost all spectra instrument manufacturers.

The Project as Implemented

In general, the project was implemented as proposed, with a few notable exceptions. As the project progressed, a decision was made to alter the scope of the proposed work. In talking with numerous users, RTI determined that the community would be better served by including more

traditional data (i.e., EI-MS, DART-TOF, and FTIR) on existing records and new legal high compounds rather than acquiring and including NMR data on relatively few compounds. An agreement was reached to drop the intention to include NMR data (and to purchase the software needed to include these data), redirect the efforts to acquiring and processing records for designer drugs and legal high compounds, and incorporate the resulting spectra into the database. Due to not including NMR data in the database, it was determined that the NMR specialty of the University of Colorado was not needed at this time.

The original proposal included plans to distribute licenses and provide software tools to each associate curator to aid in the processing and review of data. RTI did not distribute the software as planned because a more elegant solution was created. ForensicDB uses two intermediate databases—collaboration and submit—to locate and store records during different phases of the review process before adding data to the public database. Using the security structure provided by ACD/Web Librarian software, access to these intermediate databases was enabled for reviewers only while they remain hidden from public view and inaccessible to general account holders. This allows reviewers and others to use the ACD/Web Librarian interface and directly access the necessary data without requiring RTI to manage multiple desktop software licensees. Such access reduced the costs associated with software procurement and simplified the management of the system.

RTI did not pursue the subcontract with NMS because it became evident that development of the system to improve the end-user experience from Agilent ChemStation was of greater concern. A strategic decision was made to delay and alter how information was worked with NMS to free up funds to contract for software development to create plugins for Agilent ChemStation (by far the dominant instrumentation system used by the end-user population). These plugins create a "right click" option to export a given spectrum to a JCAMP file and a "right click" option to search a spectrum selected in Agilent ChemStation directly in ForensicDB. When complete, these plugins will be provided to the end user as a free download from the ForensicDB website. Both options make searching as easy as possible for those users who have a computer that is connected to the Internet, as well as facilitate searching via the instrument computer for those users who do not have easy access to the Internet (often due to security policies or to the laboratory trying to reduce costs by limiting Internet access).

Database Management

Key contributors to the construction, management, and survival of ForensicDB include the curator, collaborators (also known as associate curators), reviewers, and the community. **Figure ES-1** shows a schematic of the database structure. Management of ForensicDB is similar to a peer-reviewed journal in that the curator acts as the editor and the collaborators act as the associate editors. The curator (RTI International) is responsible for creating and maintaining the database and Web server and providing the tools necessary to access and update the database. Database collaborators work with the curator to develop the intention and design of ForensicDB, identify community needs that the database can address, and assist with creating requirements for standardization of spectral submission and criteria for evaluating spectra. In addition, collaborators can assist with processing the spectral data into an appropriate format for inclusion in the public database. The reviewers evaluate each submitted spectrum according to established evaluation criteria. The community acts as the driving force of this cheminformatic database, strengthening ForensicDB by contributing their spectral data. The survival of ForensicDB is dependent upon the public's continued use, participation, and comments on database

improvement, as well as on the community utilizing the database as part of their analytical scheme of analysis.

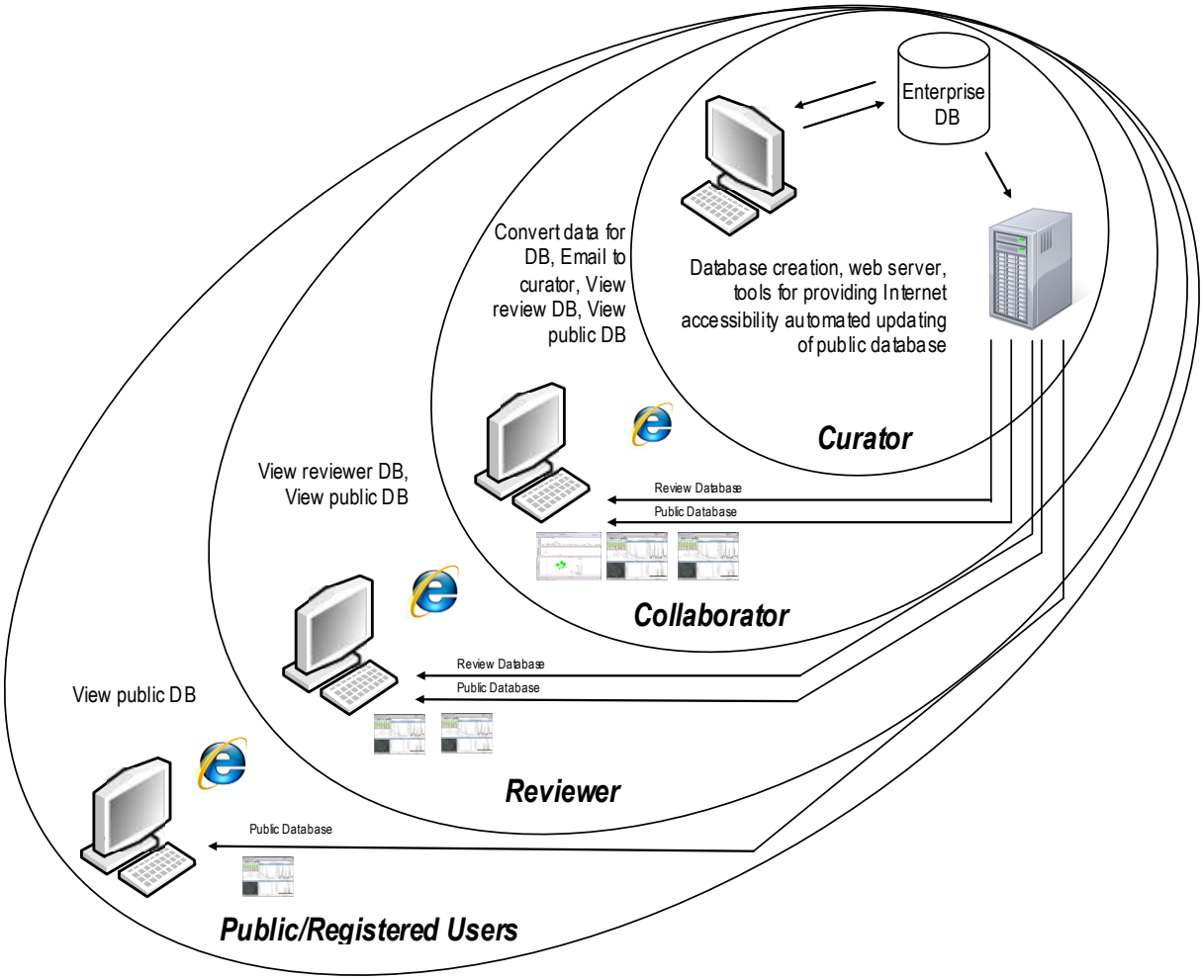

Figure ES-1. Database Structure and Functionality

Database Organization

As shown in **Figure ES-2**, the organization of ForensicDB is based on chemical structure —the only truly unambiguous means of referring to any given compound. A record indicates a specific compound structure and name, analyzed by a particular institution from a specific source material. Thus, multiple records may exist for a specific compound, reflecting a change in the major record features. Each record may contain multiple documents that indicate spectral method and instrumental parameters. Some of the general requirements for all submissions are spectral method, instrument type, scan range, and data reduction method. Other parameters are requested based on the instrumental technique, such as spectral resolution and number of scans co-added for FTIR data. Specific requirements for DART spectra include gas heater temperature, gas flow rate, type of sample introduction, and orifice 1 voltage.

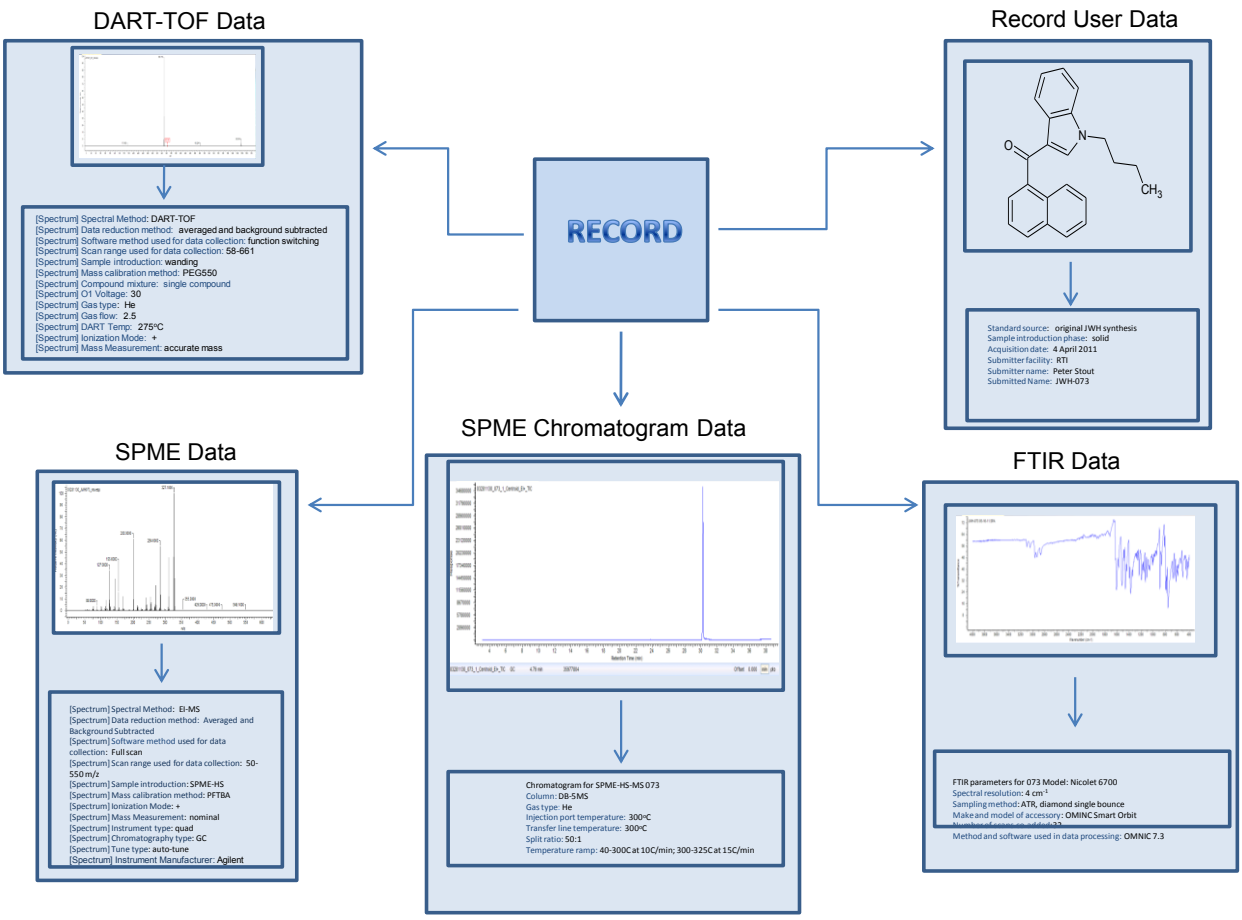

Figure ES-2. ForensicDB Database Organization

Findings (Current Status of the Database)

As of June 27, 2012, ForensicDB includes 3,108 total records representing approximately 6,374 spectra. These records were contributed by VDFS; RTI; Dr. Graham Jones (AAFS Toxicology Section's EI-GC-MS database); Cayman Chemical; the U.S. Drug Enforcement Administration (DEA) Southwest Laboratory (DEA SWL); the DEA Special Testing and Research Laboratory (DEA SFL1); and the Hillsborough County Medical Examiner's Office. The types of instrumental data represented are accurate mass, nominal mass, FTIR, and chromatographic. The types of compounds submitted to ForensicDB include JWH cannabimimetic compounds, herbal Spice products, drug standards, pharmaceutical preparations, TLC-separated pharmaceutical preparations, chemical compounds, nylon fibers, and smokeless powders.

Table ES-1 shows the approximate number of spectra in ForensicDB per instrumental method. Some of the data within Table ES-1 are presented as their own record, or are attached as a document to an existing record of the same source material, lot, and submitting institution. The public database includes a total of 2,203 EI-MS spectra. These spectra were contributed by Dr. Graham Jones (AAFS); VDFS; RTI; Cayman Chemical; and DEA SFL1. There are 958 records with DART-TOF data representing approximately 3,832 spectra submitted by RTI and VDFS. The DART spectra collected at both institutions were analyzed under the same instrumental parameters. To illustrate the characteristic fragmentation patterns, each compound record

collected using DART contains a document at voltages of 20V, 30V, 60V, and 90V. RTI contributed 34 records that contain a total of 41 ESI-QTOF spectra. The ESI-QTOF spectra of isolated synthetic cannabinoids from herbal blends were detected using mass defect filtering, as described in a recent article. The EI-MS data of isolated synthetic cannabinoids from herbal mixtures were determined by solid-phase microextraction headspace gas chromatography mass spectrometry (SPME-HS-GC-MS). ForensicDB includes 193 FTIR spectra contributed by RTI, VDFS, Cayman Chemical, DEA SWL, and DEA SFL1.

In an effort to gain more of the new and emerging designer drugs, Cayman Chemical agreed to contribute the EI-MS and FTIR data of compounds they offer in their forensics catalog. In addition, DEA SWL contributed approximately 500 FTIR spectra of drugs that are of forensic interest. The DEA SFL1 submitted 20 compounds collected by FTIR and EI-MS, including RTI-126 (2β-[1,2,4-Oxadiazol-5-methyl]-3β-phenyltropane) and its alpha isomer.

Table ES-1. Approximate Number of Spectra in ForensicDB per Instrumental Method

Data Type	Spectra
ForensicDB	
EI-MS	2,203
DART-TOF	3,832
ESI-QTOF	41
FTIR	193
Chromatography	117

ForensicDB also includes smokeless powder records submitted by VDFS. Each smokeless powder record includes a document for attenuated total reflectance (ATR)-FTIR, EI-GC-MS, and positive chemical ionization (PCI) GC-MS chromatogram; a positive and negative DART-TOF spectrum at 20 V; and an image showing the morphological characteristics.

Ames Laboratory submitted 322 different nylon fiber samples that were measured in duplicate and analyzed under two photoacoustic (PAS)-FTIR parameters. The only difference between the parameters was a scanning speed of 400 Hz or 2.5 kHz. There were a total of 1,288 spectra that required processing. These spectra were processed, but still require review.

As a result of the project rescope, ForensicDB gained approximately 135 different designer drug compounds (84 cannabimimetic compounds and 51 other designer drugs) that are publically available. Other designer drugs include compounds from the following drugs classes: cathinone, phenethylamine, tryptamine, piperazine, and arylcyclohexylamine. This total does not include duplicate compound records created for different source materials or submitting facilities. Some of these records contain up to seven spectra, which include FTIR, EI-MS, ESI-QTOF, and DART-TOF at voltages of 20V, 30V, 60V, and 90V. There a numerous other designer drugs and cannabimimetic compounds in various stages of the processing and reviewing phase.

RTI has access to all of the original JWH compounds synthesized by Dr. John Huffman, which puts the Institute in a unique position because reference standards and spectra of most of these compounds do not exist, and many of them have yet to surface as legal highs. With the inclusion of these spectra in ForensicDB, the community gains a unique advantage to help identify unknown samples.

Conclusions

RTI achieved the goal of expanding the capabilities of the ForensicDB database by upgrading server capabilities to meet the growing user demand and to increase the stability of the Web services. This was accomplished by upgrading to two more functional servers and increasing the infrastructure support to 24/7 support. RTI also developed a Web-portal for user submissions of complete data records, which is currently in the final stages of testing before deployment.

It was originally proposed to include NMR spectral data in the ForensicDB database, but with the rise in designer drug use and the challenges in identification of these drug analogs, focus shifted to including more of the new and emerging compounds. This effort was a success as the community participated in submitting records, including large data sets from collaborations with DEA SWL, DEA SFL1, and Cayman Chemical. Additionally, RTI collected analytical data for a large quantity of these emerging drugs. The records from RTI include nominal mass, accurate mass, and FTIR spectral data.

The approach to aggressively promote and expand the use of ForensicDB was successful in increasing the communities' involvement in the database. There was an increase in the number of volunteers willing to review spectral data, and more community contributions of spectra to the database were acquired. An increased presence on online forums, links from other websites, presence at conferences, and additional ForensicDB training sessions also aided in an increase of community participation in ForensicDB.

1. Introduction

1.1 Statement of the Problem

Forensic laboratories are faced with a challenge when attempting to identify an unknown compound in a sample substance. A useful tool to aid in such identification is a cheminformatic database populated with reference spectra. Although many independent laboratories create internal databases, such databases are generally small, contain limited records, and are not useful to the broader forensics community.

Private and commercial organizations provide spectral and cheminformatic databases that are widely available, such as the American Academy of Forensic Sciences' (AAFS) popular private mass spectrometry database (http://www.ualberta.ca/~gjones/mslib.htm). However, although commercial databases contain more compounds, they can be expensive to access and often require proprietary software that is designed to be installed on a single computer (Nip and Kuehl, 2000). Another constraint to the use of commercial database is that many are static or updated periodically, requiring users to download updates to a local computer. If the updates are not downloaded regularly, users may not have the most reliable data and may not realize they are using outdated information (Nip and Kuehl, 2000). In a time when new designer drugs are being discovered at a rapid rate, this lack of up-to-date data can be a significant problem.

In the past year, the rise in prevalence of the synthetic cannabinoid, or "Spice" materials (i.e., indole-derived cannabinoids originally synthesized in the laboratory of Dr. John Huffman), and other "legal high" compounds (i.e., legal products that have a similar structure and produce similar pharmacological effects as their illegal counterparts) has challenged the laboratory system's ability to reliably handle and identify these compounds. While approximately 20 primary compounds have been seen in available materials, the series of cannabimimetic compounds includes hundreds if not thousands of potential compounds. This situation is further complicated with the synthetic cathinone analogs, tryptamines, and potentially, cocaine analogs, all of which are challenging to regulate. In addition, clandestine chemists rapidly move from one compound to another as they are regulated, thereby creating an ongoing identification challenge. This challenge is evident when monitoring the clandestine laboratory investigating chemists' mailing list (CLIC List) and the "unknowns" forum on Forendex, where users are reaching out to the community to help them determine unknowns by uploading PDF files of their spectra and asking if other professionals recognize a compound.

There is a need in the community for assistance to laboratory personnel attempting to identify unknowns. ForensicDB, the cheminformatic database developed at RTI as part of this collaborative agreement, addresses this need by providing the forensics community with a free, Web-accessible, centrally curated database that is updated continuously. The database is designed to help users objectively determine their unknown compound by performing a spectral similarity search between their raw data and spectra of reference standards in the database.

1.2 Literature Review

1.2.1 Current Status of Spectral Databases

The forensic examination of controlled substances is currently dominated by the use of 70eV single quadrupole electron ionization mass spectrometry (EI-MS) for both screening and final confirmation of casework samples. Many of these databases are currently available, both

commercially (National Institute of Standards and Technology [NIST] and Wiley) and privately (AAFS). The advantage of these data is that most instruments that utilize these databases are run under similar ionization and calibration conditions. EI spectral databases are integral parts of the analytical scheme, allowing for fast computer searching of, in most cases, reliable data.

Such database searches have become a staple for forensic analytical chemistry applications. Additionally, other cheminformatic resources have gained much popularity and usage. One such resource is ChemSpider (http://www.chemspider.com/), which is a function of the Royal Society of Chemistry. ChemSpider contains a wealth of information, but often, forensic users find that it does not have spectra of relevant compounds and the spectra cannot be searched against an unknown spectrum because they are images and not tabulated in a searchable format. PubChem (http://pubchem.ncbi.nlm.nih.gov/) allows for structure and name searches and has structure activity tools, but is more geared at bioassays and drug discovery professionals than forensic users. Wikipedia (http://www.wikipedia.org/) is a widely known broad data source that has redefined community data. It too contains significant information on many compounds, but it is difficult to gauge the quality of the data, and it is often inconsistent in its information on compounds of interest to forensic practitioners. Another online resource is eMolecules (http://www.emolecules.com), which provides a convenient interface to suppliers of compounds accessible by name or structure search. Although these sites have a degree of curation, they also have significant weaknesses and inconsistencies in the data provided. Additionally, these databases are not constructed with the forensic chemist in mind, and often, forensic users find the need to return to the AAFS library or their own locally constructed databases to supplement these sources.

Other spectral libraries exist that are more geared toward the forensic community, including, Forendex; the Cayman Spectral Library (CSL); the SWGDRUG Mass Spectral Library; the Mass Spectra of Designer Drugs 2012; and the NIST/U.S. Environmental Protection Agency (EPA)/ National Institutes of Health (NIH) Mass Spectral Library.

Forendex is hosted by the Southern Association of Forensic Scientists (SAFS) (http://forendex.southernforensic.org/) and includes approximately 1600 spectra of 70eV EI-MS and IR data. The database is searchable by name and browsable by category. It is not searchable by structure or raw data. The spectra are downloadable as PDF files. Forendex is a free, Web-accessible database that is continuously updated. It has a useful forum where chemists discuss and reach out to the community for identification of unknown samples.

The Cayman Spectral Library (http://www.caymanchem.com/app/template/SpectralLibrary.vm) is hosted by Cayman Chemical. It includes 70eV EI-MS data of approximately 200 spectra of forensic compounds sold by Cayman Chemical. The library can be downloaded for free in Agilent ChemStation format. It is continuously updated, but requires a re-download for the latest data, and users must have Agilent ChemStation installed on their local computer to view the data.

The SWGDRUG Mass Spectral Library is hosted by the Scientific Working Group for the Analysis of Seized Drugs (http://www.swgdrug.org/ms.htm). It contains approximately 1600 spectra of 70eV EI-MS data. It can be downloaded for free in the NIST, Agilent, JCAMP, and Shimadzu database formats. It is updated periodically but requires the end user to download the latest version for the most accurate and up-to-date spectra.

The Mass Spectra of Designer Drugs 2012 is a commercial database curated by Dr. Peter Rösner. The stand-alone version Designer Drugs 2012 costs $4,350, and an upgrade to Designer Drugs 2012 from a previous version costs $1,995 (Scientific Instrument Services Inc., 2012a). Due to the price, the database may not be readily accessible to small and private laboratories. Dr. Rösner also offers Designer Drugs Online Mass Spectra Database (http://www.designer-drugs.de/), which is a free online resource for designer drugs emerging between the yearly database upgrade. Registration is required and is free for forensic scientists involved with the analysis and detection of new and emerging drugs. The online version contains 70eV mass spectra and is searchable by compound name, mass fragment, and mass fragment relative intensity.

NIST/EPA/NIH developed the commercial Mass Spectral Library NIST 11 in 2011 (NIST Mass Spectrometry Data Center, 2011). The software is not Web-accessible, and its cost can be significant. Purchasing the new NIST 11 Standard Version costs the end user $2,295, and to upgrade to NIST 11 Standard Version from an older version costs $1,295 (Scientific Instrument Services Inc., 2012b). As with the Mass Spectra of Designer Drugs database discussed above, the high price of the NIST Mass Spectral Library makes it not readily accessible to small and/or private laboratories. The NIST 11 version contains reviewed EI and tandem mass spectrometry (MS/MS) spectra. Reference spectra retrieved from this search include collection parameters such as instrument type, inlet, and instrument model (NIST Mass Spectrometry Data Center, 2011). These parameters help the user determine reasons for spectral variability if a reference match is not found. This commercial package allows for direct comparison of a known and unknown spectrum; however, as new compounds are synthesized and become available in the illicit market, users must wait to purchase an updated database version.

1.2.2 Current Databases Compared to ForensicDB

The forensic utility of current spectral databases varies due to the inclusion or lack of relevant compounds and spectral methods, data quality, accessibility, and the ability to search against reference spectra. Forensic users of these databases can perform searches of spectra from traditional EI-MS instrumentation, but such databases do not allow for cross searching of other spectral methods. ForensicDB contains EI-MS spectra, as well as Direct Analysis in Real Time (DART) time-of-flight (TOF) spectra, quadrupole time-of-flight (QTOF) spectra, and Fourier transform infrared (FTIR) spectra. A database that houses several instrumental techniques is advantageous because there is greater certainty of accurate identification if the same compound has a high spectral similarity for several methods (Kornakova et al., 2005).

ForensicDB is a broadly applicable and unique database and library of multiple spectral data on compounds of forensic interest, as well as a new platform capable of housing searchable data from multiple current and potential future spectral platforms. It is similar to the described databases, but is set apart by several unique advantages. Like many of the databases discussed, ForensicDB is a freely accessible database, but is unique because it allows electronic searching by raw data, as well as structure and cheminformatic properties. ForensicDB parallels NIST 11 by requesting information on instrumental parameters used for collection to help standardize data submission. It differs from NIST 11 and the Mass Spectra of Designer Drugs 2012 in that it is a free, Web-accessible spectral database with searchable nominal mass, accurate mass, and FTIR spectra. Compared to ChemSpider and Forendex, ForensicDB allows direct electronic comparison of known and unknown spectra contributed by the public, whereas ChemSpider and Forendex only provide images of spectra. Similar to ChemSpider and Forendex, ForensicDB is equipped with ACD/Labs software that calculates compound information based on the submitted

structure. All of the library efforts have some degree of internal reviewing of records, but to the best of our knowledge, ForensicDB is the only database that includes an external peer review of data. Addressing the traceability of records is a significant challenge for all library efforts. The goal of ForensicDB has been to provide a central repository of information so that practitioners have easy access to a single trusted source of multiple spectral data types from which to branch out. Web accessibility and the ability to constantly update spectra to keep up with the ever-changing illicit drug market without having users continue to download upgrades provides an advantage in a resource for practitioners. It is also useful to the forensic community because it houses not only EI-MS data but also other spectral methods relevant to forensic chemists. Like ForensicDB, the SWGDRUG Mass Spectral Database, Forendex, and the Mass Spectra of Designer Drugs 2012 rely on community involvement to submit their spectral data for inclusion in these databases.

An ongoing effort beyond the close of this particular award is to find ways of consolidation, cooperation, and reinforcing between the various databases and standard interests and efforts. The goal is to facilitate the provision of reliable, responsive data for multiple platforms to the community of practitioners in a sustainable fashion that minimizes the costs to the end user.

A comparison of some of the available databases and their functionality is shown in **Table 1-1**.

Table 1-1. Comparison of Databases

	ForensicDB	Forendex	NIST 11	ChemSpider	PubChem
Web accessible	Y	Y		Y	Y
Community driven	Y	Y		Y	
Physicochemical properties	Y			Y	
Electronic spectrum search	Y		Y		
Electronic structure search	Y		Y	Y	Y
Multiple instrumental methods	Y	Y	Y	Y	
Instrumental parameters	Y	●	Y		

● Limited

1.2.3 New and Emerging Drugs

The illegitimate use of synthetic compounds is a growing problem in the United States and other countries around the world. Most of these compounds are not newly synthesized, but have recently emerged as abused substances (Wohlfarth and Weinmann, 2010). The United Nations Office on Drugs and Crime issued the 2011 World Drug Report, which reported that there are stable or decreasing trends for heroin and cocaine use, but that these trends are being offset by increased use of synthetic and prescription drugs (United Nations Office on Drugs and Crime [UNODC], 2011). Some synthetic compounds of concern are synthetic cathinones such as mephedrone and methylenedioxypyrovalerone (MDPV), which are marketed as "bath salts" and "plant food" and have grown in popularity over recent years (Prosser and Nelson, 2012). Other synthetic drugs of concern are those advertised as "Spice" blends, such as Spice Gold, Spice Diamond, Spice Silver, K2, Skunk, and Smoke, which are sold as herbal incense products over the Internet and in local headshops to users who smoke the mixtures for their marijuana-like effects (Vardakou et al., 2010). Synthetic cannabinoids were not created for human consumption; therefore, the pharmacology of many of these compounds is unknown (Griffiths et al., 2010).

The limited information on adverse health consequences of these drugs presents a huge public health concern. Both bath salts and herbal incense products were created for the sole purpose of circumventing the legal system. There are many Internet sites that provide information on these designer drugs, such as information on the effects and dosage (Wax, 2002). These Web sites are easily accessible to the public and are particularly attractive to adolescents (Wax, 2002; Vardakou et al., 2011). The herbal incense products grab individuals' attention due to their clever marketing strategies with the product packaging and the use of forums where users discuss the product effects (Griffiths et al., 2010).

Since the end of 2010, literature reports indicated the emergence of 20 synthetic cannabinoids found in herbal incense products (Kneisel et al., 2012). The rapid emergence of synthetic compounds signifies the challenges that forensic laboratories and analytical chemists must overcome for the identification and structural elucidation of these compounds. A recent article identified a cannabimimetic compound in an herbal incense product with AM-2201 that was not one of the original Huffman synthesized compounds (Moosmann et al., 2012). The continued manufacturing of substances not currently illegal provide an alternative to cannabis for people seeking to avoid potential judicial consequences of marijuana use or those wanting to become intoxicated and still pass a drug test, factors that also increase their attraction for adolescents and young adults.

While the packaging for these products lists only natural herbs as ingredients, chemical analysis has revealed that they contain synthetic cannabinoids, including JWH-018, CP 47, 497, and HU-210 (Auwärter et al., 2009; Lindigkeit et al., 2009; Teske et al., 2010; Uchiyama et al., 2010). After these specific compounds were outlawed in some European countries, Spice blends containing other indole-derived cannabinoids, such as JWH-073 (Lindigkeit et al., 2009), were detected, suggesting that suppliers are changing formulations in order to avoid prosecution. On March 1, 2011, the U.S. Drug Enforcement Administration (DEA) temporarily banned five synthetic cannabinoids, including JWH-018, JWH-073, JWH-200, CP 47, 497, and CP 47, 497 C8 homolog (U.S. DEA, 2011a).

There have been reports of deaths associated with the "bath salts," sold under names such as White China, Cloud 9, and Vanilla Sky (Maskell et al., 2011; Torrance and Cooper, 2010). There have also been reports of deaths due to the use of methylone (Pearson et al, 2012). In October 2011, the DEA exercised its emergency scheduling authority to control mephedrone, MDPV, and methylone, making selling and possession of these compounds, as well as products containing them, illegal in the United States (U.S. DEA, 2011b). The problem with designer drugs is that as soon as one is banned, another analog is created. Although some states have started regulating some of the variants, the hundreds of possible targets limit the effectiveness of this strategy because suppliers can easily move to a non-controlled alternative. For instance, naphyrone emerged in the United Kingdom months after the ban of mephedrone (De Paoli et al., 2011).

In June 2010, the U.S. Air Force prohibited the use and possession of herbal incense products (USAF, 2010). Additionally, all five U.S. military branches banned the use and possession of synthetic cannabinoids by military personnel (U.S. DEA, 2011a). While the synthetic cannabinoids are banned in the U.S. military, a recent article in the *NavyTimes* acknowledges that the Navy and Marine Corps have started random screening tests for synthetic cannabinoids, but highlights the issue of increased bath salt use and the lack of screening tests for these compounds (Fuentes, 2012).

The use of synthetic cannabinoids and other designer drugs has grown in the United States over the past few years. Forensic laboratories have reported an increase in the use of 2C-phenethylamine, piperazine, and tryptamine designer drugs between the years of 2006 and 2011 (U.S. DEA, Office of Diversion Control, 2012). A 2010 survey of college students at the University of Florida indicated that 69 of 852 students had used a synthetic cannabinoid at least once (Hu et al., 2011). There has also been an increase in the number of emergency department visits due to the consumption of designer drugs. The Centers for Disease Control and Prevention reported 35 cases of bath salt ingestion that resulted in emergency department visits in Michigan within a 4-month period (Centers for Disease Control and Prevention, 2011). The American Association of Poison Control Centers (AAPCC) reported an increase in bath salt exposure calls from 304 calls in 2010 to 6,138 calls in 2011 (American Association of Poison Control Centers [AAPCC], 2012a). Some reported symptoms of those who ingested bath salts include agitation, increased heart rate, paranoia, and hallucinations (Spiller et al., 2011). The AAPCC also confirmed an increase in calls related to synthetic cannabinoid exposure from 2,906 calls in 2010 to 6,959 calls in 2011 (AAPCC, 2012b). Some typical symptoms related to synthetic cannabinoid containing herbal incense products include agitation, hypertension, and delusions (Simmons at al., 2011). The psychoactive and physical effects of synthetic cannabinoids in adolescents have been described (Castellanos et al., 2011). The health and societal concern associated with the use of synthetic drugs has been highlighted in recent news articles, including a recent article describing 12 resulting actions and consequences of individuals who may have consumed bath salts (Carter, 2012). Survey findings, news articles, emergency department visits, and call center reports show an increase in the number of people consuming designer drug products and seeking medical attention after exposure to products containing designer drugs.

1.3 Objectives of the Research

1.3.1 The Project as Originally Proposed

Created under a previous National Institutes of Justice (NIJ) cooperative agreement (2008-DN-BX-K180), ForensicDB (www.forensicDB.org) was originally intended to be spectral database for only Direct Analysis in Real Time/time-of-flight (DART-TOF) spectra. However, in the early stages of the project, multiple changes occurred that required adjusting the project to a much more widely applicable database that included multiple spectral methods. Thus, it was proposed to continue and extend the capabilities of ForensicDB. Currently, ForensicDB is a fully functional database, where registered users have access to nominal mass, accurate mass and Fourier transform infrared (FTIR) spectra. Users have submitted nominal mass electron ionization mass spectrometry (EI-MS) spectra and accurate mass data from DART-TOF and electrospray ionization quadrupole time-of-flight mass spectrometry (ESI-QTOF). ForensicDB has the capacity to include different instrumental techniques and is not limited to EI-MS, DART-TOF, or ESI-QTOF data.

There current project set out to accomplish four specific goals:

1. Expand the database capacity for user traffic and database queries.
2. Increase the participation of associate curators to manage the review of records submitted by the user population.

3. Extend the spectral information to include nuclear magnetic resonance (NMR) data in the database, along with routine calculation of pKa data for all records with determined structures.
4. Further develop software automation for improving the management of submitted records.

It was proposed to accomplish these goals through collaboration with several agencies and organizations:

- The Virginia Department of Forensic Science (VDFS), a public forensic laboratory that is currently a collaborator in the existing database program.
- NMS Laboratories, a well-recognized commercial private laboratory that has the unique position of providing analytical services to clients all around the world, which at times provides access to unusual compound reference materials (such as new drug metabolites) that many public laboratories have difficulty obtaining.
- Two universities, the University of Colorado and Albany Medical Center Hospital and College. The University of Colorado brings a strong background in NMR data to complement RTI's strength in this technology.
- The Southern Association of Forensic Scientists (SAFS), a professional organization working to create a database of scheduled compounds.
- Advanced Chemistry Development (ACD/Labs), a software developer that worked with RTI on the development of ForensicDB. ACD/Labs sells and supports a unique set of software that enables ForensicDB to incorporate multiple different spectral methods from almost all spectra instrument manufacturers.

1.3.2 The Project as Implemented

In general, the project was implemented as proposed, with a few notable exceptions. As the project progressed, a decision was made to alter the scope of the proposed work. In talking with numerous users, RTI determined that the community would be better served by including more traditional data (EI-MS, DART-TOF, and FTIR) on existing records and new legal high compounds rather than acquiring and including NMR data on relatively few compounds. An agreement was reached to drop the intention to include NMR data (and to purchase the software needed to include these data), and redirect the efforts to acquiring and processing records for designer drugs and legal high compounds, and incorporate the resulting spectra into the database. Due to not including NMR data in the database, it was determined that the NMR specialty of the University of Colorado was not needed at this time.

The original proposal included plans to distribute licenses and provide software tools to each associate curator to aid in the processing and review of data. RTI did not distribute the software as planned because a more elegant solution was created. ForensicDB uses two intermediate databases—collaboration and submit—to locate and store records during different phases of the review process before adding data to the public database. Using the security structure provided by ACD/Web Librarian software, access to these intermediate databases was enabled for reviewers only while they remain hidden from public view and inaccessible to general account holders. This allows reviewers and others to use the ACD/Web Librarian interface and to directly

access the necessary data without requiring RTI to manage multiple desktop software licensees. Such access reduced the costs associated with software procurement and simplified the management of the system.

RTI did not pursue the subcontract with NMS because it became evident that development of the system to improve the end-user experience from Agilent ChemStation was of greater concern. A strategic decision was made to delay and alter how information was worked with NMS to free up funds to contract for software development to create plugins for Agilent ChemStation (by far, the dominant instrumentation system used by the end-user population). These plugins create a "right click" option to export a given spectrum to a JCAMP file and a "right click" option to search a spectrum selected in Agilent ChemStation directly in ForensicDB. When complete, these plugins will be provided to the end user as a free download from the ForensicDB website. Both options make searching as easy as possible for those users who have a computer that is connected to the Internet, as well as facilitate searching via the instrument computer for those users who do not have easy access to the Internet (often due to security policies or to the laboratory trying to reduce costs by limiting Internet access).

2. Project Methods Database Structure and Functionality

ForensicDB is a Web site composed of a collection of applications that allow public users to view cheminformatic data for a given spectrum and to search these data by providing various known parameters. To achieve its functionality, ForensicDB uses the unique features and functionality of three core software suites: Microsoft's ASP.net server, Oracle Enterprise, and ACD/Web Librarian.

The base software suite in use on ForensicDB is Microsoft's ASP.net server, which provides the platform for the ACD/Web Librarian software suite and serves the basic HTML pages necessary for www.forensicDB.org to function. In addition, the platform opens a wide variety of objects to enhance functionality beyond standard HTML. The ASP suite was chosen because of its functionality and its compatibility with the ACD/Labs software.

The second software suite necessary to run ForensicDB is the ACD/Labs COTS platform ACD/Web Librarian. The ACD suite was substantially developed for such a purpose before the existence of ForensicDB and met the needs of this project without significant changes to the software code; however, it was extended to work with a publicly available Web site and database. Because of ACD/Web Librarian legacy with Oracle and ASP.net, these extensions were natural and quickly accomplished.

The third software suite necessary to ForensicDB is Oracle Enterprise—a large and capable data storage platform made for applications that must store vast amounts of data. The enterprise version of Oracle Enterprise used in ForensicDB is known for performance when dealing with large result sets, and as such, it was a natural fit for a cheminformatics database.

These three suites have been designed to operate in two ways: (1) through a workflow process initiated by the end user and (2) through a maintenance process initiated by the database curators or contributors. The first process is initiated by the end user by visiting the Web site (www.forensicDB.org), which the user can locate through many outlets, such as a search engine, email notification, or promotional flyer. Next, the user must login to the Web site or create an account. This functionality is handled by the ASP.net platform. Once the user is logged in, he/she may select the database they want to search; the navigation to and selection of the database is handled by ACD/Web Librarian. Then, the user can browse or search the database; this functionality is made possible by the interplay between ACD/Web Librarian and Oracle Enterprise. If the user chooses to browse the database, ACD/Web Librarian sends a command to Oracle Enterprise using Structured Query Language (SQL) to select all records. The search function is initiated through ACD/Web Librarian when the user chooses this option. Next, the user may select any number of parameters to search, such as by spectrum, molecular weight, or compound name. ACD/Web Librarian interprets the user-provided parameters and values and translates these into a SQL query statement to be run against the public database in Oracle Enterprise.

The second workflow process is a maintenance process initiated by ForensicDB curators or contributors (discussed in Section 2.1, Database Management). This process is intended to result in the addition of new records to the database or the revision of existing records. Tools for this process include ACD/SpecDB, a complimentary program for ACD/Web Librarian. Records may be submitted to curators by contributors through various means and in various formats. RTI will accept these records and begin a quality assurance process that involves verifying, cleaning, organizing, and testing the record before including it in the public database. The processing of

such records is completed by RTI staff or voluntary contributors, and record quality is ensured by project directors.

2.1 Database Management

Key contributors to the construction, management, and survival of ForensicDB include the curator, collaborators (also known as associate curators), reviewers, and the community. **Figure 2-1** shows a schematic of the database structure. Management of ForensicDB is similar to a peer-reviewed journal in that the curator acts as the editor and the collaborators act as the associate editors. The curator (RTI International) is responsible for creating and maintaining the database and Web server and providing the tools necessary to access and update the database. Database collaborators work with the curator to develop the intention and design of ForensicDB, identify community needs the database can address, and assist the curator with creating requirements for standardization of spectral submission and criteria for evaluating spectra. In addition, collaborators can assist with processing the spectral data into an appropriate format for inclusion in the public database. The reviewers evaluate each submitted spectrum according to established evaluation criteria. The community acts as the driving force of this cheminformatic database, strengthening ForensicDB by contributing their spectral data. The survival of ForensicDB is dependent upon the public's continued use, participation, and comments on database improvement, as well as on the community utilizing the database as part of their analytical scheme of analysis.

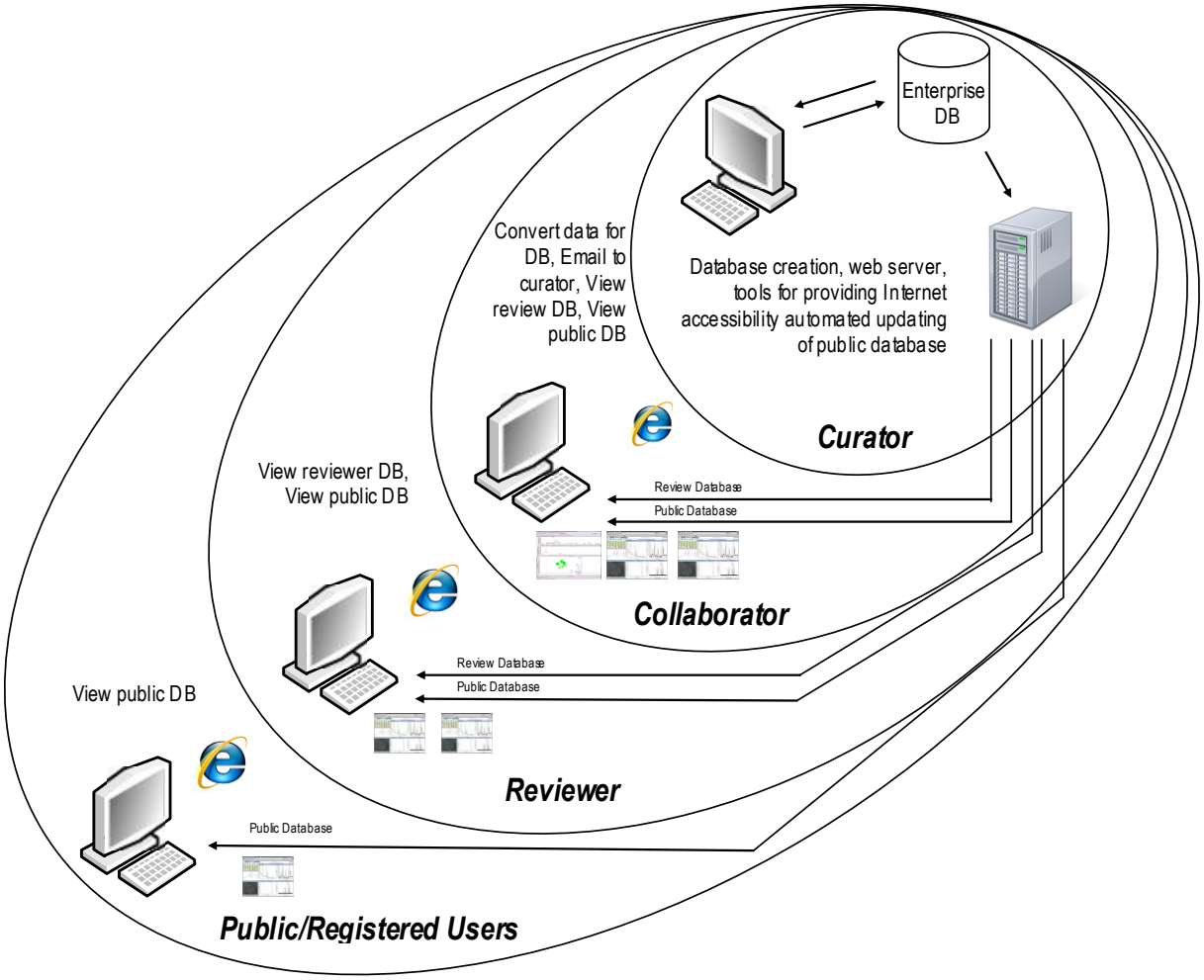

Figure 2-1. ForensicDB database structure and functionality.

While the majority of records currently in ForensicDB have come from large libraries of spectra, the intention is to provide a Web portal where registered users can upload their records for submission. Once records have been submitted, the curator or a collaborator processes the data into an acceptable file format and attaches correct documents to records with corresponding metadata. A customized code has been created with ACD/Labs to help manage the review process. Currently, the workflow is to have submitted records built in the submit database schema and pushed to the collaboration database, which triggers an automatic e-mail to the assigned reviewers. The automatic e-mail contains a direct link to the record for review. The collaboration database is a subsection of the Oracle database that is not publically accessible but can be accessed by reviewers and collaborators.

The spectral submissions are then uploaded into an editorial review board, and the curator sends an automatic e-mail containing the Web link to three reviewers to evaluate the spectra based on established criteria. Evaluations are completed online in a collaboration database. Reviewers are assigned to specific spectra based on their area of expertise. Each instrumental method included in the database has its own criteria to reflect the qualitative spectral differences in techniques. We currently have nine active reviewers and four individuals who have recently expressed

interest in becoming a reviewer, and we have seen dramatic increases in interest in the past few months of the project as the interest in the database has grown.

Reviewers have the option of accepting, rejecting, or requesting changes needed for each record. Each option requires the reviewer to make a comment on his or her decision. If all criteria are met and all three reviewers accept the spectra, the record is automatically sent to ForensicDB for public accessibility. If one of the reviewers requests changes needed or rejects the record, the database curator must evaluate the record. The database curator reviews the data and the reviewers' recommendations on revisions or record rejections. At this point, RTI serves as the database curator. A dedicated staff member surveys the reviewers' recommendations and solicits additional information from experts as needed to determine appropriate actions. Such actions may include correction to structure, additional required instrumental parameters, standard source lot number, and other information required for a complete submission, or submission of a better spectrum based on reviewers' comments. Rejected spectra may be moved into the rejected database, or the contributing user may be contacted to determine if better spectra can be submitted.

Reviewers first check to make sure that all information required of the submitter has been provided and that there are no misspellings of the compound name, record information, or document information. They confirm that the structure is correct, including chirality, based on published literature and other online or in-house resources. Reviewers make sure that the submitted names, synonyms, and compound class are correct and make notation of any that should be included or excluded. They confirm that each spectrum has the parameters associated with it (e.g., FTIR spectra have FTIR parameters). They make sure that the molecular user data calculations are performed correctly by checking the calculated formula and mass.

In evaluation of accurate mass spectra, the presence of a protonated or deprotonated molecule must be determined. For accurate mass data, the experimental mass of the protonated or deprotonated molecule must be within ±5 mDa of the compound's calculated exact mass. If a protonated or deprotonated molecule cannot be identified at the lowest collision energy spectrum, the data may be rejected or accepted with a note about the lack of parent ion and likely cause (e.g., instability of the molecule upon ionization, loss of a water molecule).

For all mass spectra, the fragmentation pattern must be reasonable based on the structure and ionization method. Spectral evaluation at all submitted collision energies is conducted to determine if the fragmentation is reasonable. Knowledge of DART ionization, ESI ionization, and EI ionization, as well as the compound of interest, is used in examination of fragment ions. Reviewers also look at 13C or other characteristic isotope ratios to make sure they are consistent in each prominent peak. The signal to noise must be evaluated as well. A comparison of the submitted compound spectrum to other spectra of the same compound is performed, and significant differences are noted and brought to the attention of the curator. If the reasons for the discrepancy are the result of different conditions likely to be encountered in the forensic community, such as different mobile-phase solvents or source material suppliers, the record is published as is. If the differences indicate unreliable data, a new spectrum is requested. If the repeat spectrum still does not agree with previous spectra of the same compound, an expert in the area of that spectral method is consulted for guidance.

When evaluating FTIR spectra, reviewers make sure the baseline and intensity is reasonable and that the absorption peaks are consistent with the major functional groups of the compound. They

also check to make sure there are no avoidable large water or carbon dioxide peaks from the background.

All new data submitted to ForensicDB goes through the peer-review process. However, in an attempt to better serve the community, large legacy libraries such as the AAFS mass spectrometry database are included in ForensicDB. The instrumental parameters and source material for these records are unknown, and they have not gone through the extensive peer-review process. Although an effort is made to ensure that all newly submitted records are accurately and thoroughly reviewed prior to public availability, ForensicDB was created as a resource for the community to access and share spectral information. ForensicDB is not intended to be used as a published source for the verification of standards. RTI and ForensicDB adhere to the SWGDRUG recommendation to run concurrent standards of traceable reference materials to support identification (Part IV B – Quality Assurance Section 2.3) (SWGDRUG, 2011).

2.2 Database Organization

Organization of ForensicDB is based on chemical structure —the only truly unambiguous means of referring to any given compound. **Figure 2-2** illustrates the organization of ForensicDB. A record indicates a specific compound structure and name, analyzed by a particular institution from a specific source material. Thus, multiple records may exist for a specific compound, reflecting a change in the major record features. Each record may contain multiple documents that indicate spectral method and instrumental parameters. Some of the general requirements for all submissions are spectral method, instrument type, scan range, and data reduction method. Other parameters are requested based on the instrumental technique, such as spectral resolution and number of scans co-added for FTIR data. Specific requirements for DART spectra include gas heater temperature, gas flow rate, type of sample introduction, and orifice 1 voltage.

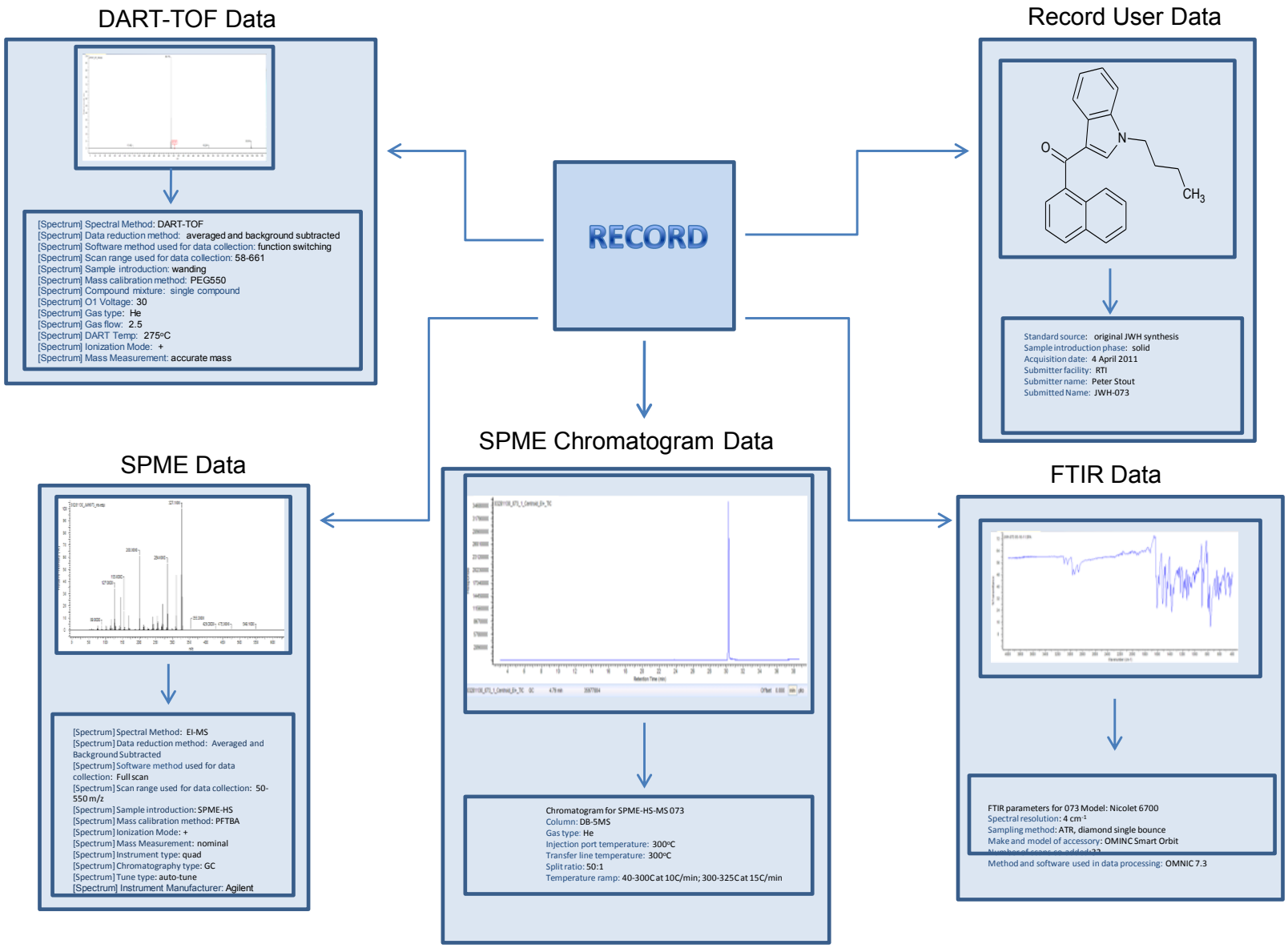

Figure 2-2. ForensicDB Database Organization.

2.3 Database Functionality

Figure 2-3 shows the main searching features of ForensicDB, which include searching by structure, spectrum, and user data information. The structure can be uploaded or created using the provided drawing applet and searched by exact structure, substructure, or structure similarity. Users can customize the settings for substructure and similarity searching. Some options include selecting a particular search algorithm and accounting for structures with chiral centers and double bonds.

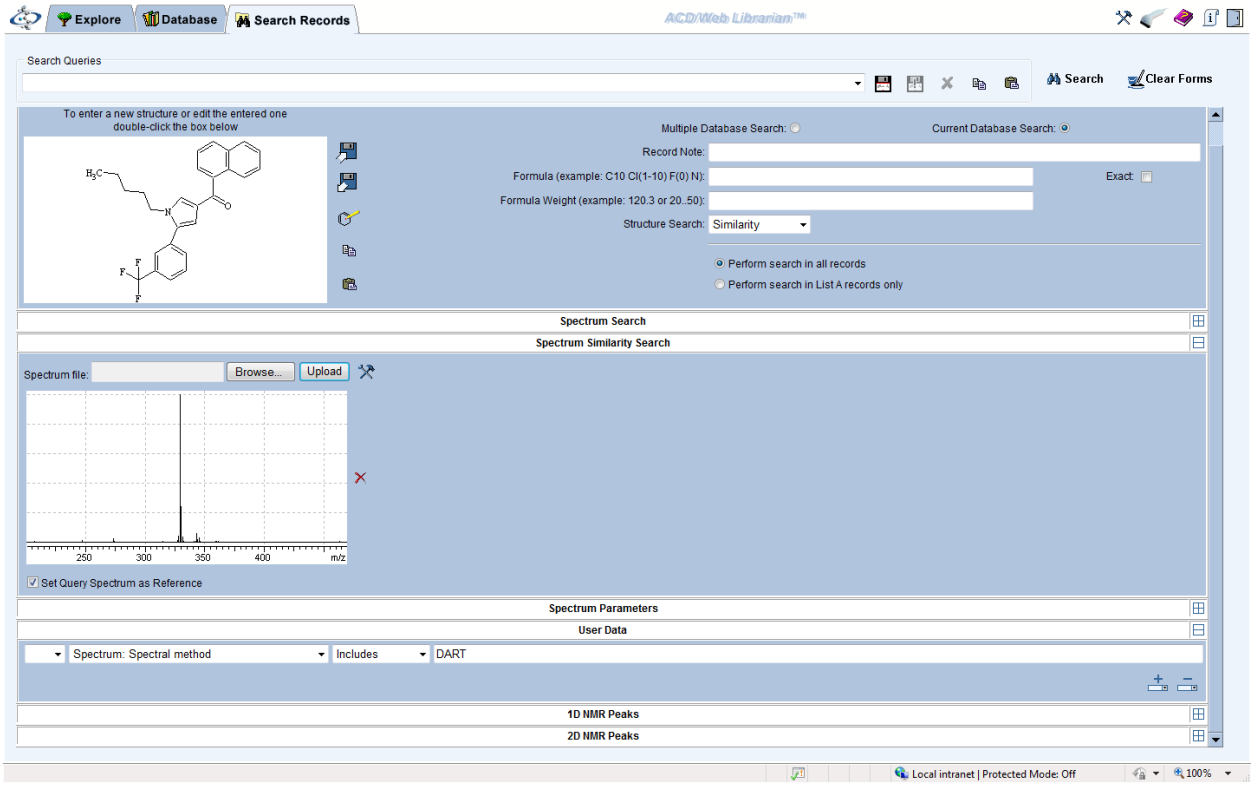

Figure 2-3. Main searching features of ForensicDB

Users can upload their unknown spectrum to search against the database by spectral similarity. The spectrum can be set to mirror the reference spectrum. Setting the searched spectrum as a reference was not an original database function, but ACD/Labs worked with RTI to create this feature for the end users. The resulting spectra can be narrowed down by options within the settings dialog box.

In the case of mass spectra, the data can be narrowed down by minimal percent similarity, number of resulting spectra, and tolerance level. The settings used to narrow search results vary due to the type of spectral method being searched. Caution should be taken when selecting the 'M ion' option. Some users may think it is used to search the molecular ion, but in fact, it is only searching for reference spectra that have the same most abundant peak in the last cluster of ions as the unknown spectrum. The use of 'M ion' may lead to false negatives.

Another function within spectral similarity search is the ability to search by .CSV, which allows users to search spectra directly from Agilent instrumentation. Although ForensicDB was originally not able to handle .CSV files, currently, there are currently two ways to handle .CSV

in the database. The first is by downloading a tool that reformats Agilent ChemStation .CSV files so that they can be subsequently uploaded to search by spectrum similarity, as shown in Figure 2-3. The second way is by selecting the "search CSV" tab on the toolbar within the public database. This allows a direct search of the .CSV file; however, this search does not provide a hit-quality index of the returned results. This occurs because the spectrum was not uploaded into the search field as shown in Figure 2-3. The .CSV files are easily exported from Agilent ChemStation, but not easily imported into ForensicDB for searching. We are working with an independent consultant to make this easier. The independent consultant is working to provide a macro that will create a JCAMP for a spectrum of interest in the Agilent ChemStation data analysis software. (JCAMP is a standard portable file format for spectral information developed by International union of Pure and Applied Chemistry [IUPAC]). JCAMP files are easily uploaded and searched in ForensicDB. Once the macro is complete, the consultant will work to create a right-click menu option in Agilent ChemStation, where users can search their spectrum directly in ForensicDB. Implementing both of these functions would appeal to a larger number of users (those with and without Internet access at their instrument), resulting in more traffic to ForensicDB.

Information in document and record forms can be searched in the user data field. This field can be used separately or in conjunction with other searches, as shown in Figure 2-3, where the search is for the spectrum, but the search occurs only within DART data. Some examples of user data searching include searching by submitted name, instrumental technique, or formula weight.

The user's view is customizable by the user and remains intact for his or her account. There are a wide variety of tools available to the user for analyzing the data. The spectrum is shown in the middle and can be set as a different window. In addition, the user can zoom in on specific ions. Documents with reported instrumental parameters can be found in the right corner, along with the percent similarity from a spectral similarity search. Record information can be found at the bottom of the layout. This also includes automatic calculations based off the structure. The structure is shown at the bottom left corner of the database layout. The top left corner contains a table of relative intensities for each fragment ion within the spectrum.

ACD/Labs is working on a 2012 release of ACD/Web Librarian. RTI has submitted several feature requests based on user feedback, which will be included in the new version of the software. The new upgrade will include a universal search feature, where users can search a term without any constraints. As shown in Figure 2-3**,** a user must first find the type of information to search from the list of parameters in the user data search section. For example, a user must find "Spectral Method" from the list and then type in the specific instrument of interest. With the new universal search field, users will only have to type in EI-MS or the compound name to retrieve search results. The new database version would also feature the ability to search by a specific peak and, potentially, the relative intensity. Both of these new features are still a work in progress, and once they have been completely tested, we will hold a database training session to educate the users on the new updates. Additionally, multi-browser support (ForensicDB currently only supports Internet Explorer) and increased capabilities for printing or saving images of spectra from records have been requested and are in development.

3. Results and Discussion of Database Status

3.1 Contents of the Database

As of June 27, 2012, ForensicDB includes 3,108 total records representing approximately 6,374 spectra. These records were contributed by VDFS; RTI; Dr. Graham Jones (AAFS); Cayman Chemical; the DEA Southwest Laboratory (DEA SWL); the DEA Special Testing and Research Laboratory (DEA SFL1); and the Hillsborough County Medical Examiner's Office. The types of instrumental data represented are accurate mass, nominal mass, FTIR, and chromatographic. The types of compounds submitted to ForensicDB include JWH cannabimimetic compounds, herbal Spice products, drug standards, pharmaceutical preparations, TLC-separated pharmaceutical preparations (Wood and Steiner, 2011), chemical compounds, nylon fibers, and smokeless powders.

Table 3-1 shows the approximate number of spectra in ForensicDB per instrumental method. Some of the data within Table 3-1 are presented as their own record, or are attached as a document to an existing record of the same source material, lot, and submitting institution. The public database includes a total of 2,203 EI-MS spectra. These spectra were contributed by Dr. Graham Jones (AAFS), VDFS, RTI, Cayman Chemical, and DEA SFL1. There are 958 records, with DART-TOF data representing approximately 3,832 spectra submitted by RTI and VDFS. The DART spectra collected at both institutions were analyzed under the same instrumental parameters. To illustrate the characteristic fragmentation patterns, each compound record collected using DART contains a document at voltages of 20V, 30V, 60V, and 90V. RTI contributed 34 records that contain a total of 41 ESI-QTOF spectra. The ESI-QTOF spectra of isolated synthetic cannabinoids from herbal blends were detected using mass defect filtering as described in a recent article (Grabenauer et al., 2012). The EI-MS data of isolated synthetic cannabinoids from herbal mixtures were determined by solid-phase microextraction headspace gas chromatography mass spectrometry (SPME-HS-GC-MS) (Cox et al., 2012). ForensicDB includes 193 FTIR spectra contributed by RTI, VDFS, Cayman Chemical, DEA SWL, and DEA SFL1.

In an effort to gain more of the new and emerging designer drugs, Cayman Chemical has agreed to contribute their EI-MS and FTIR data of compounds they offer in their forensics catalog. In addition, DEA SWL contributed approximately 500 FTIR spectra of drugs that are of forensic interest. The DEA SFL1 submitted 20 compounds collected by FTIR and EI-MS, including RTI-126 (2β-[1,2,4-Oxadiazol-5-methyl]-3β-phenyltropane) and it alpha isomer. RTI-126 has been found and described (Casale and Hays, 2011).

Table 3-1. Approximate Number of Spectra in ForensicDB per Instrumental Method

Data Type	Spectra
ForensicDB	
EI-MS	2,203
DART-TOF	3,832
ESI-QTOF	41
FTIR	193
Chromatography	117

ForensicDB also includes smokeless powder records submitted by VDFS. Each smokeless powder record includes a document for attenuated total reflectance (ATR)-FTIR, EI-GC-MS, and positive chemical ionization (PCI) GC-MS chromatogram; a positive and negative DART-TOF spectrum at 20 V; and an image showing the morphological characteristics.

Ames Laboratory submitted 322 different nylon fiber samples that were measured in duplicate and analyzed under two photoacoustic (PAS)-FTIR parameters. The only difference between the parameters was a scanning speed of 400 Hz or 2.5 kHz. This was a total of 1,288 spectra that required processing. These were processed, but still require review.

As a result of the project rescope, ForensicDB gained approximately 135 different designer drug compounds (84 cannabimimetic compounds and 51 other designer drugs) that are publically available. Other designer drugs include compounds from the following drugs classes: cathinone, phenethylamine, tryptamine, piperazine, and arylcyclohexylamine. This total does not include duplicate compound records created for different source materials or submitting facilities. Some of these records contain up to seven spectra, which include FTIR, EI-MS, ESI-QTOF, and DART-TOF at 20V, 30V, 60V, and 90V. There a numerous other designer drugs and cannabimimetic compounds in various stages of the processing and reviewing phase.

RTI has access to all of the original JWH compounds synthesized by Dr. John Huffman, which puts the Institute in a unique position because reference standards and spectra of most of these compounds do not exist, and many of them have yet to surface as legal highs. With the inclusion of these spectra in ForensicDB, the community gains a unique advantage to help identify unknown samples.

3.2 Expansion of Database Infrastructure

During the course of this project, the capacity and memory of the Web servers for ForensicDB were increased by upgrading to two more functional servers for some redundancy of function and to distribute load. This additional server capacity may also be useful for file transfers of submitted records. Server support for the infrastructure was increased from the current 9 to5 ET, Monday through Friday support to 24/7 support. Customer service for community users remains as Monday through Friday support, but the increase in server support means that the managers of the servers are available to address server issues at any time. Increased traffic from time zones around the world is expected to increase the potential for users to be affected by service failures outside of Eastern Time business hours.

More software licenses were purchased that allowed the calculation of pKa, which was not previously calculated for the database records. ACD/MS Fragmenter was acquired to help aid in fragmentation pattern of an unknown compound as needed. The database infrastructure and capacity was extended by continuing service agreements with ACD/Labs for further support and updates of the perpetual licenses of all software previously purchased.

3.3 Optimization of Record Handling and Management

Automation of the review process was implemented in the previous cheminformatic project. In the past year, the process has been further refined to reduce the burden on reviewers and allow them to focus on the scientific accuracy of the data. When a reviewer is assigned to a record, an automated e-mail is now sent out with a direct link to the record to be reviewed. Reviewers can view each other's comments and respond to each other's queries without curator involvement. If

all three reviewers fully accept a record, the record is automatically made public without further manual intervention. In the interest of learning how the user population would submit records to ForensicDB and to conserve resources establishing the database, the processing of submitted records has been mostly a manual process. In addition, because much of the data submitted to ForensicDB have been from large library collections, it was decided that internal project staff members would prepare the records manually for the review process. Users who have submitted data thus far have transferred files to RTI through secured e-mail or for large data sets compact disk sent through the mail. Project staff then processes this into the database and manually enter the metadata. Anticipating increasing submissions of records from the community, work was started on the creation of a more automated system allowing the submitter to enter metadata fields such as instrumental parameters, submitting facility, and source material from Web forms, and associate spectra and structure files. This will free up time for curators and project staff and allow them to focus on evaluating the submitted records. Users will also be able to submit complete record information with a single interaction, instead of contacting ForensicDB and awaiting further instructions. At the time of writing this report (6/20/2012), the Web-portal for spectra submissions is in final testing. The Web-portal is estimated to be deployed to the public by mid-July.

3.4 Database User and Online Training Statistics

Between June 2010 and June 2011, there were 3,635 visits to ForensicDB. New visitors represented 53.62%, while returning visitors represented 46.38% of these visits. Database user traffic from referrals (sites that link to ForensicDB) accounted for 15.5% of database access. RTI held three Web-based training classes with a total of 282 enrolled and 121 completed attendees:

- December 21, 2010: 104 registered, 40 completed
- January 20, 2011: 68 registered, 21 completed
- June 23, 2011: 110 registered, 60 completed.

Between June 2011 to June 17, 2012, there were 5, 812 visits (3,550 unique visitors) to ForensicDB consisting of 58.19% new visitors and 41.81% returning visitors. There were 1,022 visits based on referrals, mainly from www.forensiced.org, surveymonkey, and www.usdoj.gov. The database gained 644 new user accounts during this period for a total of 951 user accounts. Database users exist in 51 countries outside the United States. RTI held five Web-based training classes with a total of 581 enrolled and 286 completed attendees:

- July 21, 2011: 113 registered, 71 completed
- October 12, 2011: 30 registered, 9 completed
- November 9, 2011: 114 registered, 56 completed
- December 7, 2011: 97 registered, 36 completed
- March 20, 2012: 146 registered, 69 completed
- May 22, 2012: 81 registered, 45 completed.

After the training session, users were asked to provide feedback about the database demo. When asked to determine the biggest benefit of attending the class, users responded with the following:

- "Got me thinking how can use the DB."
- "Learned about SMILES and INCHI string and will definitely start to learn more about them and get hooked up to the ForensicDB so I can tap into the mass spectra."
- "Being able to search mass spectra that do not have a match in our current libraries."
- "It was a new and exciting and "free" tool that our lab would find very useful."
- "Ability to import MS data from various sources and do a general search."

The comments and questioned asked by users during the database training sessions exemplify the need of a freely accessible database that is continually updated to meet the growing needs of the forensic community.

3.5 Accounts of Database Usage and Outreach

Since its inception, ForensicDB has not only grown in the number of compounds, reviewers, contributors, and collaborators, but also in its outreach to other database efforts. The existence of several independent databases with unique contents makes it difficult for investigators to complete a thorough search of reference spectra to identify unknown compounds. RTI has initiated efforts to create links between database resources to better serve the forensic community. For compounds with spectra in both Forendex and ForensicDB, there is now a direct link (via the databases tab) from Forendex to the record in ForensicDB. This enables users who have identified an interest in a compound via Forendex to upload a spectrum of their unknown and perform a structural similarity comparison with the data in ForensicDB. In addition, we are working with SWGDRUG to provide them with reviewed EI-MS spectra of JWH synthetic cannabinoids for inclusion in their downloadable database. Each of these spectra appear in the SWGDRUG database with a reference to their record ID in ForensicDB, so users are encouraged to explore ForensicDB to find additional analytical data from that same source material. This collaboration is part of an effort to provide quality reference spectra to a wide audience within the forensics community.

A link to ForensicDB can be found on several websites, such as the webpages for the Northeastern Association of Forensic Scientists (NEAFS) and the Southwestern Association of Forensic Scientist (SWAFS). ForensicDB is also linked to from the Forendex forum and announcements about database trainings are posted there. We also plan to list major updates to the database such as when the new release of ACD/Web Librarian takes effect. There also are several publications that have referenced ForensicDB (Cox et al., 2012; Grabenauer et al., 2012; Wiley et al., 2011).

The effectiveness of our outreach efforts can be seen by monitoring mailing lists and forums commonly used by the forensics community. A user on LinkedIn posted a message for help trying to identify an unknown compound, suspected to be methoxetamine. ForensicDB contains FTIR and EI-MS data of methoxetamine, contributed by the DEASFL1, but unfortunately, the user was unable to find the spectrum on ForensicDB at that time because it was going through the review process. Monitoring these forums assists RTI with prioritizing data acquisition and review according to needs in the community.

ForensicDB was referenced in a forum post in Forendex where users were looking for a spectrum for 2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25I-NBOMe). All spectra available on Forendex were from the same source material. The curator of Forendex, Dr. Lee Fadness, directed the user to ForensicDB, which contains a reference spectrum from material other than the Cayman Chemical standard that most laboratories had analyzed and had questions about. This demonstrates the level of collaboration we have been able to achieve by reaching out to curators of other databases to help the greater forensics community.

RTI also has had communications with individuals through our ForensicDB@rti.org e-mail server. A forensic scientist at a crime laboratory asked to reference spectra in ForensicDB in their Crime Lab literature source. An individual inquired about the number of ESI spectra in the database and a forensic scientist sent examples of spectra they had tried to search with no success. The searching issue was resolved by adjusting the search criteria. RTI received requests on whether the spectra were reviewed and if ForensicDB could be used to verify reference standards. Requests were received for specific compounds that crime laboratories may have encountered, and the requests were used to guide decisions on which compounds to make priorities. RTI staff reached out to several authors of published literature that have presented spectra of emerging drugs. Many of these authors carried out their own syntheses and therefore provide valuable reference spectra for comparison to commercial vender supplies. These requests have a very high success rate, the most recent being acquisition of spectra of fluorotropacocaine and its 3-alpha isomer from a research group in Ireland for inclusion in ForensicDB (Kavanagh et al., 2012). Several authors have subsequently contacted ForensicDB at later dates to submit additional spectra of new synthetic products.

All of these accounts demonstrate the growth and use of ForensicDB as an analytical tool to aid the community in the identification of unknown compounds. It also shows the success of collaborative efforts between independent database efforts.

4. Conclusions

4.1 Discussion of Findings

RTI accomplished the goal of expanding the capabilities of the ForensicDB database by upgrading server capabilities to meet the growing user demand and to increase the stability of the Web services. This was accomplished by upgrading to two more functional servers and increasing the infrastructure support to 24/7 support. A Web-portal for user submissions of complete data records has also been developed and is currently in the final stages of testing before deployment.

It was originally proposed to include NMR spectral data, but with the rise in designer drug use and the challenges in identification of these drug analogs, the focus shifted on including more of the new and emerging compounds. This was a success as the community participated in submitting records, including large data sets from collaborations with DEA SWL, DEA SFL1 and Cayman Chemical. Additionally, RTI collected analytical data for a large quantity of these emerging drugs. The records from RTI include nominal mass, accurate mass, and FTIR spectral data.

The approach to aggressively promote and expand the use of the database was successful in increasing the communities' involvement in the database. The number of volunteers willing to review spectral data increased, and more community contributions of spectra to the database were acquired. Our increased presence on online forums, links from other websites, presence at conferences, and additional ForensicDB training sessions aided in an increase of community participation in ForensicDB.

4.2 Implications for Policy and Practice

The recent epidemic of legal high compounds has highlighted the challenges to the laboratories for staying ahead of illicit trends. The possibility of thousands of potential compounds being marketed has taxed the laboratory and regulatory ability to respond. ForensicDB cannot replace concurrently run standards for positive identification in case work, but it can provide a mechanism for access to spectral data on new compounds that are otherwise lacking for the community.

Many new drugs first appear internationally before surfacing in the United States several years later. RTI will leverage its international presence and the global representation of SWGDRUG to strengthen international submissions. With more international involvement, ForensicDB will incorporate spectra of unusual compounds prior to their abuse in the United States. This has the potential to reduce case backlog because the community has an immediate resource to the spectral data. The continued growth of community submissions and peer reviewers will increase the usefulness of ForensicDB.

4.3 Implications for Further Research

RTI plans to continue monitoring forensic forums to both guide users to the search capabilities of ForensicDB and to ensure that the compounds that users discuss are included in the database. RTI successfully implemented recurrent online database demonstrations to help new users adopt this technology for searching unknown spectra. It is essential to continue these monthly Web-based demonstrations to increase user support of this technology. We plan to continue holding

online database training sessions to educate users on the searching and navigating of ForensicDB. This will also remain an outlet for RTI to communicate with the community about changes that may be necessary to facilitate the use and acceptance of ForensicDB.

We plan to expand database content by focusing on the growing number of community submissions by requesting spectra from participants in online forums and discussions, as well as by promoting ForensicDB at conferences in the form of scientific presentations and at booths where users can be given a live demonstration of the database. In addition to individual data submissions, RTI will continue to reach out to the community to incorporate large spectral libraries from collaborations with manufacturers of reference material. RTI staff will also monitor current literature, such as the Microgram Journal for sources of spectra of unusual substances.

The current bottle neck of ForensicDB is the review process. Although we have gained more reviewers, we are still in need of volunteers to help with the review process. More reviewers would help with the current backlog of data, which would result in more data being publically available in a timely manner. This would be an advantage to the public and increase the usefulness of ForensicDB.

Several facilities are independently working on database efforts. There is significant overlap of the same compounds, from the same institution, and same source material in each of these databases. There exists a need to unify these efforts in order to consolidate data and make it easily accessible. RTI has initiated communications between the most prominent of these database efforts—ForensicDB, Forendex, and SWGDRUG—as well as several other organizations to discuss the best strategy moving forward to make reliable reference spectra widely available to the forensics community.

As RTI is now the holder of the Forensic Technology Center of Excellence funded by NIJ, maintaining and expanding this technology assistance to the community appears to be a viable option for maintaining ForensicDB and its availability. Also, this appears to be a viable option for addressing the critical needs of the community for more accessible information and facilitating cooperation between all of the library and standard efforts currently available. RTI and its partners are actively pursuing the concepts to be able to serve the practitioner community.

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6. Dissemination of Research Findings

The development of ForensicDB has been presented as platform presentations at several national and international forensic science conferences; at an ACD/Labs software user group meeting; and at multiple professional meetings (**Table 6-1**). The database was also mentioned in several workshops and presentations at conferences (Table 6-1). ForensicDB has been referenced in several journal articles (Cox et al., 2012; Grabenauer et al., 2012; Wiley et al., 2011) and has been highlighted in interviews for an editorial in *Scientific Computing World* for their August/September issue examining cheminformatics in forensics.

Table 6-1. Presentations at Scientific Meetings

Location and Date of Presentation	Title
Society of Forensic Toxicologists, 2010; Richmond, VA	*Development of a Web-accessible Cheminformatic Spectral Database for Shared Utilization by Forensic Laboratories*
Canadian Society of Forensic Science, 2010; Toronto, Canada	*Overview of a Public Web-accessible Cheminformatics Database for Shared Utilization by Forensic Laboratories*
American Academy of Forensic Sciences, 2011; Chicago, IL	*Development of a Web-accessible Cheminformatic Spectral Database for Shared Utilization by Forensic Laboratories*
ACD/Labs North American Users' Meeting, 2011; Princeton, NJ	*Development of a Web-accessible Cheminformatic Spectral Database for Shared Utilization by Forensic Laboratories*
Society of Forensic Toxicologists/ The International Association of Forensic Toxicologists, 2011; San Francisco, CA	*Status Update for ForensicDB: A Web-accessible Spectral Database for Shared Utilization by Forensic Laboratories*
Society of Forensic Toxicologists/ The International Association of Forensic Toxicologists, 2011; San Francisco, CA	*Advanced LC-MS Approaches for the Detection of Synthetic Cannabinoids in Unknown Samples**
Southwestern Association of Toxicologists Meeting, 2012; San Antonio, TX	Invited as a keynote speaker about the ForensicDB effort to the SAT attendance of approximately 60 toxicologists and chemists from the southwestern region.
Mid-Atlantic Association of Forensic Scientist Meeting, 2012; Ellicott City, MD	Synthetic Cannabinoids workshop and discussion of the ForensicDB effort to a workshop attendance of approximately 80 predominantly forensic chemists in the mid-Atlantic region. **
Southern Association of Forensic Scientist Meeting, 2012; Pensacola, FL	*Future workshop on Emerging Drugs and the Tools and Strategies that Forensic Chemists Can Use to Deal With Them* ***

* Poster presentation that referenced www.forensicDB.org

** ForensicDB discussion during a workshop

*** Invited to discuss ForensicDB at a future workshop

ForensicDB was promoted at several conferences at RTI's exhibit booth and will continue to be part of RTI's exhibit booth at upcoming conferences. **Table 6-2** shows a list of conferences where the database was promoted.

Table 6-2. Conferences where ForensicDB Was Promoted at RTI's Exhibit Booth

Location and Date of Presentation
American Academy of Forensic Sciences Meeting 2012, Atlanta, GA
California Homicide Investigators Association Meeting 2012, Las Vegas, NV
North Carolina Division of the International Association for Identification Meeting 2012, Wilmington, NC
Technical Working Group Meeting 2012, Washington, DC
Indigent Defense Services Meeting 2012, Durham, NC
Southwestern Association of Toxicologists Meeting 2012, San Antonio, TX
Mid-Atlantic Association of Forensic Scientist Meeting 2012, Ellicott City, MD
Midwestern Association of Crime Lab Directors Meeting 2012, Columbus, OH
NIJ Conference 2012, Washington, DC
International Association of Coroners and Medical Examiners Meeting 2012, Las Vegas, NV
Association of Firearm and Toolmark Examiners Meeting 2012, Buffalo, NY
NIJ Law Enforcement Technology Conference 2012, Stevensville, MD
Association of Forensic DNA Analysts and Administrators Meeting 2012, San Antonio, TX
Society of Forensic Toxicologists Meeting 2012, Boston, MA
National Association of Prosecutor Coordinators Meeting 2012, Deadwood, SD
National District Attorney's Association Meeting 2012, Mystic, CT
International Association for Identification Meeting 2012, Phoenix, AZ
Midwestern Association of Forensic Scientist Meeting 2012, Milwaukee, WI
International Association of Chiefs of Police Meeting 2012, San Diego, CA
Southern Association of Forensic Scientist Meeting 2012, Pensacola, FL
National Association of Medical Examiners Meeting 2012, Baltimore, MD
Southwestern Association of Forensic Scientist Meeting 2012, Scottsdale, AZ
Northeastern Association of Forensic Scientist Meeting 2012, Saratoga Springs, NY