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# The Pistoia Alliance Controlled Substance Compliance Service Project: from start to finish

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**Pharmaceutical companies and other life science R&D organizations routinely work with controlled substances, and must have adequate controls in place to meet the legislative requirements of the countries in which they operate. Controlled substances include a range of narcotics and psychotropic drugs, which are covered by increasingly complex legislation as legislators attempt to keep up with a rapidly changing environment. This legislation must be interpreted and transformed from legal wording into chemical structures to be used effectively. Over the past year a working party of pharmaceutical and technology companies has come together under the umbrella of the Pistoia Alliance to define a Controlled Substance Compliance Service. We describe the benefits of bringing together this group of experts to solve the pre-competitive issue of controlled substance management.**



## Introduction

Pharmaceutical companies and other life science R&D organizations routinely work with controlled substances. Rigorous controls must be implemented to meet the legislative requirements of the countries in which the companies operate. For example, many institutions and pharmaceutical companies conduct research aimed at increasing our understanding of the central nervous system and are developing treatments for conditions such as Schizophrenia, Depression, Alzheimer's disease and Parkinson's disease. In this context, a broad range of pharmacologically active substances, including controlled substances, are used as reference standards.

Controlled substances include a range of drug precursors, narcotics and psychotropic drugs, which are covered by increasingly complex legislation as legislators attempt to keep up with a rapidly changing environment [1]. Legislation exists at local, national and international levels [2] to restrict the production, import and export, supply, use and possession of these substances. Substances can be temporarily controlled; for example, in the USA the Drug Enforcement Administration (DEA) can temporarily place drugs in Schedule I status pending permanent placement in Schedule I or letting the scheduling lapse. Organizations must continuously monitor legislation to ensure they can identify any newly scheduled substances. The interpretation of the US Federal Analog Act is particularly challenging because the definition of analog is deliberately vague and broad. For R&D organizations to be able to comply with this legislation effectively, the legislation must be interpreted and transformed from legal wording into scientific nomenclature (i.e. words into chemical structures). Lists of controlled substances are often published in the legislation in non-systematic formats; it is a challenge for research scientists to identify them, quickly and accurately, to remain compliant with legislation. For example, during the course of this project we had the opportunity to compare different team members' translations of these controlled substance lists into chemical structures and we found some subtle differences.

The increasing externalization and globalization of the pharmaceutical industry means substances are routinely produced, stored and transported across national borders and legislative domains,


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and it is self-evident that life science organizations need to have a clear, detailed and accurate understanding of the regulations in all the regions in which they operate. Controlled drug legislation develops country by country in different timescales; it is controversial [3–6], complex and ever changing as it tries to keep ahead of substance abuse and trends in the manufacture of so-called 'legal highs' [7–10]. It is this ever changing nature and broad interpretive basis of the controlled drug legislation that causes the greatest challenges for pharmaceutical companies to keep their large and diverse compound libraries in compliance. The risks to an organization of noncompliance with controlled substance regulations are real and substantial, not only in terms of fines and revocation of licenses but also loss of reputation. There are a number of well documented examples where organizations have faced significant penalties for failing to comply with the US Controlled Substances Act (http://www.justice.gov/dea/divisions/mia/2013/mia061113.shtml; http://www.justice.gov/dea/divisions/hq/2013/hq040313.shtml; http://www.justice.gov/dea/divisions/nj/2013/nj102313.shtml).

The Pistoia Alliance is a not-for-profit, multi-company members' organization committed to lowering the barriers to innovation in life science R&D. It achieves this aim by improving the interoperability of R&D business processes through precompetitive collaboration. It draws its membership from pharmaceutical R&D and other life science R&D organizations, commercial information providers, technology companies and other publically funded research organizations. The Pistoia Alliance brings together the key stakeholders to identify the root causes of R&D inefficiencies; then it develops best practice recommendations and technology implementations to overcome common obstacles. The consistent identification of controlled substances in databases and sample collections was identified as a precompetitive challenge that is common to many life science organizations and this challenge requires a collaborative, cross-industry resolution.

## Pre-project background

The Pistoia Alliance hosted a meeting between representatives from the GlaxoSmithKline and AstraZeneca compound management groups to identify opportunities for precompetitive collaboration within the domains of screening, compound handling and logistics. From the enthusiastic discussions at this meeting, the common challenge of controlled substance legislation interpretation quickly emerged. The outcome of these discussions was recognition that no commercially available solutions addressed the requirements of the work group members. Furthermore, each individual life science organization that works with controlled substances must replicate the effort and expenditure on monitoring legislation and controlled substance compliance activities.

It was apparent that many organizations had developed custom-built in-house solutions to ensure compliance with legislative requirements for controlled substances. It was estimated that the potential savings to the industry of implementing a controlled substance compliance service (CSCS) solution were in the region of US$90 million.

## Project process

The topic of CSCS fell within the remit of precompetitive, cross-company, collaborative open innovation and, as such, was amenable to the Pistoia Alliance project process (Fig. 1). A clear business case for the project was generated and gained approval from the Pistoia Alliance board. The Pistoia Alliance extensive industry network was polled to solicit broader participation in the project.

The Pistoia Alliance proposed the use of a shared-risk funding model, where pharma project members each contributed to fund the project and, as such, formed the project steering committee. Representatives from the funding companies established a steering committee that would oversee the project and its finances. In addition, an international project team (IPT) was formed consisting of experts from pharmaceutical company chemistry and materials management, and from technology companies that specialize in chemoinformatics. The teams were supported by a Pistoia Alliance contracted project manager. Having representatives from pharmaceutical and technology companies present during the early project discussions was crucial for developing strong connections with, and across, the IPT and steering committee. This approach gave the technology suppliers a good understanding of the customers' requirements and an early indication of the potential commercial opportunities for a solution.

## Requirements analysis

The first task was to define the scope of the term 'controlled substance'. Early discussions revealed that this term had different meanings among the team members. Controlled drugs, chemical weapons and ozone-depleting substances were among examples offered. However, the discussions eventually focused on controlled drugs

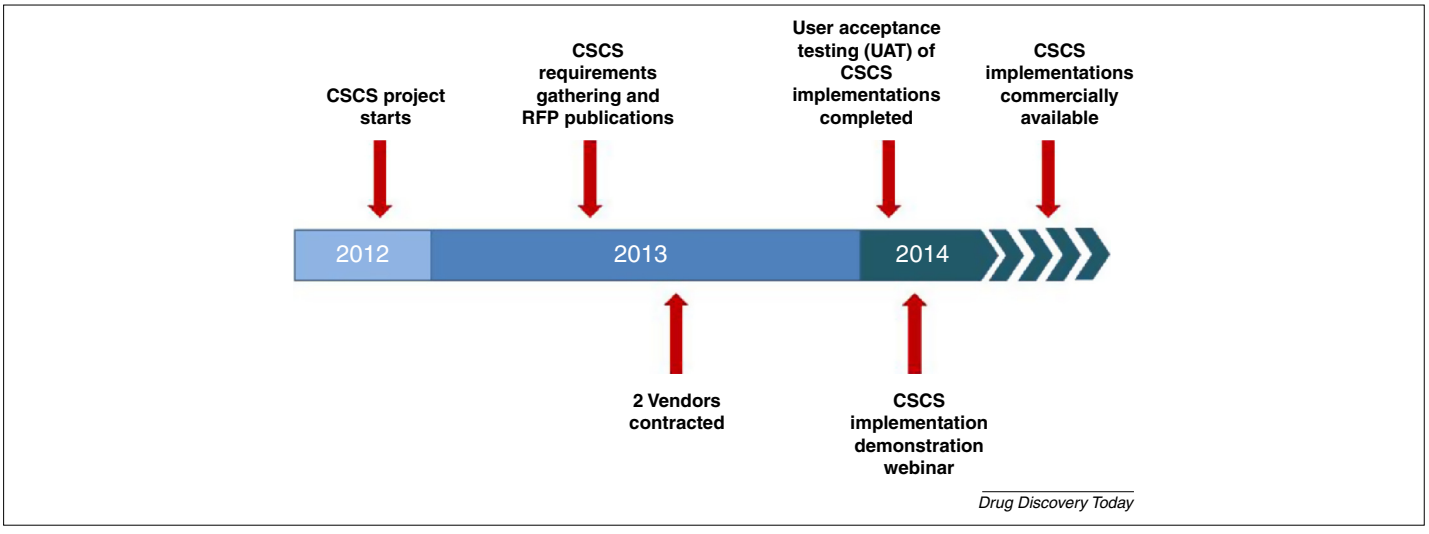



**FIGURE 1**

Project timeline showing key controlled substance compliance service (CSCS) project milestones. Abbreviation: RFP, request for proposal.

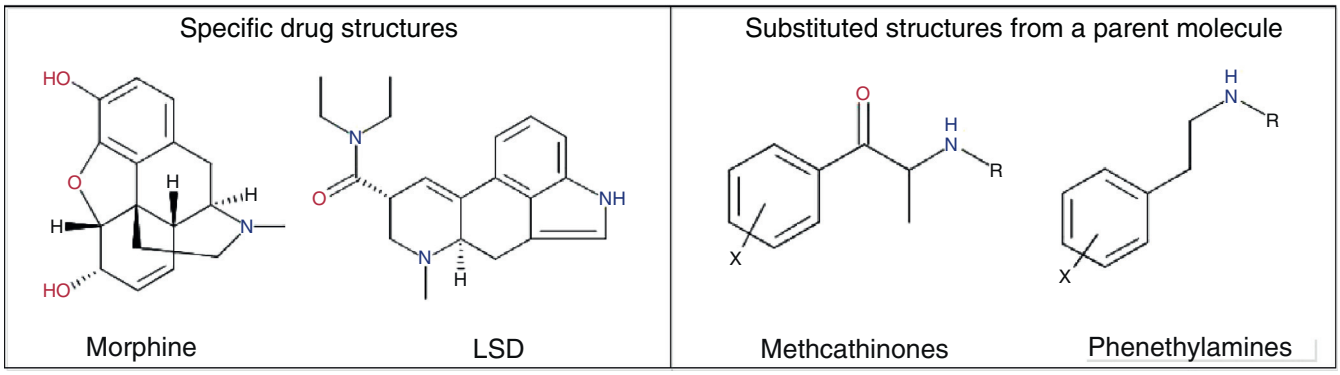



**FIGURE 2**

Examples of controlled substance structures.

and their precursors. Owing to the complexity of the legislation of controlled drugs, a compliance solution in this area would provide a strong foundation toward addressing subsequent legislation. Controlled drugs fall within regional, national and international legislation that regulates their whole lifecycle use including storage, handling, shipping and destruction or disposal. The legislation can apply controls to specific drugs such as morphine, cocaine, LSD and ecstasy but can also apply to a broad set of analogs or derivatives of a parent structure, for example methcathinones and phenethylamines (Fig. 2).

A key benefit of working in a cross-pharma project team under the umbrella of the Pistoia Alliance was building a shared understanding of the current compliance practices within each company, where their strengths lay and where the common 'pain points' were in terms of efforts to stay in compliance. It was also extremely valuable to discuss different approaches to legislative interpretation and how each company interacted with the regulatory bodies. Recognizing that there could be benefits to the international regulatory bodies from this shared and consistent approach, the Pistoia Alliance reached out to the International Narcotics Control Board (INCB) and the UK Home Office to obtain clarification on a number of queries that the project team had identified. The UK Home Office confirmed that parahexyl is controlled in the UK under Schedule 1 and the INCB provided guidance on the definition of 'isomers'. In general, the agencies were supportive of the approach and could see benefits in the tool. Indeed, one regulatory agency contacted the Pistoia Alliance for comments in advance of new drug legislation concerning NBOMe (variant of phenethylamine) and benzofuryl analogs, which were being offered for sale as legal highs (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261786/NBOMe_compounds_report.pdf).

Discussions revealed a desired future state encompassing either a database or an expert system as the basis of the solution. Initially there was a strong preference toward a database-driven system of curated lists of controlled molecular structures. As discussions progressed and the IPT started to understand the breadth and complexity of controlled substance legislation, it became clear that a database approach would not provide a satisfactory solution.

A key user requirement was the capacity to screen many millions of chemical structures efficiently against the controlled chemical legislation. There was a realization that comprehensive enumeration of the broad structural families covered in legislation would be prohibitive. For example, there are theoretically an infinite number of phenethylamine analogs, because alkyl and acyl side-chain length is not limited. Discussions moved toward expert systems that could apply chemoinformatics searching against Markush-like rules, asking questions of the datasets rather than comparing exact structures against database lists.

Detailed market research revealed no off-the-shelf solutions that met the intended scope of legislative coverage, although AstraZeneca did have an internal tool that had been adapted for controlled substance searching [11]. AstraZeneca shared this tool with the team, which provided an understanding of how the searches worked as well as a vision of what could be achieved. A limitation AstraZeneca had identified was the ongoing maintenance of their system, given the specialized nature of identification, interpretation and keeping up-to-date with relevant controlled substance legislation. This opened discussions on the expertise required of a potential vendor (e.g. software development, cheminformatics knowledge and chemically aware legal capability). Through these very open discussions between project members, a clear and shared future state was described.

## Future state

Use cases were developed, then prioritized using the MoSCoW (must, should, could, will not) methodology and a detailed set of functional and nonfunctional requirements were agreed and documented. These requirements enabled the compilation of a request for proposal (RFP). Because of time constraints, it was initially decided to split the project into a number of phases. The key deliverables of the first phase of the CSCS project were identified as a Legislation Notification Service, a Legislation Knowledgebase and an Expert System. The Legislation Notification Service would send out details of new, updated and clarified legislation to the service customers. The Legislation Knowledgebase covering North America and Europe would include interpretation of the legislation and detailed guidance information for impacted substances. The Expert System would determine whether a substance was controlled or not using a set of rules and structures derived from the legislation. To ensure the security of a customer's internal compound collection, the CSCS system architecture would need to support implementation inside the customer's firewall and would need to interface to the customer's internal chemistry systems.

## Request for proposal

The RFP was advertised on the Pistoia Alliance and the RSC Chemistry Weekly websites, and the

project team members ensured that their individual qualified technology company contacts were made aware of this document. The aim was to select up to three competing vendors, each producing their own software solution, with the rationale that this: (i) allowed customers some choice in selecting the product that met their particular needs; (ii) would keep costs competitive; and (iii) would mitigate the risk that a single vendor could fail to satisfy the project requirements. In total, 41 companies responded to an invitation to a webinar where the project was outlined and the RFP explained. It transpired that companies required a mixed skill set to implement this project: experience in the creation of chemical databases and retrieval applications as well as expertise in the interpretation of the different controlled substance legislations.

Shortlisted vendors were then invited to present their proposed solutions to the project team. These presentations were assessed against pre-defined criteria and three preferred vendors were selected to progress to contract negotiations. It was noted at this stage that, although vendors presented individual proposals, a number of those proposals represented vendor partnerships where individual vendors had some, but not all, of the expertise to deliver the solution.

## System build

Following the final selection of the two successful proposals, one by ChemAxon and Patcore with their Compliance Checker system and the other by Scitegrity with its $CS^2$ system, development was initiated. This phase of the project revealed the strength of the Pistoia Alliance shared-risk funding model. The vendors effectively became fully integrated project members. Regular feedback meetings were held as a whole group, facilitating open discussions to enable vendors to understand precisely the customer requirements. Vendors were also able to reflect back to the project team the options and challenges they were facing in building the systems, allowing the most appropriate solutions to be progressed at a greater pace.

## Testing and evaluation

Data quality and predictive accuracy were the critical quality factors required by the pharma team members for any CSCS solution. For this reason the team focused on compiling a test dataset of over 400 structures to assess the performance of the vendors' systems. The dataset contained controlled and non-controlled structures across a range of chemical classes and legislative schedules, and was provided to the vendors in the SD and SMILES chemistry data file formats. In addition to well recognized controlled substances, the dataset also included substances close to the boundaries of what would be considered controlled or not controlled, including examples that were known to be contentious.

We chose to build the test dataset from a subset of the phase 1 countries, which were of most importance to the project team members. Combining datasets from different countries to create a comprehensive dataset was challenging. The different legislative approaches of each test country resulted in significant differences in the controlled status of the individual test substances, across the test countries (Fig. 3). As a result, a particularly difficult aspect of this task was reaching agreement on whether or not specific examples in the dataset were controlled. A challenging example was the interpretation of the US Controlled Substance Act Schedule III for derivatives of barbituric acid; did the US DEA mean 5,5-disubstituted derivatives (as per the UK regulations) or should 5,5-disubstituted barbiturates only be flagged as US controlled substances if they appear on the official lists (Table 1)? It was noted that the majority of the challenges faced by the vendors were not IT related but rather the interpretation of legislation. The Pistoia Alliance network has been working actively to open lines of communication to legislative bodies to help clarify more ambiguous interpretations.

As part of the shared-risk funding model, the phased release of funding was triggered on reaching pre-agreed milestones and evaluation of system performance against pre-defined datasets. These test datasets were challenging, they contained chemicals that fell close to and across the borderlines of legislative criteria, demanding highly refined computational tools to find the correct answer. In addition to the test datasets, user acceptance testing was carried out on the systems according to the criteria documented within the use cases developed earlier in the project. Again, this provided open and honest feedback on the suitability and usability of the systems, allowing vendors to refine their tools further. The vendors then applied their systems to identify the controlled status of chemical structures with reference to legislation from the USA, UK, Switzerland, France, Sweden and Canada. In each of these countries a different approach has been taken to define controlled substances, but companies' expert systems were able to classify these test structures with high accuracy. Final

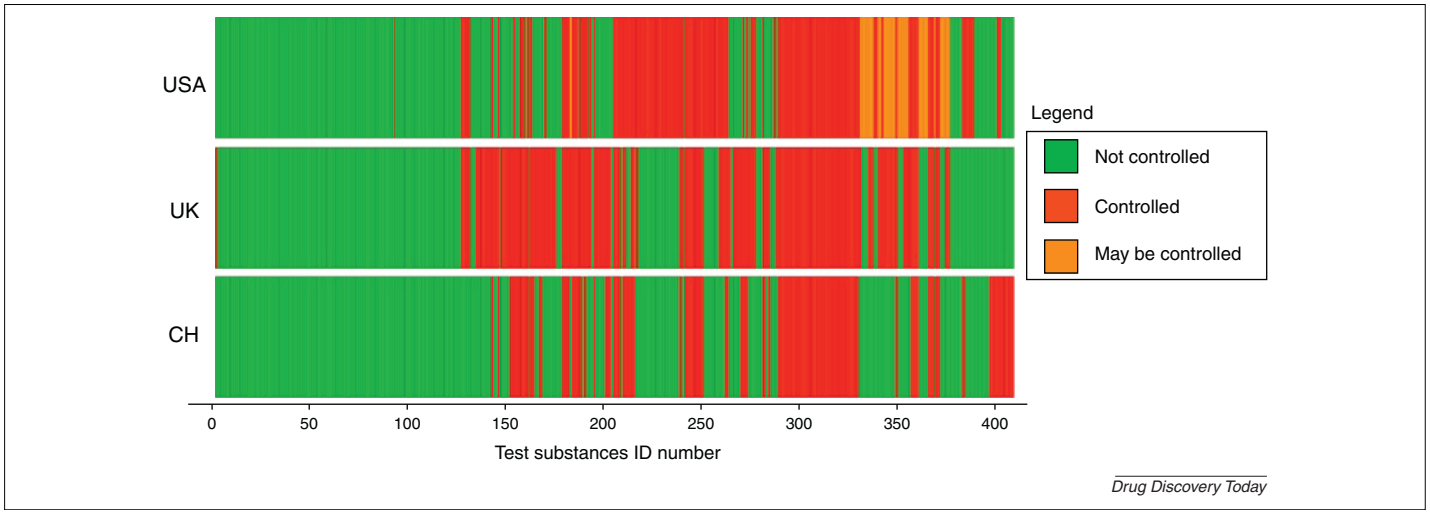
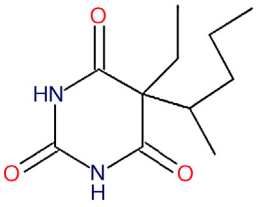
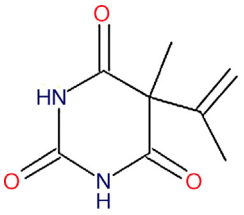
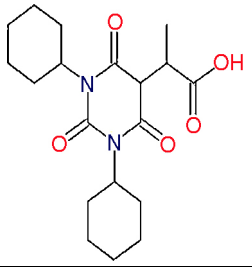



**FIGURE 3**

Test dataset substance controlled status in the USA, UK and Switzerland (CH).

**TABLE 1**

**Examples of controlled status of barbituric acids in the USA, UK and Switzerland**

| Substance | | USA | UK | Switzerland |
|---|---|---|---|---|
| **Pentobarbital** |  | US Controlled Substance Act Schedule II | Misuse of Drugs Act Schedule 3 | Swiss Controlled Substances Act (BetmVV-EDI) Narcotics List B |
| **5-Methyl-5-(1-methylethenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione** |  | Can be controlled | Misuse of Drugs Act Schedule 3 Markush Any 5,5 disubstituted barbituric acid | Not controlled |
| **Hexahydro-1,3-dicyclohexyl-alpha-methyl-2,4,6-trioxo-5-pyrimidineacetic acid** |  | Can be controlled | Not controlled | Not controlled |

results were in excess of 99% accuracy for both vendors. The 1% disagreement related mainly to differences in interpretation of the legislation, where the vendors took a conservative approach and flagged substances as controlled. Throughout vendor system development, the Pistoia Alliance project team provided continuous feedback, support, direction and advice to the vendors.

## System demonstration and commercialization

The final versions of both systems were demonstrated via webinar to a broad group of potential users, including major pharmaceutical and technology companies. The Pistoia Alliance promotes customer choice and both systems are now commercially available for potential customers to evaluate against their own internal criteria.

Compliance Checker is a software system and content package developed by Patcore and ChemAxon. Based on ChemAxon's JChem technology for structure entry and representation (a well trusted industry-leading cheminformatics platform for over 16 years), Compliance Checker allows users to perform controlled substance checks by either chemical structures (through the drawing functionalities of Marvin) or by text, CAS numbers, SMILES strings, IUPAC names or even by common names. Checks can be performed with either individual structures (inputted via Marvin) or as a large set of structures stored in SD or text files. Compliance Checker has a variety of interfaces for different user types and can be integrated with workflow tools like KNIME and Pipeline Pilot, ELN, registration or reagent management systems via web service access or command line. Compliance Checker is available as a web- or client-based system for bench access with Microsoft Office (Excel, Word), HTML and PDF output and its deployment is straightforward [12]. Compliance Checker relies on an up-to-date and extensive knowledgebase made up of relevant published legislations covering most of the North American, European and Asian countries. The software and legislation databases are created and maintained by Patcore in close collaboration with ChemAxon.

The Scitegrity Controlled Substances Squared ($CS^2$) system is a completely new system built specifically to the Pistoia CSCS requirements using tried and trusted, industry-leading core software from Biovia (formerly Accelrys), namely Pipeline Pilot and the Accelrys Direct chemistry cartridge for Oracle. These Biovia products are well known in the pharmaceutical industry and are proven to have the ability to be integrated quickly and efficiently into a company's existing IT infrastructure. This means that $CS^2$ can be called at many levels within an organization, ranging from an intuitive web browser front end, through API integration with existing applications such as electronic laboratory notebooks, materials management tools and chemistry synthesis design tools, to the storage of controlled status of complete corporate collections for almost instantaneous retrieval. All controlled substance hits are accompanied with a wealth of supporting material concerning the underlying legislation with, additionally, the ability for the customer to add their own company-specific guidance.

## Concluding remarks

This project has demonstrated the benefits of precompetitive, cross-company collaboration. Shared knowledge and expertise, open discussion and joint funding led to a faster and more-comprehensive set of requirements. Importantly, technology supplier involvement in the project at the earliest opportunity made for a dialog and ensured a good two-way understanding of business needs and technology feasibility, and easier implementation of the software solutions.

The project team has also formed a close bond through trust built up over many months. The positive experience has been relayed back into each pharmaceutical company, making it easier in the future to pursue further cross-company

precompetitive activities. As externalization and intercompany collaboration continue to gather pace, the notion of exchanging or sharing compound libraries is becoming a reality. Use of a common controlled substance compliance system will help to ensure a common process in identification of such compounds, thus avoiding potential future problems.

This phase of the CSCS project focused on the legislative regions that were of most importance to the project team. But, given the growing externalization and outsourcing within the pharmaceutical industry, legislation from other countries including China and India needs to be included in future releases. Following discussions with the project team, it was agreed that the choice of extra legislative regions was a commercial decision to be made by a vendor based on the requirements of their customers.

The legislative environment is constantly changing, new pieces of legislation are brought into force and existing legislation can be updated or clarified. It takes significant amounts of time and expertise to monitor and interpret the legislation. The key benefit of the legislation notification service is that it will free-up the individual CSCS customers from the time and effort of monitoring their legislative areas of interest. A vendor would provide this service to all their customers.

Although the project team is confident in the implementation of the chemoinformatics and the technology supplied by the vendors, it is limited by the interpretation of the legislation to generate the rules utilized by these expert systems. The regulatory authorities can sometimes appear reluctant to provide guidance on specific areas of their legislation. The team found value in bringing together experts from across the world to review the sometimes ambiguous and often difficult-to-interpret legislation. The Pistoia Alliance believes that there would be real benefit in providing a harmonized analysis and interpretation from a group of industry experts. The CSCS project now aims to create an industry-leading, CSCS expert community (http://www.cscs-experts.org). Such an organization would provide support to continue the work of this group of experts while improving the understanding and interpretation of controlled substance legislation from around the world. The project team believes that there are real benefits to be derived from standardized legislative interpretation.

## Conflict of interest

Funding for the CSCS project was provided by AstraZeneca, GlaxoSmithKline, Merck, Novartis and Roche.

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