Toward Progressive Reporting of Modeling and Simulation Results – Part 1: Analysis of KIWI™ Metadata

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TH Grasela, S Bihorel, C Walawander, J Fiedler-Kelly, D Fox, A Rokitka

Cognigen Corporation, a subsidiary of Simulations Plus, Inc.; Buffalo, NY

cognigencorp.com

INTRODUCTION

Technical reports for pharmacometric modeling provide comprehensive documentation, typically including data assembly methods and disposition, modeling strategy, and analysis results. These reports, however, are costly and time consuming and do not necessarily serve the dynamic research and development lifecycle which requires an ongoing accretion of data from Phase 1, 2, and 3 trials. Cognigen implemented KIWI™ in 2011, a secure internet-based service providing high throughput NONMEM® processing. KIWI is the basis for a progressive reporting process that facilitates the capture of critical information during model development; enables team access to evolving, interim results; and facilitates rapid assembly of technical reports.

OBJECTIVE

Perform an analysis of KIWI metadata to assess system performance and evaluate its use in facilitating progressive reporting.

METHODS

KIWI

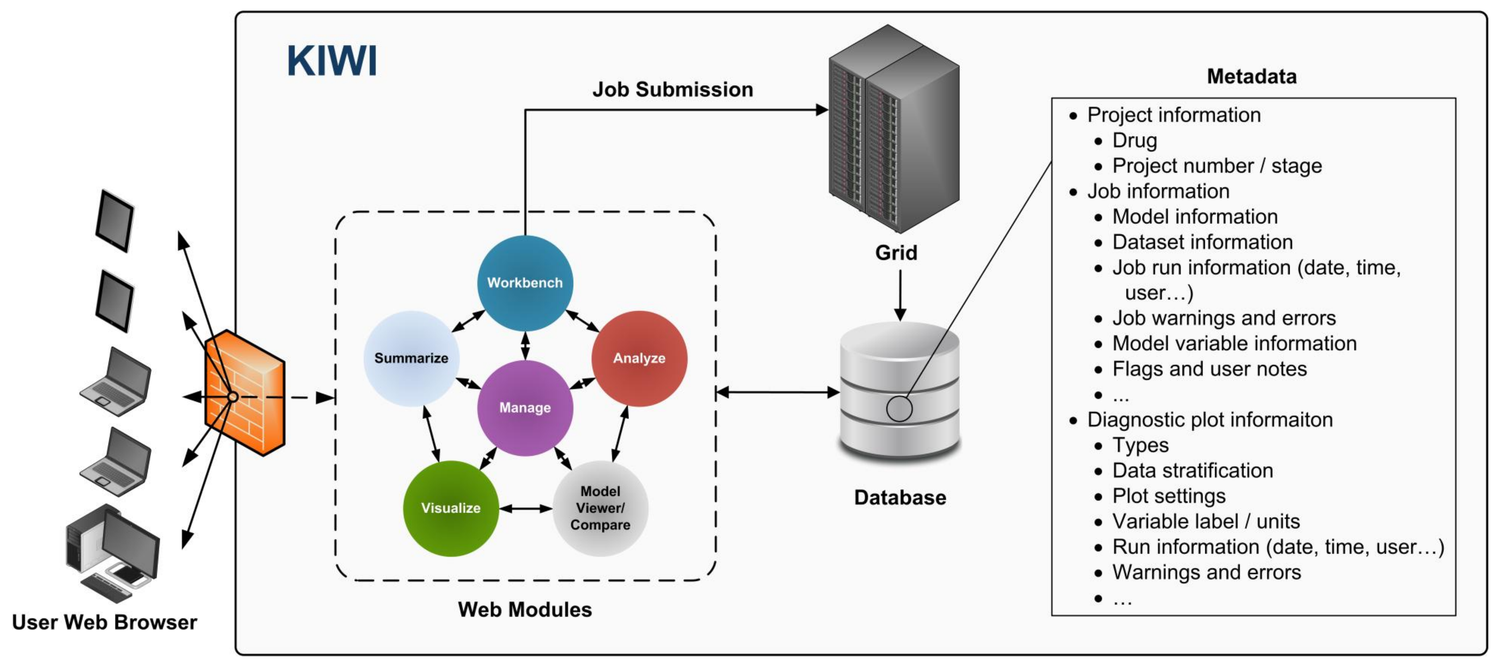
KIWI is a private, cloud-based platform to efficiently and consistently organize, process, evaluate, and communicate modeling and simulation results.[1] KIWI relies on a validated hardware and software infrastructure which allows:

- user interactions through a simple web browser,
- NONMEM[2] and Perl-speaks-NONMEM (PsN)[3] job submission to a dedicated Linux-based computing grid,
- storage of run information,
- post processing of run results with creation of customizable summary statistic tables,
- creation of diagnostic plots,
- comparison of parameter estimates, control stream code, and diagnostic plots to facilitate model discrimination and quality assurance checking,
- annotation of run results with electronic notes and flags, and
- export of validated tabular and graphical reports.

Metadata

The informatic infrastructure described above supports the collection of metadata which is stored using a relational database management system, broadly grouped into categories of project management and run-specific information. Metadata include, among others, the information shown in Figure 1.

Figure 1. KIWI Work Flow



Metadata can also be provided in the form of flags attached to the runs. Flags can be created by users to mark important runs, include runs in the critical modeling path, categorize runs, or simply annotate them (Figure 2). KIWI can also automatically generate connection flags which denote the use of specific runs for activities such as performing a visual predictive check or the creation of diagnostic plots.

Figure 2. A Selection of KIWI Flags

Critical path run	Final model	Good code example
Diagnotic plot created for this run	Final base model	User-commented flag
Run linked to another run (eg, VPC)	Key run	User-commented flag

Metadata Processing

Extraction and transformation of the metadata from the database was achieved using standard tools of the Business Intelligence / Business Analytic industry. The SQL language was the primary method of data retrieval.[4] Shell scripting was also used to extract data from system web logs. The R language was used to compute statistics and to summarize data in tabular and graphical forms.[5]

The entire KIWI database was considered for this analysis with the exception of projects used for testing or projects associated with a very small number of runs, resulting in the use of more than 90% of the database. Duration of analysis subsets were based upon the dates and times at which runs were loaded and does not take into account activities performed outside KIWI, for example, data assembly.

RESULTS

Generally, the results of the pre-clinical and clinical trials involved in typical research and development drug programs become available in sequence. Consequently, modeling and simulation analyses are typically conducted in separated efforts as the study data become available. The interval between analyses ranges from several months to several years depending on the duration and progress of the programs. Facilitating the consistent capture and retrieval of important decision steps taken during each analysis project or project stage is critical for successful model development across the duration of the program. Analysis projects are defined hereafter as a modeling effort based on a specific set of data collected in 1 or more studies and involving the development of 1 or more models. Analysis projects can be divided into stages representing the development of a particular model (for example, for a pharmacokinetic (PK) endpoint, an efficacy endpoint, or safety endpoint) using a particular subset of the data (for example, preliminary, soft-lock data, or hard-lock data).

From the point of view of program management, efficiency can also be gained by allocating proper resources to new projects based upon the analysis of previous project characteristics.

Metadata Analysis

Simple database queries can provide the distribution of project-related metadata metrics (Table 1).

Table 1. Distribution of Project-Related Metrics (N = 33 Projects)

Metrics	Median	5th Percentile	95th Percentile	Total Analyzed
Number of projects per program	1	1	4.4	33
Number of stages per project	2	1	10	60
Duration of program (days)	315.4	6.6	967.0	33
Duration of project (days)	124.6	3.7	685.7	60
Duration of pharmacokinetic stage (days)	66.2	0.2	506.8	129
Duration of pharmacodynamic stage (days)	17.4	0.1	230.9	36
Number of modelers per project	2	1	7.1	60
Number of runs included in the critical path per project	28.5	8.3	54.0	8
Percentage of runs included in the critical path out of all runs submitted per project	2.20	0.55	3.39	8

Metadata information can be crossed to evaluate correlations between metrics. For instance, the distribution of the individual run duration can be determined by the category of model defined by the type of ADVAN routine used in $PK or the use of $PRED in NONMEM (Table 2).

Table 2. Distribution of Individual Run Duration (h) by Model Type

Model Type	Median	5th Percentile	95th Percentile	Number of Runs
PRED	0.22	0.02	2.27	5096
ADVAN 1/2	1.52	0.18	8.83	3591
ADVAN 3/4	5.62	0.12	24.61	4578
ADVAN 11/12	5.74	0.27	519.21	1942
ADVAN 5/7	5.67	1.70	72.37	496
ADVAN 6/8/9/13	74.98	0.18	3578.29	13824

Table 2 shows that, across projects, the median run time of 1-compartment PK models (ADVAN 1/2) is 3.7-times lower than the median run time of 2-compartment PK models (ADVAN 3/4), while more complex models based upon ordinary differential equations (ADVAN 6/8/9/13) generally require approximately 3 days per run.

Project and project stage metrics can be explored as a function of resources allocated to them (Figure 3).

Figure 3. Exploration of Project and Project Stage Metrics

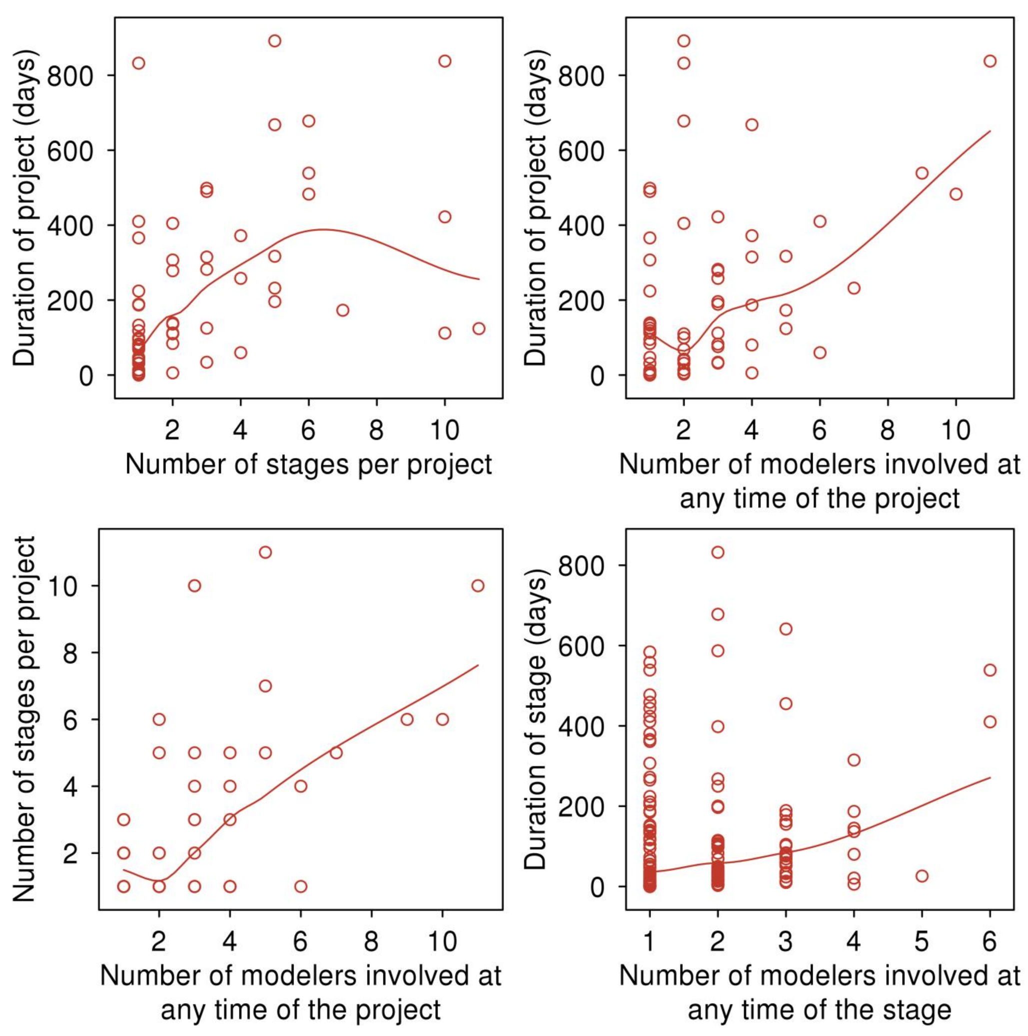


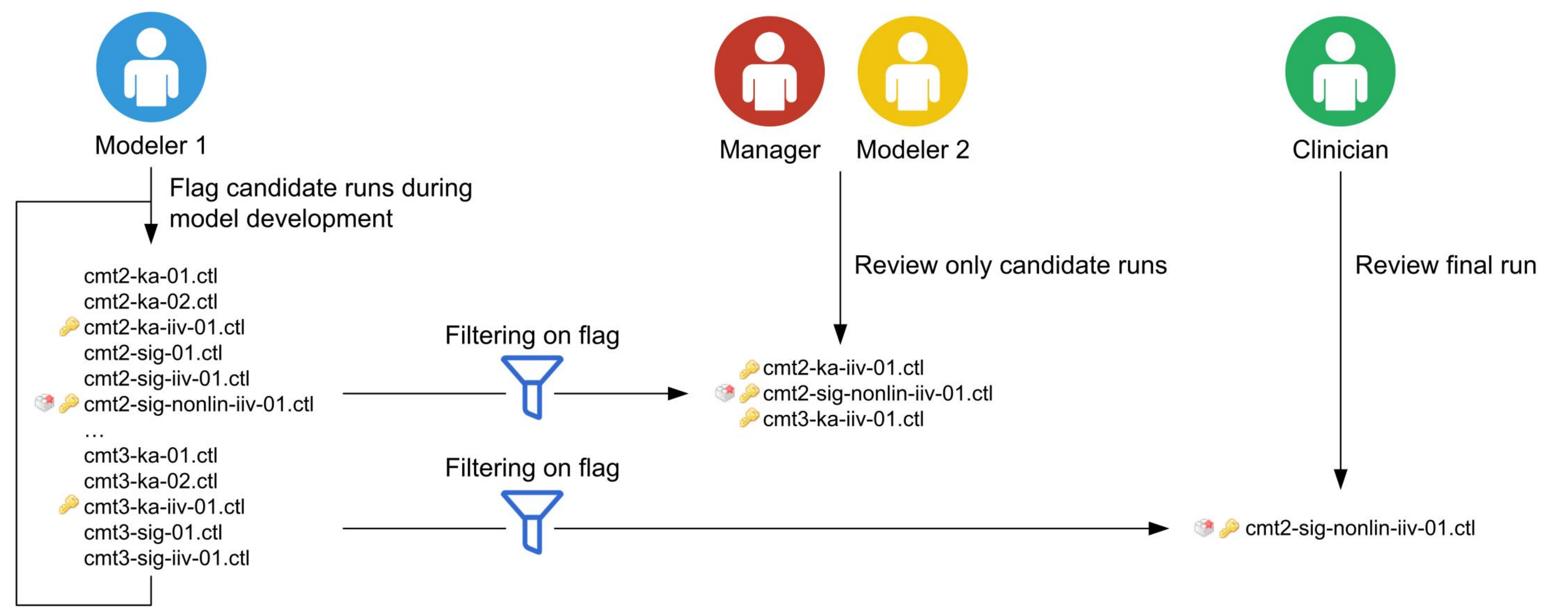
Figure 3 shows that the:

- duration of projects increases with the number of stages,
- duration of modeling projects typically decreases when 2 modelers are assigned to them instead of 1,
- duration of modeling projects increases when more than 2 modelers are assigned to projects (note that this number includes the number of modelers ever involved with the project, not necessarily the number of modelers working concurrently on the project),
- number of stages per project positively correlates with the number of modelers per project, most likely explaining the trend reported in the previous point, and
- duration of stages generally appears to increase with the number of modelers per stage, suggesting either that assigning more resources to a modeling stage is detrimental to the completion of this stage or that more resources are assigned to particularly long and complex analysis stages.

Metadata Use for Progressive Reporting

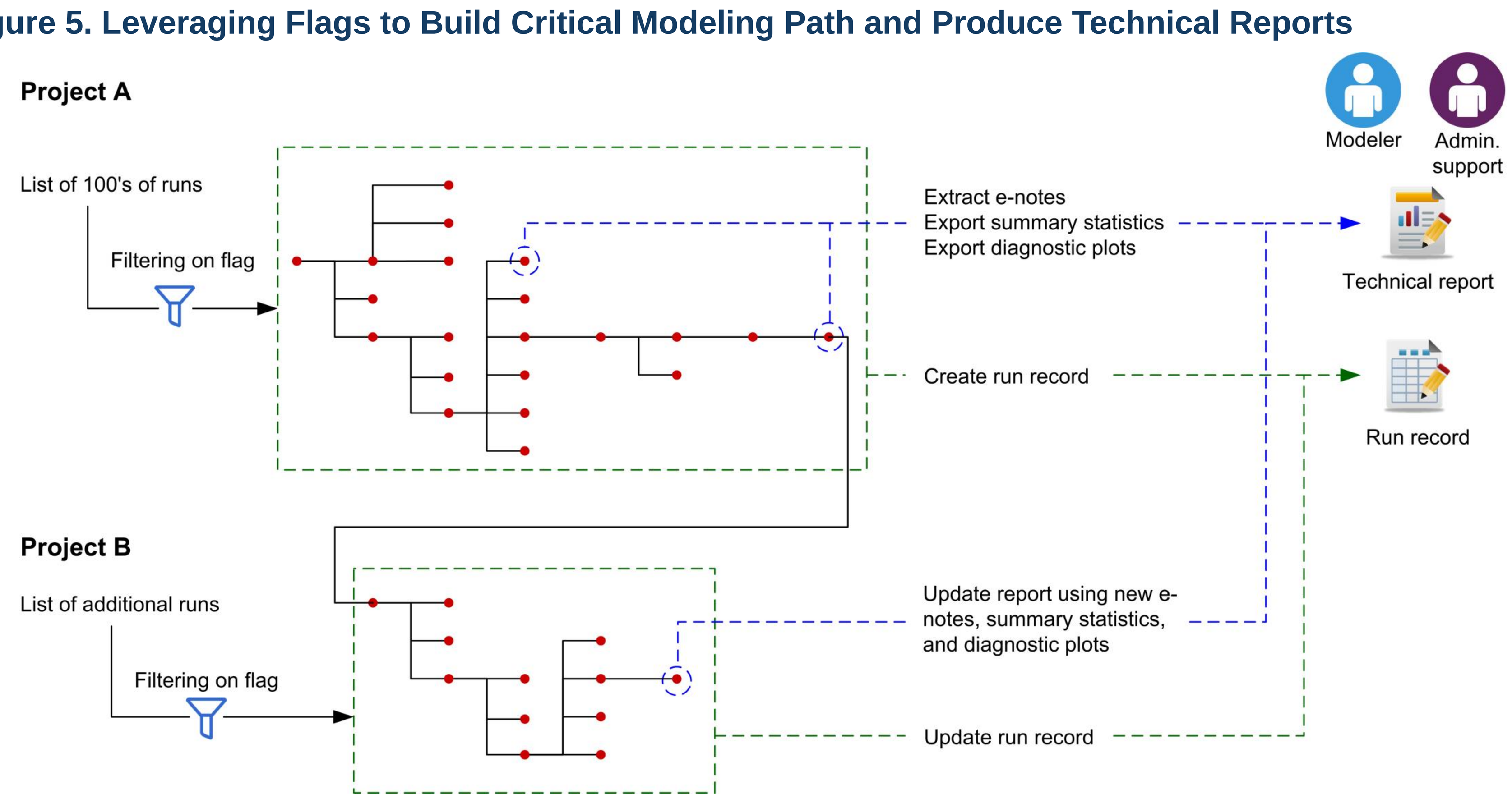
Metadata can help progressive reporting and scientific review while a project is ongoing (Figure 4).

Figure 4. Collaborative Scientific Review During Model Development



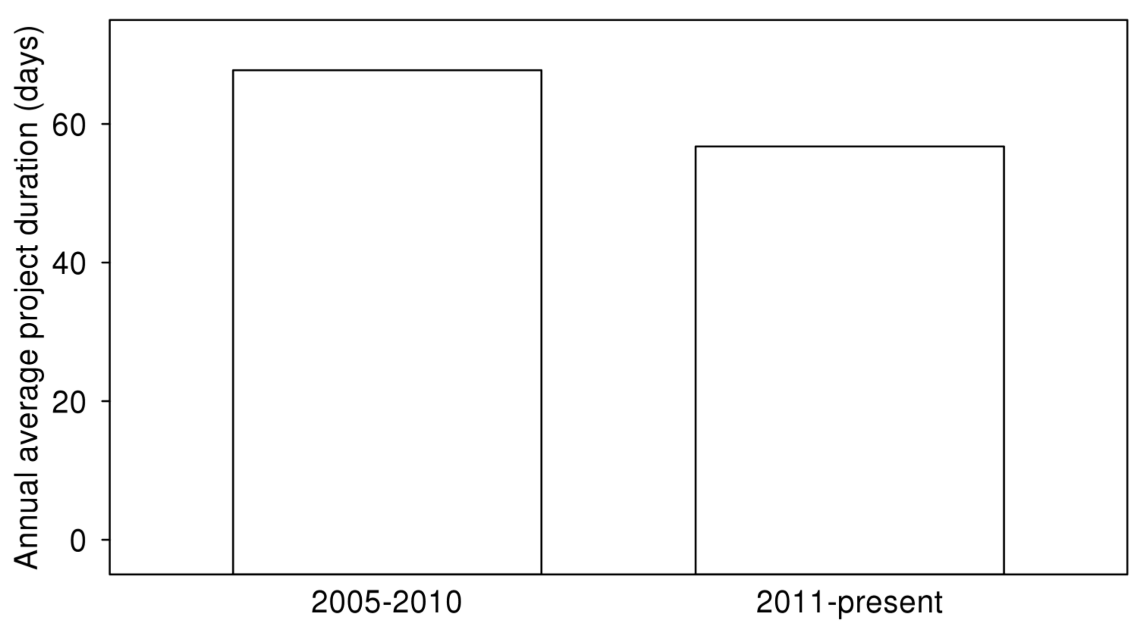
KIWI metadata also supports the creation of the critical modeling path and facilitates the creation of technical reports and run records when a project is complete (top portion of Figure 5). When a project expands on modeling results obtained in a previous project, metadata combined with the systematic organization implemented in KIWI will help users retrieve this prior information and link it to the new modeling results (bottom portion of Figure 5).

Figure 5. Leveraging Flags to Build Critical Modeling Path and Produce Technical Reports



The automated export of graphs and pre-formatted, report-quality tables of results from KIWI can save upwards of 2 hours per run. A retrospective analysis of project information shows a **16% reduction in project duration** since KIWI was introduced in 2011 to support these modeling projects (Figure 6).

Figure 6. Average Project Duration



CONCLUSIONS

KIWI provides ready access to analysis metadata that can be used to monitor system requirements and analysis status, as well as forecast resource needs for subsequent modeling efforts. Ongoing efforts are directed at leveraging metadata and run connections to automate progressive reporting and further facilitate the preparation of technical reports.

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For additional information, please contact
Cindy Walawander
Cognigen Corporation, a subsidiary of Simulations Plus, Inc.
1780 Wehrle Drive, Suite 110, Buffalo, NY 14221 USA
+1-716-633-3463, ext. 229 or cindy.walawander@cognigencorp.com