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Visualisation & Management of First Time in Human Safety data.

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ABSTRACT

This paper presents iNCAS; a technical solution for the interactive presentation of key information upon which further compound development and first time in human dosing decisions can be made.

INTRODUCTION

An important milestone in the drug development process is the first time a drug is administered to a human subject. Before moving to this stage, it is essential that relevant pre-clinical information is utilised in order to identify safe doses for the human subjects and that that data be presented to the safety board or committee in a consistent and readily understandable format. In order to aid the decision making process regarding dose levels, or even a go/no-go decision about further trials, a number of information sources can be investigated. These must include:

- Pre-clinical (animal subject) data
- Toxicology findings
- Establishment of No Observed Adverse Effect (NOAEL) and Adverse Effect Levels (AEL)
- Predicted human exposure

THE BUSINESS DRIVERS

Mango worked closely with GSK in order to design an application and visual display for the presentation of information on which first time in human dosing decisions could be made.

The issues that needed to be addressed were:

- Different project teams and individuals presenting their findings to the safety board in their own “styles”, leading to a lack of consistency in presentation and interpretation.
- Data for presentations had to be drawn from many different sources.
- Geographically distributed project teams had no common data repository, so time and effort was being taken in sending data, files, slides, back and forth to build up more complete pictures.
- Presentations graphics were taking a long time to produce, and invariably resulted in major difficulties in getting all the graphical objects to scale appropriately
- Trying to represent predicted human exposures on the same graphic(s) as preclinical was difficult due to lack or correlation points.
- Representation of receptor occupancy and bio-marker data on the same graph as AUC or Cmax exposures was difficult to produce and scale.
- Logarithmic scales are extremely difficult to represent accurately in (say) PowerPoint.

Additionally, opportunities were discussed to facilitate further functions to enhance knowledge about compound development over time. These included:

- Ability to add actual/observed human exposures once the data became available, allowing differences between predicted and observed to be readily viewable.
- This would likewise provide feedback on the relevance / closeness of fit of the observed human observations when compared to animal studies for the same compound.

- The same data can also be used to compare class effects of different compounds. This allows apples-to-apples comparison of the relative efficacies and safety of different compounds of the same class, on a number of different animal studies of the same type.

APPLICATION CONCEPTS

The application was to be web-based, thus providing access across the organisation via a humble web browser. This obviates the need for any application installation and maintenance on many individual users' workstations/laptops.

At the back-end, the iNCAS application comprises a structured database storage environment. Because there is the single data store, the problems of data proliferation, location and provenance are avoided.

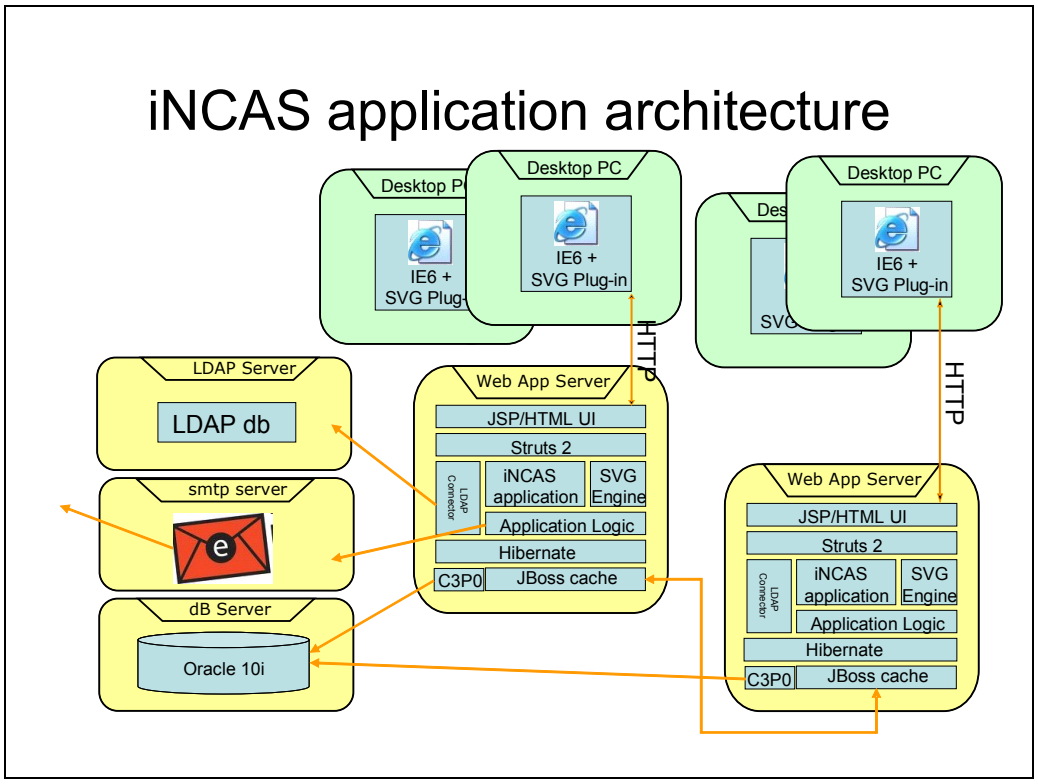
The middle tier of the application provides data entry, navigation and administration and manages all this information within the database system, allowing users to readily access the information via a web interface. Users then create advanced graphical reports to present the information. The application core is written in Java.

Naturally, the application provides audit-trails to comply with regulatory requirements.

TECHNICAL

The application consists of an underlying Oracle or MySQL database, using the Tomcat or WebSphere application server to provide functionality via a (JSP) web front end. The visualisations (graphs) themselves are provided using the SVG technology, allowing interactive analysis to the user. All data inputs, edits and decisions are tracked through the database providing a full audit trail of user actions.

APPLICATION ARCHITECTURE



iNCAS has been designed and developed as a multi-user, non-location-dependent application

which can be load-balanced across a number of application servers to provide a consistent application performance profile.

APPLICATION LAYERS

- Desktop / laptop running Internet Explorer + Adobe SVG plugin. All user activity and response is via the browser.
- Web application server: Currently IBM WebSphere and Apache Tomcat application servers can be used as the application hosting environment.
- Web content is formatted and generated by the JSP layer prior to sending back to the browser.
- The Struts2 layer handles any incoming requests from the browser, mapping the url to an action or servlet within the application.
- The iNCAS application contains the code to process the users' requests, calling the application layer logic for any rules processing and returning results back to Struts. Upon certain events, emails are sent out from the application to certain configured users. The application calls en external smtp service to perform the send.
- The SVG (Scalable Vector Graphics) engine is used to produce the graphical output displayed on the users' browser when requested.
- The LDAP connector is an API to call a remote LDAP server to perform login authorisation against a central/organisational user repository.
- The application logic contains the "business rules": Who may access what; what and how data objects are used.
- Hibernate provides a database abstraction layer and transaction management to maintain database integrity.
- C3P0 is a database connection pooling mechanism to allow rapid connection to the database in a multi-user environment
- The JBoss cache maintains certain portions of the database locally within the application server and so provides rapid access to the cached data. It also provides a means of keeping the caches synchronised across multiple application servers when data is changed.

APPLICATION USE

The iNCAS application can be simultaneously used by multiple project teams and multiple study teams – a project generally being related to a compound, and one or more studies on one or more species generally being a part of a project. The application manages the relationships between project teams, compounds and studies.

The project teams enter findings into the application as the project progresses. At any time, users can graphically display their results on the screen.

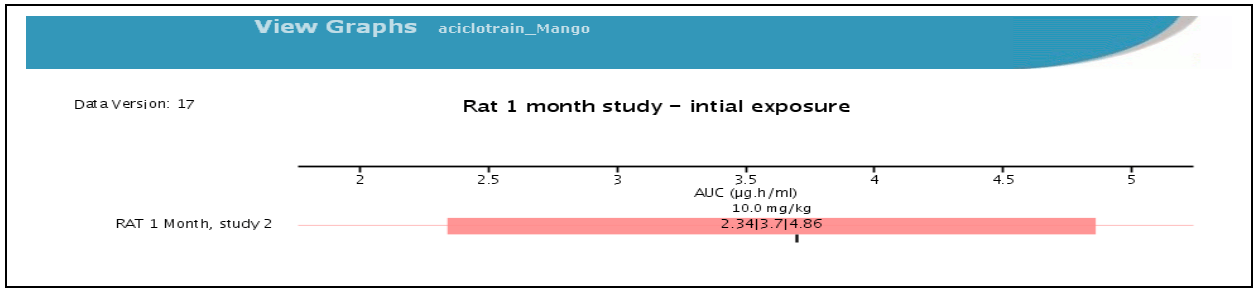
The data that are captured includes:

- Species
- Dose levels
- Measured exposure levels – usually as AUC or Cmax, though other measurements may be added
- Receptor Occupancy or biomarker levels
- Toxicological findings for each exposure level
- Overall exposure range within the study
- NOAEL and AEL values
- Most sensitive species: IE: Which species shows greatest sensitivity to the compound.
- Predicted (and observed) Human dose and exposure levels

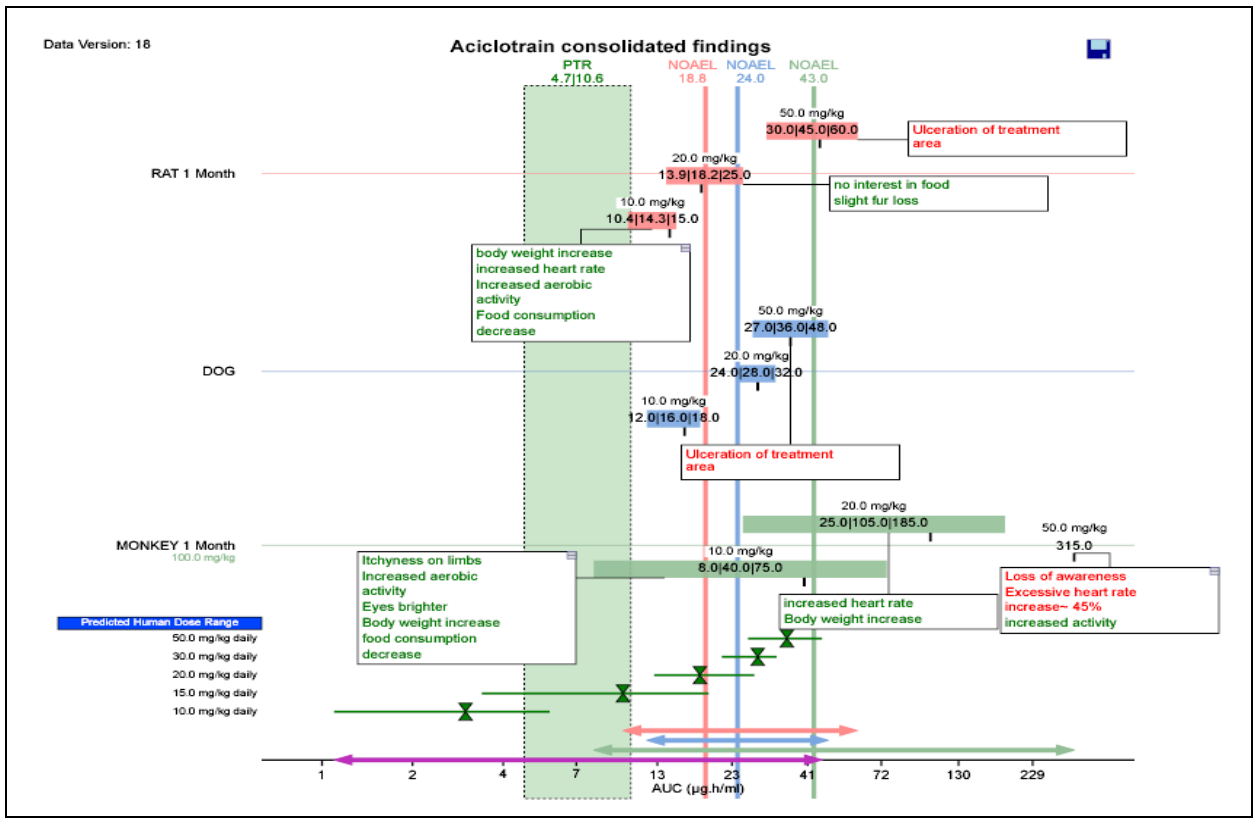
- Predicted (and observed) Therapeutic exposure ranges
- Predicted (and observed) overall human dose exposure ranges

GRAPHICAL PRESENTATION OF FINDINGS

Once data are entered, users can display those results graphically. At it's simplest, the bare minimum data required being a single preclinical or Human dose and corresponding exposure.



At the other end of the spectrum, the application can display multiple doses and exposures, from multiple studies, including toxicological findings; can display NOAEL values for each study along with predicted or observed human dose exposures, predicted or observed therapeutic ranges, and receptor occupancy or biomarker detail related to the measurement (usually AUC or Cmax).

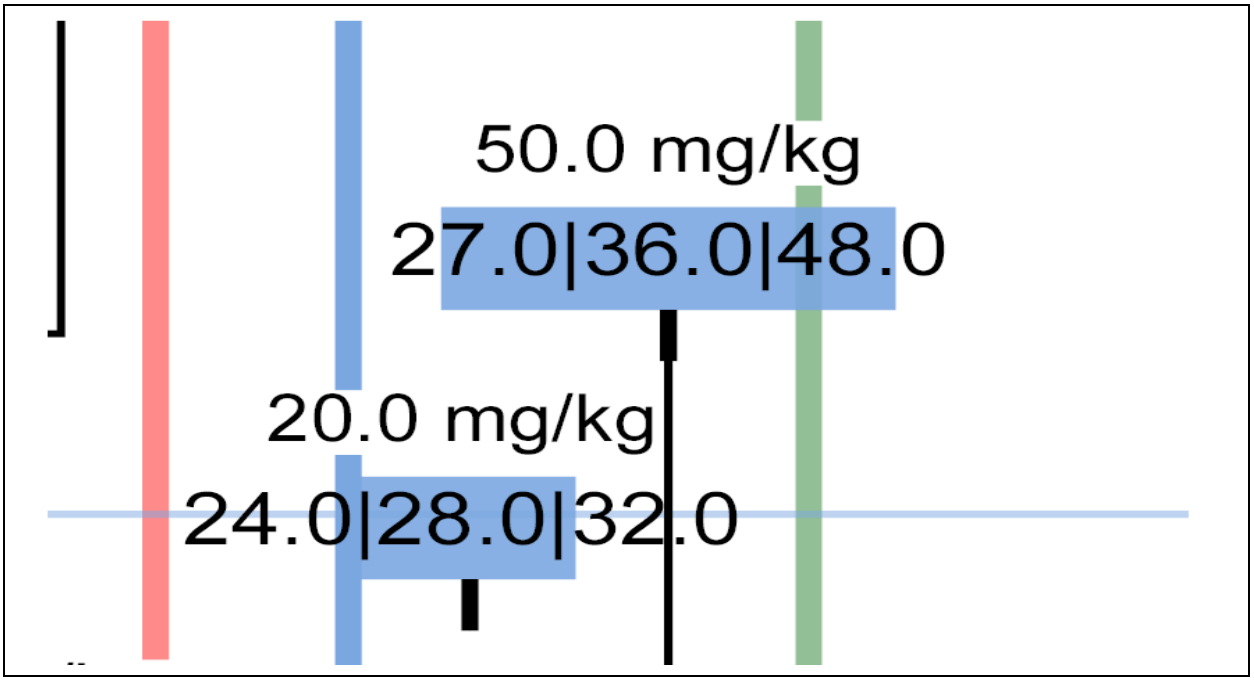


iNCAS provides colour coding to aid identification of different species, so all display objects of the same colour belong to the same species. Similarly, toxicological findings are colour-coded: Red for adverse findings, green for non-adverse findings.

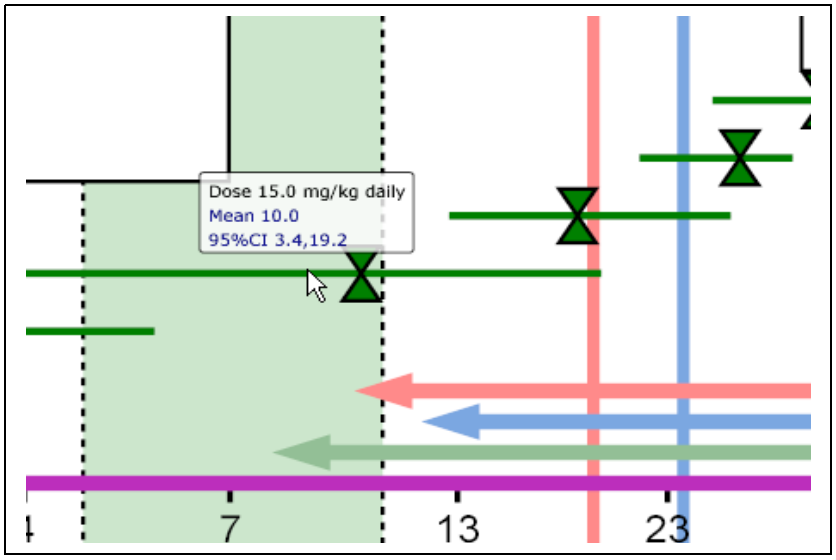
SVG FUNCTIONALITY

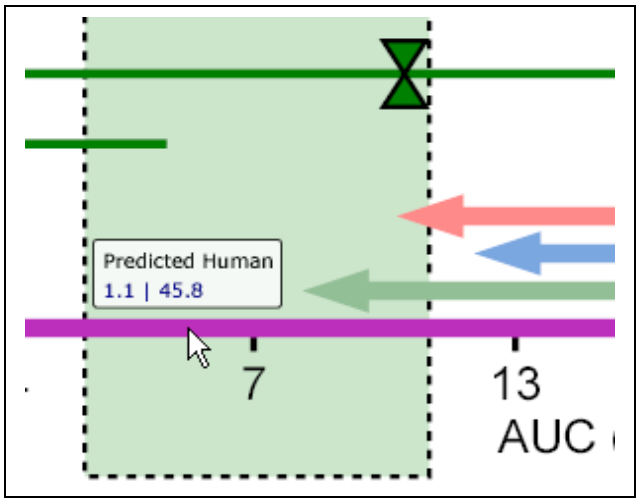
SVG provides a number of very useful features. For example – on a "busy" graph, the toxicology findings may not – by default - be positioned in the optimum location: A user has the ability to move the toxicology findings boxes by simply dragging them to a new location on the graph.

SVG also allows the user to zoom in, and to pan…



…and to use tooltip (mouse hover) features to display further information about the graph objects…

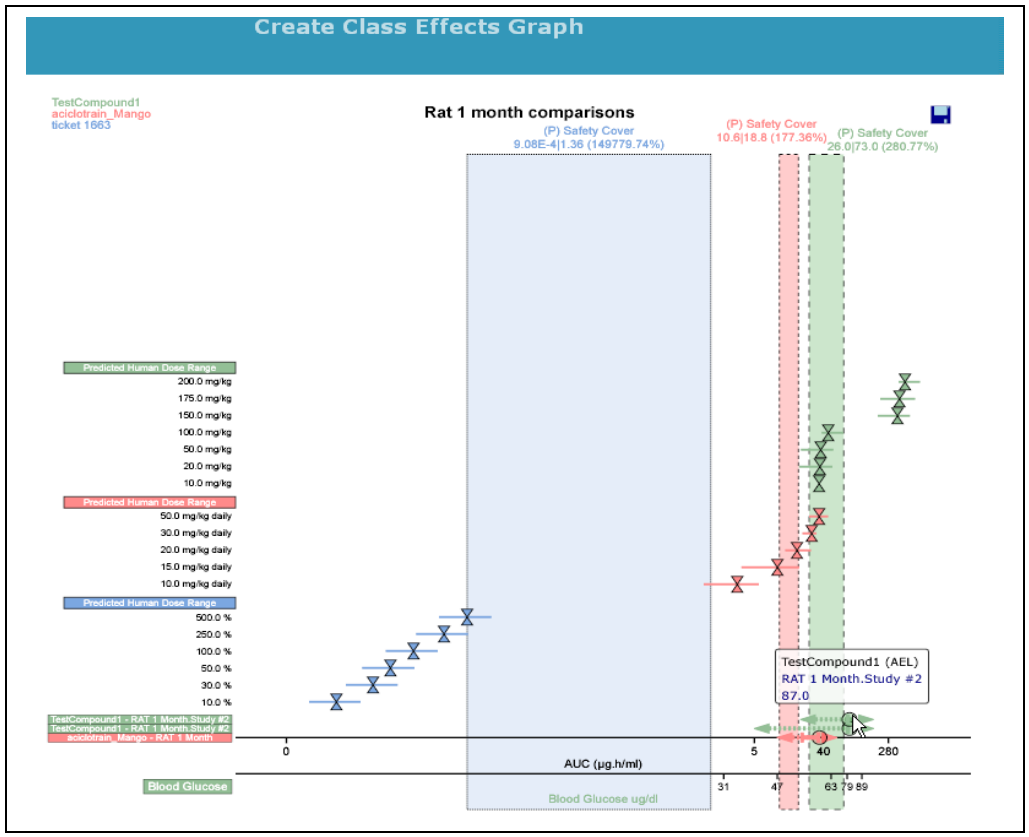




Because SVG uses vector, rather than bitmap graphics, there is no loss of quality when zooming in to areas of the graph.

CLASS EFFECTS GRAPH

This is another SVG graphic that allows the user to compare safety data for different compounds on a particular species and study type, allowing visual display of complex data from multiple compounds:



CONCLUSION

The SVG technology, together with the Java application and database architecture, has provided a vital tool that supports Safety Decision-making prior to first time in human trials. It may also help visually identify compounds that should not be developed and tested further, leading to earlier savings.

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