A Data Sharing Initiative on the Toxicity of Excipients

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Introduction

For optimal drug presentation, active pharmaceutical ingredients (APIs) are often combined with a complex system of excipients in the final dosage form. While these additional components are considered to be inactive, they are not always inert and may be associated with toxic effects.

Databases are an important tool through which to share data, thereby reducing the need for toxicity testing. A wealth of knowledge on the toxicity of vehicles is currently held in non-searchable archives. By saving this information in database format it could be more effectively searched and used, thereby preventing repetition of a number of toxicity studies. Reciprocal sharing of this data between organisations could further extend the usefulness of this information. Here we report on a data sharing initiative involving a consortium of 10 pharmaceutical companies who are contributing unpublished data on the toxicity of excipients.

Method

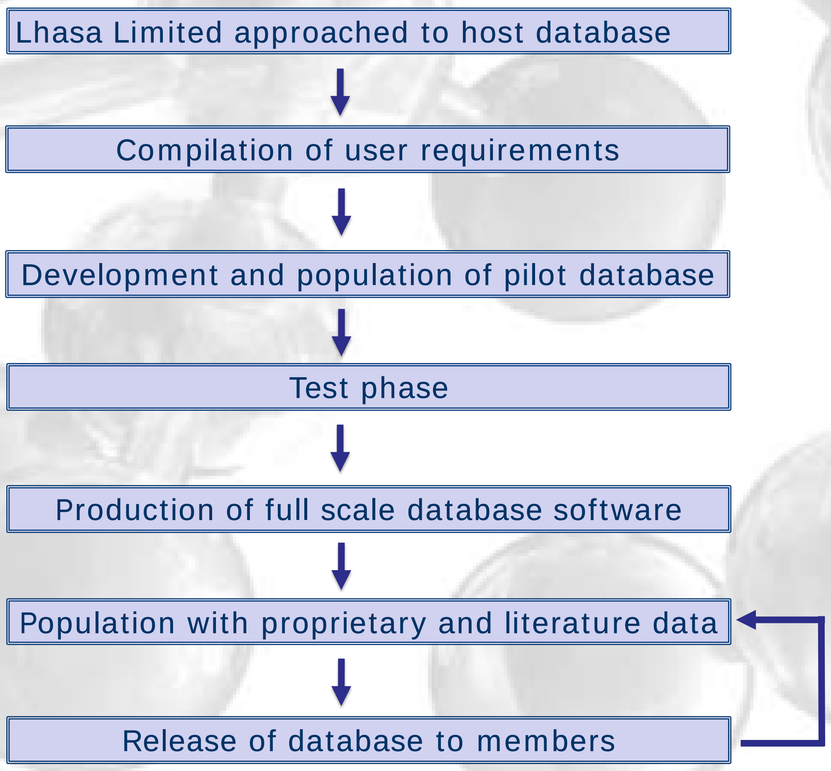

Figure 1. Flow chart showing the major milestones in the development of the Excipients database

The database initiative was set up by a consortium of 10 pharmaceutical companies, along with the charities FRAME (Fund for the Replacement of Animals in Medical Experiments) and the RSPCA (Royal Society for the Prevention of Cruelty to Animals).

The steering committee had a list of questions they required the database to answer, including:

- Has a specific component been tested in a specific species by a specific route?
- What is the maximum volume and maximum concentration that a component or combination of components has been tolerated at?
- Which components have evoked convulsions in rats?
- Has liver toxicity ever been noted for a particular component?
- Have studies been carried out using combined administration of two or more specific components?

They also had a list of specific fields they wished to be in the database. Some of these are included in Table 1.

Table name	Field name	Data Type
Single and repeat dose data	Dose volume	Number
Single and repeat dose data	Dose units	List
Single and repeat dose data	pH	String
Single and repeat dose data	Admin. regimen	List
Single and repeat dose data	Treatment duration/units	Virtual column
Single and repeat dose data	Frequency of admin.	List
Single and repeat dose data	Species	List
Single and repeat dose data	Strain	List
Single and repeat dose data	Sex	List
Single and repeat dose data	Approx. age at start	String
Single and repeat dose data	No. animals per group	Number
Single and repeat dose data	Route of admin.	List
Single and repeat dose data	Injection/infusion rate	String
Single and repeat dose data	Tolerability	List
Single and repeat dose data	Mortality	String
Single and repeat dose data	Bodyweight	String
Single and repeat dose data	Food/water consumption	String
Single and repeat dose data	GLP status	List
Blood compatibility	pH	String
Blood compatibility	Species	List
Blood compatibility	Strain	List
Blood compatibility	Test system	List
Blood compatibility	Result	Number
Blood compatibility	Result units	List

Table 1. Some relevant fields from the single and repeat dose data, and blood compatibility tables.

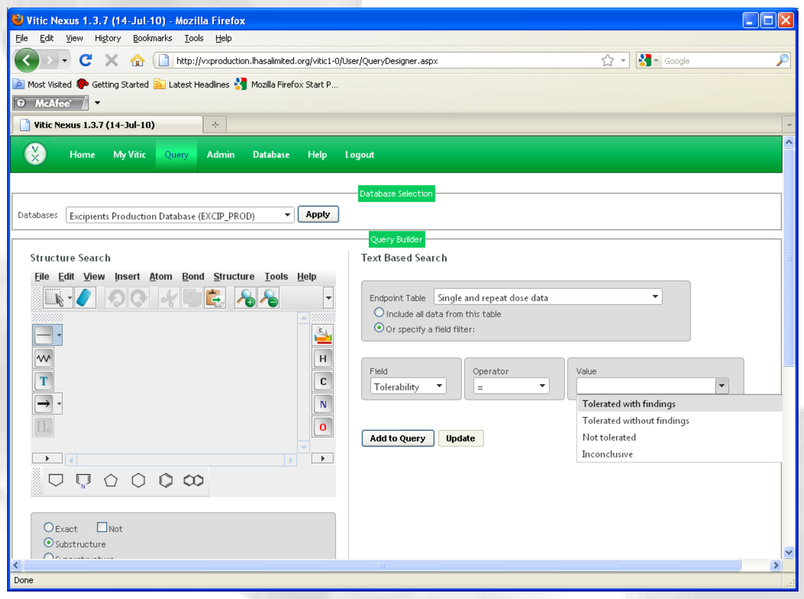

Figure 2. Screen shot of Vitic Nexus software showing construction of a query.

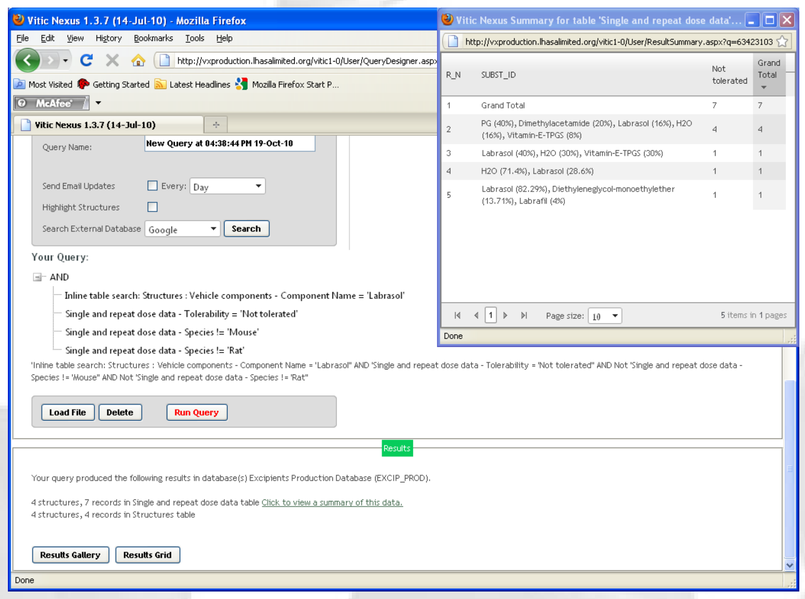

Figure 3. Number of records returned by searching for a previously constructed query. Top right shows the summary table which provides information on the vehicles returned and their overall tolerability.

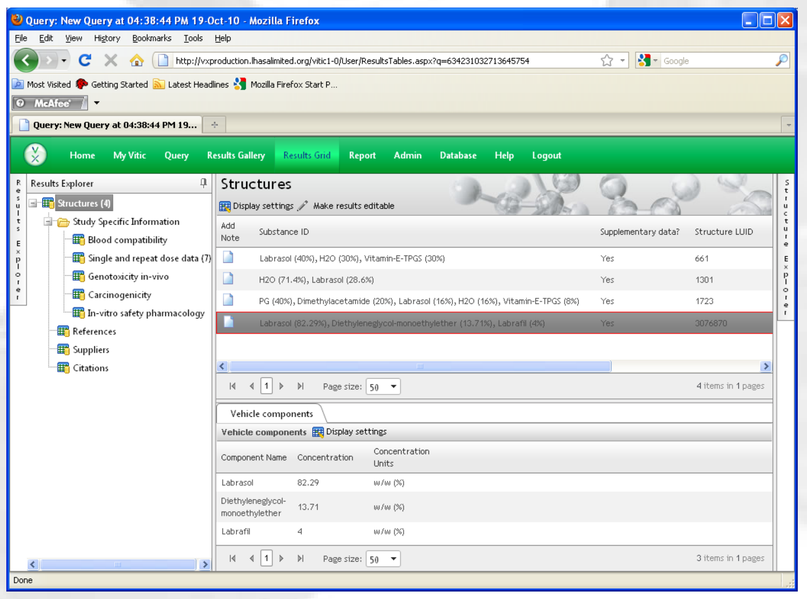

Figure 4. Results grid showing the vehicle information table and associated inline table of vehicle component information.

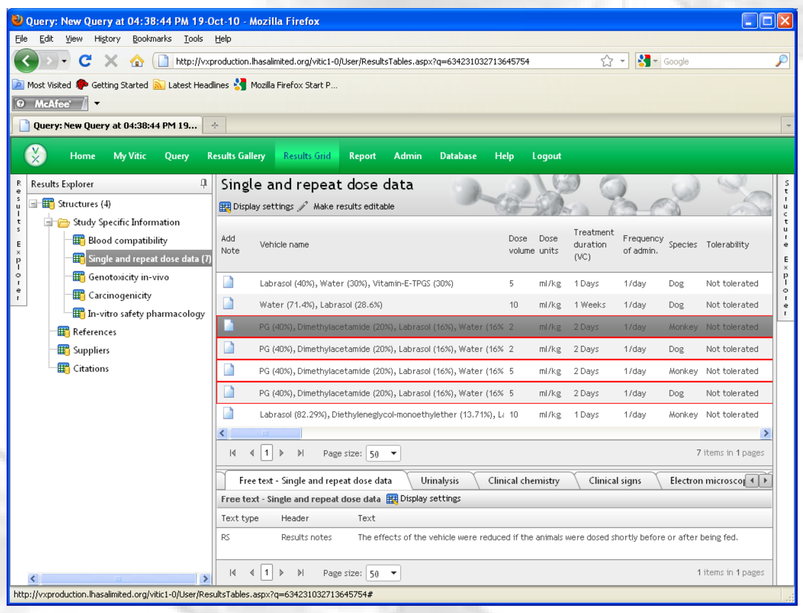

Figure 5. Results grid showing the single and repeat dose data information table and associated freetext inline table for the vehicle Propylene glycol (40%), Dimethylacetamide (20%), Labrasol (16%), Water (16%), Vitamin E-TPGS (8%).

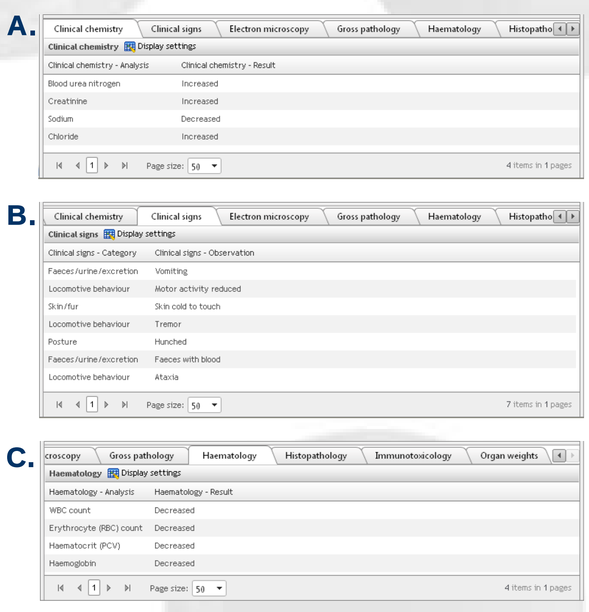

Figure 6. Inline tables containing example information on: (A) clinical chemistry findings, (B) clinical signs observed, and (C) haematology findings.

A.

Tolerability	Vehicles	Records
Tolerated without findings	278	623
Tolerated with findings	119	224
Not tolerated	35	46
Inconclusive	45	47

B.

Route of Admin	Vehicles	Records
Dermal	15	23
Intraarterial	3	3
Intranasal	1	4
Intraperitoneal	15	17
Intravenous (bolus)	103	189
Intravenous (infusion)	39	57
Intravenous (unspecified)	28	44
Occular	1	1
Oral (gavage)	217	470
Oral (dietary admixture)	3	17
Perivenous	3	3
Subcutaneous	23	37

C.

Species	Vehicles	Records
Dog	133	201
Guinea Pig	5	5
Miniature Swine	15	16
Monkey	45	65
Mouse	52	92
Rabbit	41	60
Rat	268	490

D.

Length of study	Vehicles	Records
1 day (single dose)	142	231
2 – 7 days	88	133
8 – 14 days	120	191
15 – 31 days	138	223
32 – 93 days	58	104
94 – 273 days	21	29
>= 274 days	5	16

Table 2. Showing the spread of data currently in the database, including information on the tolerability of vehicles (A), as well as showing the route of administration (B) and species (C) used and the distribution of study lengths (D) within the database.

Results

The database has been released to the participants yearly since 2009. The current release contains 1030 data records in the blood compatibility and single and repeat dose tables. These records cover 454 different vehicle compositions. There are data on vehicle studies carried out in 7 different species, by 10 different routes of administration and for varying length of time (see Table 2).

Conclusion

The development and success of this database demonstrates that data sharing is possible for non-commercially sensitive structures, even in the case of complex endpoints such as repeat dose toxicity. Feedback has been sought from members, and has shown that the database is benefitting users by avoiding unnecessary testing on laboratory animals and aiding selection of appropriate vehicles.

Acknowledgements

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