THOMSON REUTERS INTEGRITYᔆᴹ FAQs

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CONTENT

WHAT CAN I FIND IN INTEGRITY?

The *Thomson Reuters Integrity*ᔆᴹ drug discovery and development portal encompasses essential information on over:

- **320,000** bioactive compounds
- **2,350** precedented targets with pathway information
- **9,600** genomics records with gene-related studies
- **20,000** synthesis schemes, including more than **92,000** organic synthesis intermediates and reagents
- **4,450** companies and research institutions, including sales information on more than **365**

It also includes more than:

- **855,000** data values from experimental pharmacology studies that delineate drug/receptor and enzyme/target cell interactions
- **440,000** data values on pharmacokinetics/metabolism for parent compounds and active metabolites
- **105,000** references to clinical trials of compounds currently under study and/or in use in humans
- **115** disease briefings giving background references on diseases with full-color multimedia illustrations and web enhancements
- **1,075,000** references to the current literature, abstracts and proceedings from congresses and symposia and company communications
- **139,500** patent families from 4 leading sources.

WHAT ARE THE INFORMATION SOURCES FOR INTEGRITY?

Principal information sources are the patent literature, biomedical literature and congresses, company communications and internet monitoring. *Integrity* covers more than 1,500 journals and 400 conferences annually in the areas of medicinal chemistry, organic synthesis, experimental pharmacology, clinical pharmacology, biomarkers and genomics, as well as tracking the activity of key pharmaceutical and biotechnology companies.

HOW FAR BACK DOES THE INFORMATION IN INTEGRITY GO?

The focus of *Integrity* is on products in discovery or development since 1988. The information in the Drugs & Biologics, Patents and Literature Knowledge Areas dates back to 1988, with more than 1,500 selected back records added for Drugs & Biologics (e.g., aspirin). The other Knowledge Areas have continuous coverage from different dates, the 1970s for Organic Synthesis, 1998 for Experimental Pharmacology, 2000 for Clinical Studies, Disease Briefings, Companies & Research Institutions and Pharmacokinetics/Metabolism, 2001for Genomics, 2004 for Targets & Pathways and 2007 for Biomarkers, again with selected back records entered.

WHAT IS THE LAG TIME FOR THE INCORPORATION OF PATENT DATA INTO INTEGRITY?

WO, EP and US patent citations are available 24 hours after publication, and JP patent citations are available within 5 days of publication. Patents are fully analyzed with the inclusion of added value chemistry and pharmacology within 1-2 weeks following their inclusion in our system. The time for literature and congress records to be included is usually 0–2 weeks (from the date the information is first made available to incorporation).

WHAT TYPES OF PATENTS DO WE ANALYZE?

For all patents with a basic patent publication date from 2005, full analysis is systematically included for those covering human drug substances, targets, biomarkers, gene therapy and screenings, vaccines and a few other categories. Prior to 2005 the focus was on drug substances.

REGISTRATION & LOGON

HOW DO I LOG ON TO INTEGRITY?

Go to http://integrity.prous.com (or alternatively, https://integrity.prous.com for an SSL connection).To use *Integrity* after you have registered the first time or if you have been provided with a User Name/Password combination by Thomson Reuters, type your User Name and Password in the spaces provided under Registered Users and click Login.

CAN I SELF-REGISTER?

You can self-register for Integrity if your company agreement with Thomson Reuters allows this option. To do so, click the Self-Register Button. Review the Terms of Use and click to accept them.

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Then click Continue. Complete the registration form. Check the information, particularly your e-mail address, and then click Send. Make a note of your chosen User Name and Password. Registration is immediate. Now you can log on by entering your newly created User Name and Password and clicking Login. This takes you to the *Integrity* Home Page.

CAN I SHARE MY PASSWORD WITH A COLLEAGUE?

Integrity user names and passwords are personal and nontransferable under the *Integrity* Terms of Use. A user name/password combination defines an individual user account in *Integrity*, and each account may have a single e-mail address entered for receiving Alerts. Sharing a user name/password combination violates the confidentiality of the original user's Saved Queries and Alerts and prevents the other user from using the Alert feature. If two users attempt to use a user name/password combination simultaneously, they will be ejected from the system.

DEFINITIONS AND ABBREVIATIONS

WHAT IS UNDER ACTIVE DEVELOPMENT?

The Under Active Development label appears on records for products that are actively moving through the drug R&D pipeline from preclinical stages through registration (i.e., preclinical, IND filed, phase I, phase I/II, phase II, phase II/III, phase III, preregistered, recommended approval and registered).

The criteria for labeling a compound Under Active Development include the following, which must have occurred over the last 12-18 months: a) the company is actively informing the public on the development of the product via press releases, mention in annual reports, citation on the company's website (particularly, if the company publishes a "pipeline" and the product is included in it); and/or b) references to the compound that indicate its progress are being published in the biomedical literature (journals and congresses).

The Under Active Development Checkbox can be used as a filter to restrict searches to retrieve only those compounds that are under active development. The Under Active Development Search Field (in the pulldown menu) is used when this search criterion is to be linked with other criteria with the AND or OR Boolean operators (example: Under Active Development = Y OR Highest Phase = Launched).

Under Active Development is indicated in the Full Product Record. The Entry Numbers of UAD products appear in red and are marked with an asterisk.

Compounds that are in very early stages of development are not considered to be Under Active Development and will be excluded from searches using the Under Active Development filter.

Compounds that are launched and are not being investigated for new conditions, in new regions or by new organizations are not considered Under Active development and will be excluded from searches using the Under Active Development filter.

WHAT IS A LEAD COMPOUND?

When a series of "sister" compounds are derived from a single patent or literature reference, the series has a designated "lead compound." If there is only one specifically claimed compound in the patent, this will be the lead compound. Or, in a case where pharmacology data are presented (e.g., IC50 values), the most active compound will be the one designated as the lead compound in our series (other things such as administration routes cited or any toxicity data being equal). Nevertheless, the use of the term "lead compound" by Thomson Reuters is not a prediction of which compound from the series will go into preclinical or later development. It is simply a tool that allows users who are searching for large volumes of data to pull out a single representative compound from a series, thereby reducing the "background noise." The Lead Compound Checkbox can be used as a filter to restrict searches to only lead compounds. It is particularly useful when searching on compounds in the earliest stage of development (i.e., Biological Testing).

WHAT IS AN ENTRY NUMBER (EN)?

The Entry Number is a 6-digit compound ID number assigned to every bioactive compound found in the Thomson Reuters databases. It serves as a compound identifier throughout a drug's life. ENs are assigned sequentially.

WHAT IS A NEW MOLECULAR ENTITY (NME)?

A new molecular entity in *Integrity* is a compound described for the first time in the biomedical literature, at a congress or in a company communication that is identified by an investigational code or chemical name. The NME status is retained for 4 months.

WHAT ARE TARGETSCAPES?

Images that map the molecular landscapes for a given condition with links to the specific target

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records for precedented targets. If a target is not precedented then there will not be an active link in the Targetscape, although users can search in Genomics to see a combined gene and protein record with associated gene-related studies.

WHAT DO VALIDATED AND CANDIDATE MEAN WHEN ASSOCIATED WITH CONDITIONS IN TARGET RECORDS?

An algorithm is used to give an indication of how valid a target is for a condition by labeling the condition validated if a product acting on the target and associated with the condition has been tagged Under Active Development. The Candidate label is used if there are associated products for that condition but they are not Under Active Development.

WHAT ARE DISEASE BRIEFINGS?

Dynamic executive summaries on the current status and future trends in drug therapy for specific diseases. These include background information on the disease, compounds currently used to treat it and those under study for this condition, as well as links to related information and sites.

WHAT IS THE LINK TO POTENTIALLY RELATED PATENTS IN INTEGRITY?

This is a link from compound records with undisclosed structures. It links to patents for compounds with the same mechanism(s) of action by the same applicant organization.

WHAT IS THE DIFFERENCE BETWEEN LAST UPDATED AND AVAILABLE SINCE?

The Available Since search field retrieves records according to when the record first appeared in *Integrity*. The Last Updated search field retrieves records according to the date in which any information contained in that record (e.g., development phase) was last updated.

WHAT ARE UPDATES?

Product records that have been updated since late 2005 have the update history reflected in the Updates pop-up. Click on the Updates button (just to the right of the entry number when looking at a product full record) to open the updates history pop-up, with all updates displayed in reverse chronological order (most recent first). Records that do not have an updates button have not been updated either since late 2005 or since their inclusion in *Integrity*.

WHAT IS THE DIFFERENCE BETWEEN HIGHEST PHASE, PHASE UNDER THE DEVELOPMENT STATUS SUBMENU AND PHASE UNDER THE MILESTONE SUBMENU?

An explanation corresponding to that below also applies to other similar fields that appear repeated at different levels, for example, Condition, Organization, Brand Name and Under Active Development. The distinct search fields allow for very precise searching. Where possible, there are "higher" and "lower" level search fields in all Knowledge Areas to allow increased specificity and targeted results. Higher level search fields are all of the search fields that appear immediately in a drop down field selector. For lower level fields, the name of the search field category appears in bold and has a plus sign next to it. Users only need to rollover the bold term to open the side menu and select a lower level search field.

Higher Level - **Highest Phase** is an example of a higher level search field, as are the checkboxes for Lead Compound and Under Active Development. Highest Phase is found in the Full Product Record near the top left-hand side of the page. Each compound has only one highest phase. This is the appropriate field when a user wants to retrieve all compounds that have reached a specified phase.

Development Status Level - **Development Status -> Phase** is an example of a lower level search field. Development Status Phase looks in the phase column of the Development Status table. The Development Status Summary in the Full Product record shows the highest phase reached for each condition, and the Details button in the table header opens the Development Status table. There will often be multiple repeated phases in the table as each line corresponds to a development program. A product can be developed by different organizations, for different conditions and in different regions and each one of these will have separate development programs which may be in a different phase. A Development Status Phase search will pick up all lines in the table that match the criteria. This is the appropriate field when you want to match criteria found in the program lines, for example, the search under active development in phase II for cancer would be run using the Development Status fields.

Milestone level - **Milestone -> Phase** is another lower level search field and it searches in the Phase column of the Milestones table which opens in a pop-up by clicking the Milestones button found in the header of the Development Status Summary. There may be multiple Milestone Phases as

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Milestones are always company, phase and condition specific and will have a concrete Milestones date.

TO CONSIDER WHEN SEARCHING USING LOWER LEVEL SEARCH FIELDS:

Not all products will have a Development Status table or Milestones table, as products that never move out of early phases are determined to not have a development history or Milestone. Therefore, very early stage compounds will not be retrieved by searches with Development Status or Milestones search fields as they have no Development Status or Milestones for the search to examine.

A search using Highest Phase will return results in a product list, while searching with Development Status criteria will return results in a Program List and a search in Milestones will return a Milestones List. A product list will have one result per compound, no matter how many development programs or milestones that product has, while the development programs list and Milestones lists may have multiple lines of results if there are multiple development programs or milestones that meet the search criteria. Users can switch between displays using the Options menu.

Using two or more fields from the same lower level set of search fields will cross the criteria to retrieve very specific results. For example, searching on Development Status -> Phase = Phase I and Development Status Condition = cancer will retrieve only those results where the product has a development program in Phase I for cancer, regardless of how many other programs it might have for cancer that are not in Phase I or how many other development programs it might have in Phase I that are not for cancer. This allows users to specify the results they want to see very clearly and avoids problems with having too many results that are not relevant when searching on broad topics such as "cancer".

Users will get different numbers of results using the different level search fields because of the logic of where the field looks and the display format of the results.

WHAT IS THE DIFFERENCE BETWEEN THE MECHANISM OF ACTION, THERAPEUTIC GROUP, CONDITION AND PRODUCT CATEGORY SEARCH FIELDS AND HOW DO THEY WORK?

Integrity contains various types of information on the way in which drugs and biologics act and the diseases they target. This information can be searched for by using the following search fields:

- Mechanism of Action
- Therapeutic Group
- Condition
- Product Category

HOW DOES THE MECHANISM OF ACTION SEARCH FIELD WORK IN INTEGRITY?

The **Mechanism of Action** field utilizes a controlled vocabulary that describes the various types of mechanisms of action for bioactive compounds — for example, Angiotensin-I Converting Enzyme (ACE) Inhibitors, Calcium Channel Blockers, Angiotensin Receptor Antagonists, Dopamine D1 Agonists, etc. The Mechanism of Action search field is useful for retrieving very specific groups of compounds that work by the same mechanism. It can also be used with the Boolean operator AND to search for compounds with a dual mechanism of action — such a search example would "Angiotensin-I Converting Enzyme (ACE) Inhibitors" AND "Neprilysin (Enkephalinase, Neutral Endopeptidase, NEP) Inhibitors". The Browse Index for the **Mechanism of Action** search field provides a highly targeted approach to selecting search terminology for use in accordance with a hierarchical scheme. This search field can also be used to select terms from an alphabetic list or users can use the pre-search field (Lookup box) to create a short list of potential search terms.

WHAT ARE THE TYPES OF MECHANISMS OF ACTION IN INTEGRITY?

There are two types of Mechanisms of Action in *Integrity*: Cellular Mechanisms and Molecular Mechanisms. Any one compound can have multiple mechanisms of either or both types. Using Filter by Statistics in Drugs & Biologics and selecting Mechanistic Scope (Compounds by Mechanism Type) generates two charts showing the mechanisms divided by mechanism type:

- Molecular Mechanisms (Compounds by Molecular Mechanism)
- Cellular Mechanisms (Compounds by Cellular Mechanism)

HOW IS ACTIVITY DESCRIBED BY MECHANISMS OF ACTION IN INTEGRITY?

Ligands are products that bind to a receptor (they have an affinity constant for the given receptor) but it is not known if they act as agonists or antagonists. Modulators are products that bind to an allosteric

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site rather than the orthosteric site of the receptor and modulate the effect of the orthosteric ligands. Modulator is also used to describe mechanisms that are not acting on receptors. This is a wide definition meaning that a product modulates the activity of an effector (eg. an enzyme or protein) without the exact mechanism being specified. The terms "drugs acting on X receptors" are used when products act on a family of receptors (for example acetylcholine receptors) but information on which receptor is being bound is not specified.

HOW DOES THE THERAPEUTIC GROUP SEARCH FIELD WORK IN INTEGRITY?

The **Therapeutic Group** field utilizes a controlled vocabulary that describes the various types of pharmacological/therapeutic groups into which bioactive compounds can be classified. These can be broad groups (for example, Cardiovascular Drugs, Neurologic Drugs) or more specific groups (for example, Antihypertensive Drugs, Antiarrhythmic Drugs). This field does not include terminology for mechanisms of action (inhibitors, agonists, antagonists, potentiators, sensitizers, etc.). The Therapeutic Group search field is useful for retrieving compounds that are relevant to a specific (broad or narrow) condition where all types of mechanisms of action are of interest — for example, a search for Therapeutic Group = Antihypertensive Drugs finds compounds that are ACE inhibitors, calcium antagonists, endothelin ETB antagonists, angiotensin AT1 antagonists, etc. The Browse Index for the **Therapeutic Group** search field provides a highly targeted approach to selecting search terminology for use in accordance with a hierarchical scheme. This search field can also be used to select terms from an alphabetic list or users can use the pre-search field to create a short list of potential search terms.

HOW DOES THE CONDITION SEARCH FIELD WORK IN INTEGRITY?

The **Condition** search field takes a medical approach to the matter and utilizes a controlled vocabulary that describes the type of disorder the bioactive compound treats – for example, a search for the condition Hypertension will pull up the drug diuretic, used to treat Hypertension. The Browse Index for the **Condition** search field provides a highly targeted approach to selecting search terminology for use in accordance with a hierarchical scheme. This search field can also be used to select terms from an alphabetic list or users can use the pre-search field to create a short list of potential search terms.

HOW DOES THE PRODUCT CATEGORY SEARCH FIELD WORK IN INTEGRITY?

The **Product Category** field utilizes a controlled vocabulary that describes the various grouping into which bioactive compounds can be classified in terms of what they are rather than how they work or what they are used for. These groups include Chemical Categories, Biological Factors, Biotechnology Medicines (Antibodies, Vaccines etc.), Delivery Systems, Hormones etc.... The Browse Index for the **Product Category** search field provides a highly targeted approach to selecting search terminology for use in accordance with a hierarchical scheme. This search field can also be used to select terms from an alphabetic list or users can use the pre-search field to create a short list of potential search terms.

WHAT ARE THE DEFINITIONS FOR THE DEVELOPMENT PHASE TERMINOLOGY IN INTEGRITY?

Biological Testing: Products from patents are entered into this phase. Synthesis and preliminary pharmacology (in vitro testing) data may be available.

Preclinical: In vivo testing; testing in animals has started.

IND Filed: Application has been filed with the competent authority requesting permission to test the drug in humans (IND = Investigational New Drug Application in U.S.).

Clinical: Used when it is known that the drug is in clinical testing, but the exact phase is not known.

Phase 0: an FDA approved trial which tests small quantities of experimental drugs on humans.

Phase I: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness have started; usually conducted in healthy volunteers.

Phase I/II: Studies that combine certain aspects of phase I trials and phase II trials: example, a safety study in patients.

Phase II: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks have started.

Phase II/III: Studies that combine certain aspects of phase II trials and phase III trials.

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Phase III: Expanded controlled and uncontrolled trials have started after preliminary evidence suggesting effectiveness of the drug has been obtained. These are intended to gather additional information to evaluate the overall relationship of the drug and provide an adequate basis for physician labeling benefit-risk.

Pre-registered: Application to market the drug (e.g., New Drug Application or Marketing Authorisation Application) has been filed.

Recommended Approval: Approval of the drug has been recommended by the corresponding FDA Advisory Committee or a Positive Opinion has been issued by the CHMP.

Registered: The competent regulatory authority has approved the drug for marketing, but the drug is not yet available on the market.

Launched: The drug is being marketed.

Discontinued: Development of the product has stopped before a registration dossier has been filed.

Suspended: The product is stopped when undergoing regulatory review.

Withdrawn: The product is withdrawn from the market after launch.

Undetermined: Development status is unknown.

Not Applicable: A preparation or extract that is under study as a drug is also possibly (or definitely) already available on the market as an unregulated health food supplement.

WHAT IS BIOLOGICAL TESTING AND WHY ARE THERE SO MANY COMPOUNDS IN THIS PHASE?

Products from patents are entered into this phase, meaning that almost all product records start in Biological Testing. They only move on to higher phases if there is information published to show that they have moved any further. Over 80% of all compounds in *Integrity* are in Biological testing.

WHAT ARE THE DEFINITIONS FOR THE MILESTONES TERMINOLOGY IN INTEGRITY?

Acquired: A product is acquired by a new company, usually by acquisition/merger with another company.

ANDA Filed or Approved: (Only applicable for the U.S. Food and Drug Administration, ANDA stands for Abbreviated New Drug Application). Contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs (ANDA Filed), provides for the review and ultimate approval of a generic drug product. Generic drug applications are called "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the innovator drug). Once approved (ANDA Approved), an applicant may manufacture and market the generic drug product to provide a safe, effective, low-cost alternative.

Application withdrawn: An application for approval (NDA filed, sNDA filed, BLA filed, sBLA filed, ANDA filed in US; MAA filed in EU; pre-registered in other countries) is withdrawn when the Company is unable to satisfy the Administration requirements. If an applicant withdraws an original application for approval or supplement before FDA has completed its review, the review clock stops on the date FDA receives the letter notifying it of the withdrawal. As an example, if new data are required by the Administration before giving the approval and the Company is unable to perform the trials in time, it withdraws the application and resubmits it later with the entirety of data available.

Approvable Letter: (Only applicable for the U.S. Food and Drug Administration).

An official communication from FDA to an application for approval sponsor that allows the commercial marketing of the product. An approvable letter informs the applicant that FDA has completed the scientific review of its application for approval and determined that it can be approved pending resolution of minor deficiencies identified in the letter or during FDA's inspection of the device's manufacturing facilities. No longer being issued as of August 2008 (see Complete Response Letter).

Available for outlicensing: A product which is available for licensing.

BLA Filed or Approved: (Only applicable for the U.S. Food and Drug Administration, BLA stands for Biologic License Application). Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm who manufactures a biologic for sale in interstate commerce to hold a license for the product. A biologic license application is a submission (BLA filed) that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical affects of the biologic product. If the information provided meets FDA requirements, the application is approved (BLA Approved) and a

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license is issued allowing the firm to market the product.

Clinical: See above for Development Phase definitions.

Codeveloped: A product which is being developed by more than one company.

Complete Response Letter: In August 2008, the FDA began issuing complete response letters when communicating a decision to a drug company that a new drug application (NDA) or abbreviated new drug application (ANDA) to market a new or generic drug will not be approved in its present form. Currently FDA issues either approvable or not approvable letters in these cases. Complete response letters will only be issued for applications that are not approved; this rule will not impact how FDA communicates decisions to approve an application.

CTA filed: (Only applicable for the E.U. European Medicines Agency – EMEA, CTA stands for Clinical Trial Authorization). Application for authorization for the beginning of a clinical trial.

Discontinued: See above for Development Phase definitions.

Fast Track Designation: (Only applicable for the U.S. Food and Drug Administration).

A designation that the US Food and Drug Administration (FDA) reserves for products intended to treat a serious or life threatening condition, and that have the potential to address an unmet medical need. The FDA takes appropriate actions to expedite the development and review of the approval applications for fast track products. The Fast Track program enables a company to file an NDA on a rolling basis as data becomes available. This permits the FDA to review the filing as it is received, rather than waiting for the entire document prior to commencing the review process. With a Fast Track designation, there is an opportunity for more frequent interactions with the FDA and possibility of a priority review, which could decrease the length of a typical review period.

IDE filed: (Only applicable for the US Food and Drug Administration, IDE stands for Investigational Device Exemption). An application for authorization for an investigational device to be used in a clinical study in order to collect safety and efficacy data required to support a Premarket Approval Application (PMA).

IND filed: (Only applicable for the US Food and Drug Administration, IND stands for Investigational New Drug). An application for authorization for a drug product to be used in a clinical study in order to collect safety and efficacy data required to support a New Drug Application (NDA).

Launched: See above for Development Phase definitions.

Licensed: A company licenses a drug when it sells all or part of the rights it holds from the drug to another company. As an example, the owner company can just sell rights for a certain condition or for development and/or marketing in certain countries, only.

Licensee agreement terminated: When a previous license agreement has expired or has been cancelled.

MAA Filed or Approved: (Only applicable for the E.U. European Medicines Agency – EMEA, MAA stands for Marketing Authorization Application). MAA filed is the submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical affects of the biologic product. If the information provided meets EMEA requirements, the application is approved (MAA Approved) and a license is issued allowing the firm to market the product.

NDA Filed or Approved: (Only applicable for the U.S. Food and Drug Administration, NDA stands for New Drug Application). When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA Filed). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved (NDA Approved), the product may be marketed in the United States.

Negative Opinion: (Only applicable for the E.U. European Medicines Agency - EMEA).

The Committee for Medicinal Products for Human Use (CHMP) of the EMEA is responsible for preparing the Agency's opinions on all questions concerning medicinal products for human use. In the "Community" or "centralized" procedure, the CHMP is responsible for conducting the initial assessment of medicinal products for which a Community-wide marketing authorization is sought. If CHMP considers that the medicinal product is not approvable, it gives a Negative Opinion.

Not Approvable Letter: (Only applicable for the U.S. Food and Drug Administration).

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A not approvable letter informs the PMA applicant that FDA has completed the scientific review of the PMA and does not believe that the PMA can be approved because of the significant deficiencies identified in the letter. After the applicant receives a not approvable letter, he or she may: amend the PMA to address the deficiencies; withdraw the PMA; or consider this letter to be a denial of approval of the application.

For original applications, a not approvable letter is issued after FDA has conducted a complete review of the application, including any recommendations by an FDA advisory panel, if applicable, and determines that the available data in the application do not support a determination of reasonable assurance of safety and effectiveness. Generally, before FDA issues a not approvable letter, the agency provides the applicant with an opportunity to address its concerns through a major deficiency letter. No longer being issued as of August 2008 (see Complete Response Letter).

Not Recommended Approval: (Only applicable for the U.S. Food and Drug Administration).

In some cases, FDA seeks the recommendations of advisory committees made up of outside experts. These expert advisers add to FDA's understanding, so that final agency decisions will more likely reflect a balanced evaluation. Committee recommendations are not binding on FDA, but the agency considers them carefully when deciding drug issues. Not Recommended Approval means that the advisory committee considers that the drug is not approvable.

On Hold: A product development is placed temporarily on hold by the company, usually as a voluntary measure. As an example, if the Data Monitoring Committee (DMC) has requested additional data, if protocol revisions are needed, etc.

On Hold Lifted: A temporary, and usually voluntary by the company, hold on a product's development is lifted.

Orphan Drug Designation: There are many diseases and conditions which affect such small numbers of individuals that are considered rare and adequate drugs for many of such diseases and conditions have not been developed. Drugs for these diseases and conditions are commonly referred to as "orphan drugs". It is in the public interest to provide incentives for the development of orphan drugs. In the EU, the term "Orphan Drug" refers to a product that treats a serious or life-threatening disease that affects fewer than five people per 10,000 population. In the US, the term "Orphan Drug" refers to a product that treats a disease that affects fewer than 200,000 people in the country. Orphan drug designation may qualify recipients for exclusive marketing rights in the United States for seven years and in the EU for ten years if the company is first to receive marketing approval for this product.

Phase 0: See above for Development Phase definitions.

Phase I: See above for Development Phase definitions.

Phase I/II: See above for Development Phase definitions.

Phase II: See above for Development Phase definitions.

Phase II/III: See above for Development Phase definitions.

Phase III: See above for Development Phase definitions.

PMA Filed or Approved: (Only applicable for the U.S. Food and Drug Administration, PMA stands for Premarket Approval Application). Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices. A Class III device is defined as one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury. The applicant submits to FDA a PMA (PMA filed). If the license is granted (PMA approved), the applicant is authorised for marketing a particular medical device.

Preclinical: See above for Development Phase definitions.

Pre-registered: See above for Development Phase definitions.

Positive Opinion: (Only applicable for the EU European Medicines Agency - EMEA).

The Committee for Medicinal Products for Human Use (CHMP) of the EMEA is responsible for preparing the Agency's opinions on all questions concerning medicinal products for human use. In the "Community" or "centralized" procedure, the CHMP is responsible for conducting the initial assessment of medicinal products for which a Community-wide marketing authorization is sought. If CHMP considers that the medicinal product is approvable, it gives a Positive Opinion.

Recommended Approval: (Only applicable for the U.S. Food and Drug Administration).

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In some cases, FDA seeks the recommendations of advisory committees made up of outside experts. These expert advisers add to FDA's understanding, so that final agency decisions will more likely reflect a balanced evaluation. Committee recommendations are not binding on FDA, but the agency considers them carefully when deciding drug issues. Recommended Approval means that the advisory committee considers that the drug is approvable.

Recommended Approval: Approval of the drug has been recommended by the corresponding FDA Advisory Committee or a Positive Opinion has been issued by the CHMP.

Registered: See above for Development Phase definitions.

sBLA Filed or Approved: (Only applicable for the U.S. Food and Drug Administration, sBLA stands for Supplemental Biologic License Application). A supplemental biologic license application submission (sBLA filed) is required by the FDA for biologic products when changes are made in the manufacturing processes or label, for the marketing authorization of a new formulation, strength or indication. If the information provided meets FDA requirements, the application is approved (sBLA Approved).

(sNDA Filed or Approved: (Only applicable for the U.S. Food and Drug Administration, sNDA stands for Supplemental New Drug Application). A supplemental new drug application submission (sNDA filed) is required by the FDA when changes are made in the manufacturing processes or label of a drug, and for the marketing authorization of a new formulation, strength or indication. If the information provided meets FDA requirements, the application is approved (sNDA Approved).

Suspended: A trial is suspended (enrollment or patients treatments) usually following the recommendation of a Data Safety Monitoring Board (DSMB). The company temporarily suspends a trial as a precaution when adverse events are detected, new data are required, etc.

Withdrawn: See above for Development Phase definitions.

WHAT ABBREVIATIONS ARE USED FOR PARAMETERS IN EXPERIMENTAL PHARMACOLOGY?

- **CC** - Cytotoxicity
- **EC** - Effective Concentration
- **ED** - Effective Dose

- **IC** - Inhibitory Concentration
- **ka -** Absorption constant
- **Kb** - Equilibrium Dissociation Constant for an antagonist
- **Kd** - Equilibrium Dissociation Constant
- **Ki** - Affinity/Inhibitory Constant
- **Ki(h**) - Affinity/Inhibitory Constant (high affinity component)
- **Ki(l)** - Affinity/Inhibitory Constant (low affinity component)
- **LD** - Lethal Dose
- **MBC** - Minimum bactericidal concentration
- **MCC**- Minimum cytotoxic concentration
- **MEC** - Minimum effective concentration
- **MED** - Minimum effective dose
- **MFC** - Minimum Fungicidal Concentration
- **MIC** - Minimum Inhibitory Concentration
- **MID** - Maximum Inactive Dose
- **MLD** -Minimum Lethal Dose
- **MPC**- Mutation Prevention Concentration
- **MTD** - Minimum Tolerated Dose
- **MUD** - Minimum Ulcerogenic Dose
- **NTD** - Non-toxic Dose
- **TC** – Toxic Concentration
- **UD** - Ulcerogenic Dose
- **pA-2** -Antagonism Constant
- Modifier used is **p** to indicate the log form

WHAT ABBREVIATIONS ARE USED FOR PARAMETERS IN THE PHARMACOKINETICS/METABOLISM KNOWLEDGE AREA?

- **AUC (A-B) -** Area under curve for a given interval from time A to time B in hours
- **BR (A-B)** - Biliary recovery between time A and time B (in hours).
- **Cl** – Clearance; the rate of elimination by all routes (or by specified route(s) and mechanism(s) of elimination, as indicated by a letter in parenthesis

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- **Cl(B) -** Biliary clearance
- **Cl(H) -** Hepatic clearance
- **Cl(I)** – Intestinal (or Fecal) clearance
- **Cl(R) -** Renal clearance
- **Cl(XR) -** Extra-renal clearance
- **Cmax -** Peak concentration
- **Cmin -** Trough concentration
- **Css -** Average plasma concentration of an administered drug at steady state.
- **ER (A-B) -** Recovery in exhaled air from time A to time B (in hours)
- **F** - Bioavailability
- **FR (A-B) -**Fecal Recovery between time A and time B (in hours)
- **GIR (A-B) =** Gastrointestinal recovery
- **ka -** Absorption constant
- **kel -** Elimination rate constant
- **MAT -** Mean Adsorption Time
- **MR -** Milk Recovery
- **MRT** - Mean Retention Time
- **PB -** Protein Binding
- **Q -** Intercompartmental clearance
- **t1/2 -** Half-life
- **$t_{½\ alfa}$**: distribution half life
- **$t_{½\ beta}$**: elimination half life or terminal elimination half life
- **$t_{½(a)}$**: absorption half life
- **tlag** - Lag time
- **Tmax -** Time to peak concentration
- **Tss -** Time to steady state
- **UR (A-B) -** Urinary Recovery from time A to time B (in hours).
- **Vd -** Volume of distribution
- **Vd(c) -** Central volume of distribution
- **Vd(p) -** Peripheral volume of distribution
- **Vss** - Volume of distribution steady state
- **Vss(c) -** Central volume of distribution steady state

- **Vss(p) -** Peripheral volume of distribution steady state
- **Vss(e) -** The proportionality constant that relates the amount of drug in the body to the serum concentration under steady state conditions in the elimination phase

WHAT MODIFIERS ARE USED FOR PARAMETERS IN THE PHARMACOKINETICS / METABOLISM KNOWLEDGE AREA?

- **(A-B):** Time A to Time B in hours
- **_b:** bound drug
- **_t:** total (drug plus metabolite)
- **_u:** unbound drug
- **_p:** parent drug (excluding metabolites)
- **_r:** ratio (This only applies to expositional parameters (AUC Cmax, Cmin, Css, etc.) and not to those related to speed (Cl, t1/2, etc.). As a relation, the parameter is adimensional.)
- **(c):** central
- **(p):** peripheral
- **(e):** elimination phase
- **(B):** biliary
- **(H):** hepatic
- **(R):** renal
- **(XR):** extrarenal

WHAT ABBREVIATIONS ARE USED FOR ADMINISTRATION ROUTE IN THE PK/METABOLISM KNOWLEDGE AREA?

- bucc.: buccal
- e.d.: epidural
- i.a.: intraarterial
- i.art.: intraarticular
- i.b.: intrabiliar (bile duct cannulation)
- i.car.: intracardiac
- i.col.: intracolonic
- i.cor.: intracoronary
- i.c.v.: intracerebroventricular
- i.d.: intraduodenal

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- i.g.: intragastric
- i.i.: intraileal
- i.int.: intraintstinal
- i.j.: intrajejunal
- i.m.: intramuscular
- i.n.: intranasal
- i.o.: intraocular
- i.otic: intraotic
- i.p.: intraperitoneal
- i.p.v.: intra portal vein
- i.str: intrastriatal
- i.t.: intratracheal
- i.thec.: intrathecal
- i.tymp: intratympanic
- i.uter: intrauterin
- i.v.: intravenous
- i.vag: intravaginal
- i.ves.inst.: intravessical instillation
- i.vitr. : intravitreous
- infiltr.: infiltration
- inhal.: inhaled
- p.o.: per os; oral
- pharing: oro-pharingeal
- rect.: rectally
- rinse: mouth rinse
- s.c.: subcutaneous
- s.conj.: subconjuntiva
- s.gin.: subgingivally
- s.l.: sublingual
- top.: topical

WHAT ABBREVIATIONS ARE USED FOR DOSAGE IN THE PK/METABOLISM KNOWLEDGE AREA?

- **b.i.d.:** (twice daily)
- **o.d.:** (once daily)
- **s.d.:** (single dose)

- **t.i.d.:** (three times daily)
- **q.i.d.:** (four times daily)

The remaining dosage abbreviations utilized tend to follow a pattern as per below:

o.d. x 3d = once daily for 3 days

1x/3 wks x 2h = once every three weeks for two hours

SEARCHING

WHAT ARE THE METHODS FOR OBTAINING DATA FROM INTEGRITY?

There are four ways of searching in *Integrity*:

- Search forms (found in each Knowledge Area).
- Quick Search (found on each page in *Integrity*)
- Quick access links (e.g., Pipeline on the Move, Today's Patents etc…)
- Disease Briefings (searching based on a medical condition or disease)

SEARCH FORMS

WHERE DO I FIND THE SEARCH FORM?

There is an Advanced Search form associated with each of the Knowledge Areas in *Integrity*. This is accessed by clicking the relevant Knowledge Area on the *Integrity* Home Page.

HOW DO I CHOOSE A KNOWLEDGE AREA?

The type of results you would like to view first determines which Knowledge Area you should choose. This does not affect your access to the complete set of data in *Integrity* as all data are integrated.

HOW DO I KNOW WHEN TO SEARCH IN TARGETS & PATHWAYS AND WHEN TO SEARCH IN GENOMICS?

Targets & Pathways contains information on precedented targets with separate gene and protein records. It has links and information on associated products. A gene record in Targets & Pathways will always have an associated Genomics record. Genomics has combined gene a protein records and contains information on gene-related studies. There are no links between the genomics record and products.

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HOW DO I KNOW WHAT TERMS ARE AVAILABLE AND HOW TO ENTER THEM FOR A GIVEN SEARCH FIELD?

Select a search field and click Index to the right of the field to open the browse Index.

WHAT IS A BROWSE INDEX?

There are four types of Indices in *Integrity* that indicate how to enter terms.

- Tip – offers hints on the format for entering criteria (eg. Available Since)

- Masterlist – contains the complete database content (eg. Drug Name)

- Controlled Vocabulary –unique terms for given criteria (eg. Phase)

- Controlled Vocabulary: hierarchical –unique terms for given criteria searchable by hierarchy (eg. Mechanism of Action)

WHY SHOULD I USE THE BROWSE INDEX?

Selecting specific terms, those used by *Integrity*, ensures that if what you are searching for is in *Integrity*, you will get results. For example, *Integrity* standardizes to one term for all masterlists and controlled vocabulary indices, so using abbreviations, alternate terms, or alternate spellings of a given term will result in missing results whereas selecting from the index will retrieve them all.

WHY CAN I FIND A TERM MORE THAN ONCE IN A LIST OF SEARCH FIELDS?

Related criteria search fields in *Integrity* allow users to specify exactly what they want a specific term to relate to. Example: Condition appears three times as a product search field, once in the main list (the condition is associated to the compound in a general sense), once under Development Status (to search phase information for the condition) and once under Milestones (to search for milestones related to the condition).

HOW MANY SEARCH FIELDS CAN I USE IN ONE SEARCH?

Every section of search fields has 3 fields which can be set to any of the available search fields in the drop down menu. Multiple fields are automatically linked with a Boolean operators AND, but users can change this Boolean operator to OR by adjusting the Boolean Operator drop down menu on the right hand side, just to the right of the Index button. Additionally, the Product section of search fields has 2 checkboxes to add the option to filter by Lead

Compound and/or Under Active Development (please see elsewhere in this FAQ for definitions of these terms). Users can also open the Structure Search tool (available in most knowledge areas, please see elsewhere in this guide for more on structure searching) to add a structure to the search criteria. All Knowledge Areas have at least 2 sections of search fields, one of which will be the Knowledge Area specific set of search fields (for example, fields such as applicant in Patents and author in Literature) and in most cases one will be the Product Section of Search fields. Some Knowledge Areas will also have additional sections of search fields if this is relevant to the content of that Knowledge Area.

HOW MANY CHARACTERS CAN I USE IN A SEARCH FIELD?

The search field can contain up to 300 characters allowing the use of Boolean Operators AND and OR within the field as well as between fields. For example, Phase = "Phase III" or "Pre-Registered" or "Recommended Approval" or "Registered"

CAN I USE A NOT OPERATOR?

"NOT" is not a valid operator in *Integrity*. We recommend using the Filter by Statistics charts to refine the search and select subsets of data to exclude criteria.

WHAT IF I WANT MORE SEARCH FIELDS THAN ARE AVAILABLE?

If users need more search fields or if there are not enough fields available for the Knowledge Area specific search fields that the user needs, then the search can be refined from the results page by using the Filter by Statistics charts on the right hand side of the results page. The charts available are Knowledge Area specific and offer the option to refine the search or view the results by many of the same criteria as the original search field choices. These charts display a visual representation of the results in a bar chart (users can change to another display format from the Filter by Statistics chart page) allowing the user to view the breakdown by the selected criteria and select subsets of the data, export the chart results, or take a screen capture of the chart. Rollover the bars in a chart to see a rollover indicator of the exact number of results represented by the bar. Mark the checkboxes on the left of each bar and click the View Subset button to refine move to the subset of results.

WHERE DO I FIND THE STRUCTURE SEARCHING FUNCTION?

The Structure Search is available in all Knowledge Areas (except Targets & Pathways, Genomics, Biomarkers) and can be found under the button

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marked Structure Search. This button is found on the right hand side of the advanced search page and is usually on the same line as the header for the Product Section of search fields, because the structures are associated directly with product records. The exception is in Organic Synthesis, where the structures are associated with organic synthesis records and will find structures that match either end products or intermediates.

WHAT PROGRAMS ARE USED FOR THE CHEMICAL STRUCTURE SEARCH?

Integrity now includes compatibility with four different programs for drawing structures to submit for chemical structure searches in the portal. Users can select any option at any time; and the last option selected will become the individual user's new default option. The options are available in all Knowledge Areas enabled for structure searching. They are:

Symyx® Draw

Users must have an existing license and installation of the Symyx® Draw software in order to use this option.

Symyx MDL® ISIS/Draw + Symyx MDL® Chime

Users must have an existing license and installation of the Symyx MDL® ISIS/Draw software in order to use this option. They also must have installed the Symyx MDL® ChimePro or Symyx MDL® Chime plugin. The Symyx MDL® Chime plugin can be downloaded at no charge from the MDL® website (http://www.mdl.com/downloads) or by following the link inside *Integrity*.

ChemAxon Marvin Applet

The ChemAxon Marvin applet installs automatically when users select this structure drawing option inside *Integrity*. No previous license or installation is required for this option; however, user computers must be Java-enabled.

CambridgeSoft CS ChemDraw™ Plugin

Users must have installed the CambridgeSoft CS ChemDraw™ Pro Plugin or the CS ChemDraw™ Net Plugin in order to use this option. The CS ChemDraw™ Net Plugin can be downloaded at no charge from the CambridgeSoft website (http://www.cambridgesoft.com/) or by following the link inside *Integrity*. The *Integrity* portal detects which program is needed for the user's computer configuration and assists users in installing the correct version. The CS ChemDraw™ Plugin does not have a separate manual. Information on

structure drawing conventions can be found in the standard CS ChemDraw™ manuals. To display or download this manual in PDF format, go to the above URL and click the appropriate version number in the ChemDraw™ line in the ChemDraw™ Manuals table.

WHAT TYPES OF SEARCHING CAN I SPECIFY USING THE STRUCTURE SEARCH OPTIONS?

Users are able to select between Substructure, Exact Structure and Similarity searches.

CAN I SPECIFY EXACT STEREOCHEMISTRY IN MY SEARCHES?

The Match Stereochemistry option allows users to select to consider (Match Stereochemistry enabled) or ignore stereochemistry when running Exact or Substructure searches.

HOW CAN I FIND MORE INFORMATION ON STRUCTURE SEARCHING IN INTEGRITY?

Go to the Guide to Structure Search Options for more information.

WHAT DO I DO IF THE CHEMDRAW TOOLBAR HAS DISAPPEARED?

If the toolbar has been closed, it will not reappear until you right click on the drawing window, select View and then Show Main Tools.

ARE THERE MINIMUM AND MAXIMUM NUMBERS OF FIELDS FOR SEQUENCE SEARCHING?

Eighteen bases are considered defining in the sequence search; however, up to 300 bases can be entered in the search field. In the search field truncation is automatic left and right of the sequence.

HOW DOES QUICK SEARCH WORK?

This is a feature to see at a glance the information available in all Knowledge Areas of *Integrity*. The Quick Search searches across the most relevant text-based fields in each Knowledge Area. It does not search across date fields or Y/N fields and it does not search fields that are not directly applicable to the Knowledge Area (i.e. does not search condition in Companies & Research Institutions because there is no condition field in a Companies & Research Institutions full record). Do not use hyphens or apostrophes in search terms; instead, use an asterisk as a substitute for one or more characters. An asterisk can also be used as a truncation indicator on either the left or the right.

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When entering a company code drug name, omit the hyphen: Ex: FK506.

WHAT ARE THE QUICK ACCESS LINKS?

These are links found on the *Integrity* home page or on the Knowledge Area pages that directly access specific information in the database. These include:

- **Today's News**: Links to the 5-10 most significant news items entered in the last 24 hours

- **Today's Featured Patents**: A link to a selection of fully analyzed patents entered in the last 24 hours

- **Conferences**: Links to selected references from recent conferences

- **The Starting Line**: A link to a table, updated weekly, of the most promising compounds entering preclinical development. These compounds are usually lead compounds or with new mechanisms of action that have been cited for the first time in Literature references

- **Pipeline on the Move**: A link to a table, updated weekly, of changes detected in the status of drugs currently under active development. Presented in database format, with access to previous weeks' data and the ability to sort and export information.

- **Gateways to Gene-related Studies**: A link to a list of new studies on targets that have entered in *Integrity* during the previous business week

- **Gateways to Patents**: A link to the list of the Featured Patents from the previous business week

- **Gateways to Clinical Trials**: A link to a table of new Clinical Studies references entered in *Integrity* during the previous business week

- **Gateways to Development Status**: A link to all compounds launched or under active development for a specific condition (either a broad group or one or more "subgroups" can be selected).

DATA MANAGEMENT

WHAT DISPLAY FORMATS ARE AVAILABLE FOR MY RESULTS?

The display formats available to choose from will depend on the Knowledge Area in which the results are found. Drugs & Biologics, for example, has Product List, Product List with structure, Full Records, Gateways to Development Status List,

and Milestones list while the Literature Knowledge Area has a References List and References with Associated Text List. From any Knowledge Area, open the Options menu to view the full selection of display formats and to select the display format of choice.

PRINTER FRIENDLY FORMAT

All Knowledge Areas and all display formats have the option to display the results in a Printer Friendly Format. For most Knowledge Areas, open the Options menu and select Printer Friendly Format. In Disease Briefings, click on the little printer icon on each page to be printed, or on the Print Full Document button at the bottom of the Disease Briefings Chapters menu on the left hand side of the screen.

CAN I SEE ALL RECORDS FOUND IN ALL KNOWLEDGE AREAS RELATED TO A PAGE OF RESULTS?

Almost all records in *Integrity* will have related records in other Knowledge Areas. Links to these related records are found at the bottom of the full records and following these links will take the user directly to the associated record in the other Knowledge Area. All Related Information via Quick Search found under the Options menu gives the user a summary of all of the Related Information links for all the results displayed. The user can see how many records are related to the original results in each Knowledge Area and can move to those records simply by clicking on the bar for the Knowledge Area of choice.

IS IT POSSIBLE TO EXPORT RECORDS?

Users can export records to Excel, MS Word, BizInt, SDFile and RDFile format via the Export Center. Each export operation exports a standard maximum of 100 records per batch (other restrictions may apply).

CAN CHEMICAL STRUCTURES BE EXPORTED?

Chemical structures can be exported from the Drugs & Biologics Knowledge Area in SDFile format for use in chemical structure database management programs such as CS ChemFinder™ and Symyx MDL ISIS™. They can be exported from the Patents and Experimental Pharmacology Knowledge Areas in RDFile format. Finally they can also be exported in MS Word and Excel formats as images.

CAN INFORMATION BE EXPORTED FROM MORE THAN ONE KNOWLEDGE AREA AT THE SAME TIME?

Selected reports that combine information from different Knowledge Areas are available, in Word Format, via *Integrity* Reports. There are currently 11 different types of Reports available in *Integrity*:

- **Product Report** – product information including recent updates, development status, milestones plus a table with the number of associated records in other Knowledge Areas for the compounds selected

- **Sales & Intellectual Property Report** – combined product, sales and patent information for the compounds selected

- **Chemistry Report** – product information and synthesis schemes for the compounds selected

- **Target Pipeline Report** – basic target information with a table of related products

- **Organic Synthesis Report** – synthesis schemes with end product, intermediate and reagent information

- **Experimental Pharmacology Report** – table of experimental pharmacology data combined with product information for the associated compounds

- **Pharmacokinetics Report** – table of PK data combined with product information for the associated compounds

- **Clinical Studies Report** – clinical trial information combined with product information for the associated compounds

- **Company Report** – company information plus a table with the number of associated records in other Knowledge Areas for the organizations selected

- **Literature Report** – full citation with related information from other Knowledge Areas (e.g., PK data, synthesis schemes) for the reference(s) selected

- **Patent Report with related information** – patent information combined with information from associated product, experimental pharmacology, organic synthesis, targets, genomics and/or biomarkers records for the patent(s) selected

ALERTS

WHAT ALERTS DO I HAVE IN INTEGRITY?

There are three types of alert: Saved Query, Keep Me Posted and Controlled Vocabulary. These Alerts can be managed using the **Query Manager / Alert Center**.

WHEN DO I USE A SAVED QUERY?

To track new results that would be included if a search with the same criteria was re-executed.

WHEN DO I USE KEEP ME POSTED?

To receive notification of updates to existing records.

WHAT IS CONTROLLED VOCABULARY TRACKING FOR?

To receive notification of new mechanisms, therapeutic groups, conditions and organizations appearing in the Browse Indexes

HOW CAN I USE MY SESSION HISTORY?

To retrace queries submitted and results obtained during the past 24 hours. This is very useful if a query was not initially saved, it can be saved from the Session History. Changes can also be made to the query using the edit button.

HOW DO I SET UP ALERTS?

Saved Query alerts can be set using the Options menu after running a search. It is possible to set up an alert even if the original query did not give results.

Keep Me Posted alerts can be set up from results pages, selecting records and using the option pull-down menu.

Controlled Vocabulary alerts are set up in the **Query Manager / Alert Center.**

HOW MANY QUERIES CAN BE SAVED AND ALERTS SET UP?

The Query Manager allows an unlimited number of queries to be saved, including queries that utilize structure searching. Saved Queries can also be set up as Alerts, where queries are run automatically and users notified when new results are obtained.

HOW DOES THE ALERT CENTER NOTIFY ME THAT NEW INFORMATION IS AVAILABLE IN INTEGRITY?

An e-mail message notifies users when new results are obtained. With a Saved Query and Keep Me Posted, users receive a message that identifies the

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query and contains two "Follow This Link" hyperlinks that take them directly to a page in *Integrity* where results are displayed. The first link takes them to only the new records, the second link re-executes the query and gives all results. With Controlled Vocabulary alerts, an e-mail arrives specifying the type of change (ex. Mechanism of Action) and a description of what has been added.

HOW OFTEN WILL I RECEIVE A MESSAGE FROM THE ALERT CENTER?

Users can establish Alerts to be run on a daily, weekly or monthly basis. Users are notified only when new information relevant to the Alert is added to *Integrity*.

CUSTOMER SUPPORT

HOW DO I CONTACT THOMSON REUTERS FOR TECHNICAL SUPPORT OR CONTENT QUESTIONS?

Send questions, comments and suggestions to *Integrity* Support by completing and sending the Help Request Form found under Support/Help or by e-mailing **integritysupport@prous.com**

HOW ARE MY QUESTIONS TO INTEGRITY SUPPORT DEALT WITH?

When an inquiry is received, it is assigned to a Help Desk staff member to resolve and answer. Most inquiries having to do with the database content or with how to accomplish a certain task are resolved directly by the Help Desk staff. For those cases where additional expertise is required, inquiries are referred to a member of the Content Department or the Engineering/IT Department. Such referrals are anonymous, and do not indicate who asked the question.

Many new features included in *Integrity* are developed in direct response to suggestions received from end users and users are therefore encouraged to send suggestions for enhancements to **integritysupport@prous.com**