Regulatory Intelligence 101

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Agenda

- What Regulatory Intelligence (RI) is and why it is important to companies
- The Divisions of RI and what each function provides
- Sources of RI
- Monitoring the ever changing regulatory landscape
- Transforming regulatory information into Intelligence

"An organization's ability to learn, and translate that learning into action rapidly, is the ultimate competitive advantage."

Jack Welch

"If Only HP Knew What HP Knows We Would be Three Times as Profitable"

Lew Platt
Former HP CEO

WHAT IS REGULATORY INTELLIGENCE

What is Regulatory Information?

- Can be oral, written, published, unpublished, etc.
- Basic building blocks of intelligence, the raw information

What is Intelligence?

- The capacity to acquire knowledge (facts)
- Experiences (life lessons)
- Ability to apply life lessons

Information vs. Intelligence

- Information is the raw data used to create intelligence; a data dump, no analysis
- Intelligence is active and related to analysis
- The data analysis and integration into company practice and procedures produces regulatory intelligence

What is Regulatory Intelligence

- Per the RING (Regulatory Intelligence Network Group) a DIA SIAC, RI is:

"The act of gathering and analyzing publicly available regulatory information. This includes communicating the implications of that information, and monitoring the current regulatory environment for opportunities to shape future regulations, guidance, policy, and legislation."

What is Regulatory Intelligence?

"Act of gathering and analyzing regulatory information and monitoring current regulatory climate …"

Regulatory Intelligence 101, M. Brown Tuttle

… and using this data to generate creative and innovative regulatory strategies designed to obtain and maintain product approvals in a timely and efficient manner.

What it is not…..

- Competitive intelligence (sometimes done by the regulatory department, more often done by the marketing department)
- Proprietary information
- Sales or marketing information
- Drug pricing or insurance information
- Reimbursement issues
- **Regulatory Information**

Why is Regulatory Intelligence Important?

- Provides the regulatory professional with information to:
  - Identify opportunities
    - Broader indications, precise pre-clinical /clinical development programs
    - Expedite development/increase efficiency
  - Identify possible pitfalls
    - Compliance issues, change in requirements for specific indication
  - Predict review times for product and/or change to product
  - Answer specific development questions poised by team

Benefits of Regulatory Intelligence

- Increased compliance
- Increase likelihood of marketing application approval
- Shorten time from filing to approval
- Increased efficiency
- Optimize study design for regulatory endpoints
- Optimize messaging about product benefit
- Maximize target market potential

What does RI Provide?

- Information for product teams (research)
- Supports executive strategy
- Comments on policy to shape legislation
- Track legislation
- Track approvals, non-approvals and withdrawals
- Knowledge management
- Training
- Creation of corporate policy

What does RI Provide?

- RI allows a regulatory professional to:
  - Create a strategy for a product
  - Create a development plan for a product
  - Research past precedence and adjust for current regulatory climate
  - Advise personnel
  - Write or construct a marketing application incorporating all Agency requirements
  - Adjust marketing application to ROW needs
- RI can be divided into Policy, Strategy and Operations; however there is some overlap….

RI Policy

This function of RI typically conducts the following activities:

- commenting
- government affairs
- trade group participation
- professional associations

RI Strategy

This function of RI typically conducts the following activities:

- regulatory strategy, development plan or therapeutic area analysis for a product
- guidance interpretation and application
- due diligence
- Citizen's Petitions
- participation or observation of Advisory Committee or other public meetings
- identifying regulatory trends and anticipating effect on company and products
- monitoring health authority organizational changes
- white papers or position statements

RI Operations

This function of RI typically conducts the following activities:

- regulatory research
- monitoring and surveillance of the regulatory landscape, including specific therapeutic areas
- drug approval summaries
- freedom of information (FOI) requests
- newsletters
- hot topics (analysis of regulatory trends)
- training
- Advisory Committee member or reviewer profiles
- knowledge management

POLICY

RI Policy

This function of RI typically conducts the following activities:

- commenting
- government affairs
- trade group participation
- professional associations

What is Regulatory Policy?

- A policy is a statement of intent and is implemented as a principle or protocol to guide decisions and achieve rational outcomes.
- Policy differs from rules or law; while law can compel or prohibit behaviors, policy merely guides actions toward those that are most likely to achieve a desired outcome such as to change or implement a law and in turn a regulation.

Regulatory Policy as a Regulatory Intelligence Function

- Regulatory policies are created by each company to align with company goals across multiple regions.
- These regulatory policies are then implemented through exerting influence on the legislative process and Health Authorities by the RI professional through a variety of methodologies.
- This position can be part of RI, legal or government affairs.
- As well this type of RI professional is proactive in influencing policy and shaping the landscape where as RI operations monitors the landscape looking for changes and reacting to them.

RI Policy

- This side of RI helps to guide and set policy with the FDA by influencing the policies made
- Companies that help set RI Policy usually have offices in Washington DC or surrounding areas
- Influence is outward, while RI Strategy and Operations is internally persuasive

Policy

Determine

- Why the agency takes the positions it does
  - Usually some function of serving the public health
- "Policy Intelligence" is understanding the shifting emphasis, so that the details and effects can be understood and predicted for optimal planning

RI Policy

- Coordinate across pharmaceutical businesses
- Speak with one voice to FDA and trade associations on regulatory policies
- Influence FDA policy
- Predict the future bases on trends, lobbying and proposed/pending legislation

STRATEGIC

RI Strategy

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What is Strategy

- The *Merriam-Webster Medical Dictionary (2002)* defines strategy as: an adaptation or complex of adaptations (as of behavior, metabolism, or structure) that serves or appears to serve an important function in achieving evolutionary success.

What is Regulatory Strategy

- Regulatory strategy could be seen as the adaptations a company makes to move its product from the development state to achieving marketing approval.
- Regulatory strategy incorporates the drug development plan, an outstanding issue or question, background information, regulations and/or guidance documents, strategic advice and recommendations on implementation.
- The definition all depends on the company you work for, their culture and needs and the backgrounds of the people who trained you

Strategy Further Defined

- Strategy can relate to:
  - Individual question as it pertains to development program or as regulations change
  - How handle a health agency interaction, meeting or information request
  - A review of the development plan (GAP analysis)
  - Drug/device development plan (US, EU or global)
- Suggest strategy relate holistically to the whole development program, so can prospectively find the landmines, not have them randomly explode
  - This means you have to consider CMC, Nonclinical, Clinical and Regulatory at all times and the impact they have on each other (think "Butterfly Effect")

Why Implement a Strategy

- "If you fail to plan then you plan to fail."
- Implementing a strategy allows a company to map your path forward and examine the pitfalls and mitigate any risks, challenges or issues that the product might face.
- In the long run, developing a strategy will save time and money and focus the development team.

Why Implement a Strategy

- Allow strategy to be dynamic and change as:
  - the company focus changes
  - The regulatory landscape shifts (new regulation or guidance document)
  - More is known about the compound and the indication chosen
    - Emerging nonclinical study results or Serious Adverse Events
    - Competitor/class of drug information emerges
- Update it as things change and view strategy as a process that grows and changes with the product

Why Document a Strategy?

- Strategies developed today are a snapshot of the current regulatory, scientific, and legislative environment.
- Importance of lifecycle management when new or revised laws/regulations, guidances or scientific data present themselves

What Does Strategy Encompass?

- Regulatory strategy incorporates a development plan or device plan, an issue, background information, regulations/ guidances/policies, strategic advice and recommendations on how to move forward.

OPERATIONS

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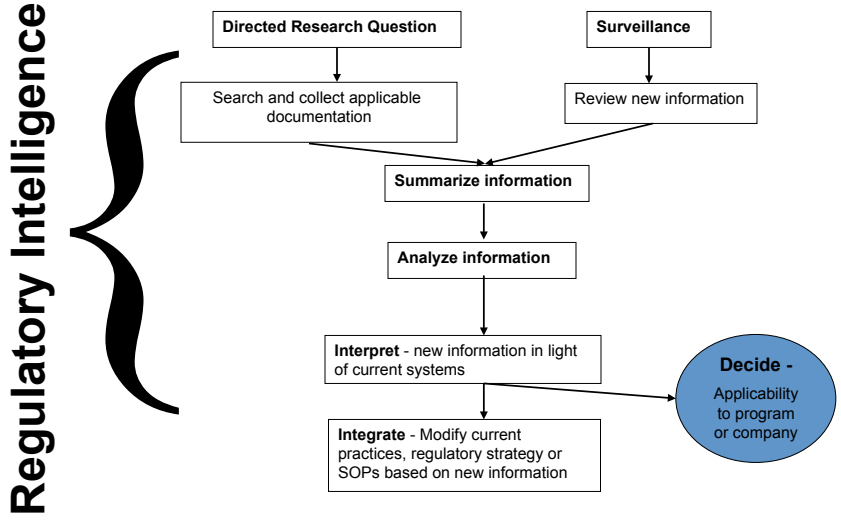
Regulatory Intelligence Overview



Regulatory Information

- Finding regulatory information is not usually found in one location
- You need to have numerous sleuthing techniques in your armamentarium to be able to address the scope and breadth of questions posed to you
- For each question put forth, there are numerous sources to begin your search or project

More than Regulations and Guidance Documents

- Regulations and guidance documents tell ½ the story.
- These sources describe the black and white story … most of regulatory is gray!
- Guidance may be waived
- There might be no guidance at all
- Interpretation of guidance varies with company and their experience

Sources of Regulatory Information (free)

- Common:
  - Regulations
  - Guidance Documents (preamble and comments)
  - Panel Meetings
  - Previous approvals
  - Previous submissions
- Less common
  - Global regulatory agency websites
  - Interactions with reviewers
  - Warning Letters/Untitled Letters
  - Interactions with other regulatory professionals
  - FDA presentations
  - Competitor information
  - FOI requests
  - Clinicaltrials.gov

Sources of Regulatory Information (free)

- Email alerts or RSS feeds from Health Authorities
- Regulatory reference and information sites (such as Regulatorium.com)
- Local chapter meetings of various organizations
- Colleagues
- Business intelligence websites
- FDA Advisory Committee meeting minutes
- Clinical trial registries

Please see "RI Tools I cannot live without: Top 5 free and for a fee" article on Regulatorium.com

Sources of Regulatory Information (fee)

- On-line professional and scientific article subscriptions
- Educational conferences
- Specialized regulatory intelligence software
- Clinical trial summary databases
- Business intelligence databases
- Books
- Consultants

Regulatory Intelligence Tools

One of the most important RI skills you can develop is……..

NETWORKING

Within your department, company, working groups and at trade/industry/professional association meetings.

REGULATORY INTELLIGENCE DATABASES

Regulatory Information Databases

- Provide worldwide regulatory information (over 75+ countries) for both drugs and devices
- Explanatory documents that guide you through a country's drug/device registration process
  - How to start a clinical trial
  - Maintenance of a clinical trial
  - Adverse Event Reporting
  - Scientific Advice
  - Orphan application
  - How to construct a marketing application
  - How to deal with variations or changes of marketed products

Regulatory Information Databases

- Use to compile, manage and archive information
- Global regulatory information available instantly
- Information frequently reviewed can be bookmarked for easy reference
- Documents can be printed for hard copy archival
- Provide daily or weekly updates (they provide surveillance and monitor the landscape for changes)

Regulatory Information Databases

- Country specific regulations provided in the local language (can translate for a fee)
- Key word or full text searches by country of choice
- Provide the ability to conduct focused research and surveillance, some summarizing and integration
- Information structured logically by subject matter
- Access to current, revoked and draft documentation/information

Regulatory Information Databases

- Some provide limited analysis of documents
- Still need to do analysis of information and impact to current program/product
- Downloadable forms – country specific
- Information is available in one place (no need to travel to multiple websites…unless you want to)

Example of Utility

- Conduct search on the web and utilized country-specific websites
- Then use an intelligence database, expert reports for "How to Initiate Clinical Trials" for each country
- What would normally take a week or more, took only a day …If you used the cross country tables this would take 5 minutes

Global Dossier Example

United Stated[1]	EU[1,2]	Japan[3]	Australia[4]	Canada[5]
Investigational New Drug Application (IND)	*Request for Clinical Trial Authorization*	*Clinical Trial Notification*	*Clinical Trials Exemption (CTX)*	*Clinical Trials Application (CTA)*
Food and Drug Administration	Competent Authority of Member State(s) where study is to be performed	Ministry of Health and Welfare	Therapeutic Goods Administration	Health Products and Food Branch
• Cover letter • Form 1571	• Cover letter • Application Form including unique EUDRACT database number	• Cover letter • CTN Forms No. 1 or 8	• Cover letter • CTX application form • Pharmaceutical datasheet	• Cover letter • Form HC/SC 3011 • CTA application form
Table of Contents	Checklist	Table of Contents	Table of Contents	Table of Contents
Introductory Statement and General Investigational Plan		• Justification for conducting trial • Summary of the Trial	Summary of Scientific Information	Protocol synopsis or Submission rationale
Reserved		• Sample Case Report Forms • Compensation • Financial Disclosure • Consent Form	• Consent Form • Plain language statement	• Consent form • List of proposed sites or Completed Clinical Trial Site Information
Investigator's Brochure	Investigator's Brochure	Investigator's Brochure	Investigator's Brochure	Investigator's Brochure
Phase I Clinical Protocol(s)	Protocol and all amendments	Protocol and all amendments	Protocol	Protocol
Chemistry, Manufacturing and Control Information (CMC) (Module 2/3)	*Investigational Medicinal Product Dossier(IMPD)* Containing: 1 Quality data (Module 2/3)	Method of Manufacture (similar to CMC requirements)	Chemistry, Manufacturing and Control Information	Chemistry, Manufacturing and Control Information (Module 2/3)
Pharmacology and Toxicology Information	2 Pharmacology and Toxicology Information	Pharmacology and Toxicology Information	Pharmacology and Toxicology	• Tabular listing of pre-clinical studies (Module 4) • Toxicology manifestations and impact in humans
Previous Human Experience with the Drug	3 Previous clinical trial and human experience data 4 Overall risk and benefit assessment	Clinical trial and previous experience data	• Clinical Trials experience (including adverse events) • Usage Guidelines	• Tabular listing of clinical studies (Module 2) • Observed adverse events and potential safety problems (module 2)
Additional Information	For marketed products the Summary of Product Characteristics can replace the IMPD	• CRO information • Institution(s) info • In-country caretaker • Entrusted person • Proposed investigators	• Information for Human Research Ethics Committee • Letter from investigator requesting review of the research proposal	• Pre-CTA consultation • EC refusal to approve protocol • Import information
Relevant Information				• Letters of Access

Regulatory Information Databases

www.tarius.com

www.idrac.com

www.mediregs.com

www.compliance-control.com

www.pharmapendium.com

Monitoring the Regulatory Landscape

SURVEILLANCE

Surveillance

- What is surveillance
- How to conduct surveillance
- When to conduct surveillance
- Outcomes of surveillance

What is Surveillance

Worldwide monitoring of regulatory information looking for changes in the in the regulatory landscape

How to Conduct Surveillance

- Employ a regulatory information database
- Monitor applicable regulatory websites
- Get daily e-mails from:
  - Regulatory websites
  - Commercial information provider websites
- Attend professional/advisory meetings
- Talk to colleagues and/or consultants

Surveillance Intervals

- Periodic surveillance
  - Conducted only when a question comes up
  - Available resources to do continual surveillance might be limited
  - Topics of interest might be missed depending on timeframes between surveillance
- On-going surveillance
  - Issues tend not to be missed
  - Can employ a database to conduct continual surveillance (can use key-word searches)

Surveillance Outcomes

- Impact on development program or approved products
  - Summarize new information - if applicable to program
  - Analyze for impact on current program/product
  - Provide information to team members information impacts or whole development/marketing team
  - Develop strategy based on new information
  - Implement strategy by integrating new information into development/product program or provide justification for not integrating information

Surveillance Outcomes

- No impact on current program or product
  - Keep in library for future reference
  - Do not store information (example a drug company does not summarize or analyze biologic specific information)

REGULATORY RESEARCH

Typical Topics for Research

- Clinical – IRB, Informed Consent, Indications, Pathways
- CMC/Quality Issues
- GXP Trends
- Advisory Committee Broadcast (US)
- Pending legislation

Hot Topics

Researching the Topic

- Need to understand from the research requester:
  - Question to be answered
  - Assumption or specifications about the product in question
  - Sources or location of potential information (start at Regulatorium.com)
  - Add these to appropriate section in research review template

TRANSFORMING INFORMATION INTO INTELLIGENCE

Researching the Topic

- Define your topic with key words or concepts such as:
  - transdermal patch validation batch
  - 505(b)(2) done to date for analgesics
  - How to file a 505(b)(2)
  - Will an application be a 505(b)(2) or 505(b)(1)
  - How to file Canadian CTA, INN Name, etc.
  - How many products received fast track, priority review and received orphan designation

Checklists

- Start all searches with a checklists
- Use different checklists for a different subject matter
- Develop checklists for all questions
- Checklist example is available on Regulatorium.com

Transforming Information into Intelligence

- Research topic and cull all pertinent information about your research topic from resources
- Read pertinent information about the research topic
- Write a summary of each piece of information once read
- Pull together all pieces of information and analyze how they fit and impact each other
- Write up your analysis and make recommendations

Transforming Information into Intelligence

- Once you have summarized the information, you will need to put it in a standard format to integrate the current position and recent information to deliver information to your target audience
- Target audience can be:
  - Regulatory department
  - Product team
  - General distribution to company as a whole
  - Management
  - Various departments

Let Audience Dictate Format

Team Level	Effective Intelligence Level
Management (VP or "C" Level)	Give a succinct overview keeping it to 3-5 slides with 3-5 bullet points and always let them know: • The problem • The impact to company (short term and long term; include fiscal impact) • Your proposed resolution to the problem and management buy-in Tip: Never go to management with a problem that you don't at least have a proposed solution for
Core Team/Product Development Team	Construct a presentation 5-20 slides in length giving: • Question • Background of why it is important to the team • High level summary (that is/can be presented to the "C" team because management will probably elevate it if needed) • Details of the development plan or question addressed • Conclusion • Impact to company • Proposed Solution and Discussion
Company Wide (on a SharePoint or IntraNet Site)	Just include the front page of the Regulatory Research or overview; support documents are available on request so that out-dated documents will not be used when the research is reviewed by members outside of regulatory
Department Specific Regulatory Research	Give a copy of the Regulatory Research format to the requestor; typically without all the backup but include a list of hyperlinked references. Typically regulatory wants synthesized information with all the back-up details available.
Regulatory	Use Regulatory Research format and make all back-up documents available

Transforming Information into Intelligence

- Subject: CMC, Clinical, Safety, non-clinical, etc.
- Regulations, directives, guidance documents, etc. affected
- Proposed or recently codified regulation/directive/ guidance document
- Explanation of how recent information will affect current practice and proposed changes (if any) to current practices to comply or be in-line with new information
- How will new information affect your target audience/team or strategy

REGULATORY STRATEGY	
Type: Drug/Device combination	**Drug:** Hydromorphone hydrochloride
	Device: Transdermal patch with electrical components
Indication: Management of chronic pain	**Claimed effect (proposed):** Management of moderate to severe chronic pain due to malignant conditions
Principal Mechanism of Action: Pharmacologic	
Question: *Will this drug/device be regulated as a drug or device or combination product in Canada?*	
SUMMARY	
Background and Definitions • Health Canada defines a combination product as "a therapeutic product that combines a drug component and a device component, such that the distinctive nature of the drug component and device component is integrated in a singular product." Within this definition, "drug" refers to both drug and biologic products. • Where the principal mechanism of action by which the claimed effect or purpose is achieved by **pharmacological**, immunological, or metabolic means, the combination product will be subject to the *Food and Drug Regulations*, unless that action occurs in vitro, without reintroducing a modified cellular substance to the patient, in which case the product will be subject to the *Medical Devices Regulations*.[1] • ***Pharmacological*** is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent and, for the purposes of this policy, includes anti-infective activity.[2] • The Combination Product policy does not apply to combinations of drugs and medical devices where the drug component and the device component can be used separately (e.g., products sold together in procedure packages and trays). The *Food and Drug Regulations* shall apply to the drug component of such a product and the *Medical Devices Regulations* shall apply to the device component.[2]	
Assumptions • Put in assumptions about drug and device	
Strategic Advice • The primary mechanism of action is due to the pharmacological means; therefore, in Canada, this will be regulated as a drug combination product and subject to the *Food and Drug Regulations*.	
Recommendation • Example: File a Clinical Trials Application for a drug	
References: 1 Drug and Medical Device Combination Product Decisions, June 7, 1999 2 Drug/Medical Device Combination Products, June 12, 1997, revised May 1999	
Signature:	Date:

Why Document Regulatory Intelligence

- Constructing or documenting a formal written analysis of the regulatory strategy for personal use or presentation to the team allows future reference to determine why a decision was made at a particular time in the development timeline.
- In addition, it can serve as the foundation document for any future updates and analysis, as needed for that topic.

RI OUTPUT/ DELIVERABLES

Structured RI Services

- Services often include:
  - News (newsletters or bulletins)
  - Commenting/Consultation Process
  - Search and Analysis
  - Building Strategies
  - Knowledge Management
  - Research/Answers to specific questions
  - FOI requests

News

- Discussion Topics:
  - Organizational changes within HA
  - Performance indicators
  - Draft and finalized policies, guidances, regulations
  - Product approvals
  - Product changes (CMC, new indications, safety)
  - Registration Procedures

Comments

- Coordination of the internal commenting process for draft guidances and regulations
  - Identify experts
  - Track the progress
  - Send in the response
  - Archive the data
  - Maintain repository
  - Does the final guidance include your comments?

Search and Analysis

- In-depth analysis upon request
- Provide trends
- Advisory Committee profiles (US)
- Division/Reviewer profiles (US)
- Freedom Of Information requests (US)
  - Approval packages
  - Inspection reports

Therapeutic Overview

- Looking for competitor/therapeutic information about:
  - Therapeutic area
  - Administration method
  - Clinical Endpoints
  - Status of competitive drug
  - Advisory committee meeting findings
  - Withdrawals, rejections or safety alerts (black box warnings)
  - Trade names/INNs

Knowledge Management

- Develop and maintain RI database
- Hot Topics Updates
- Internal regulatory workshops
- Conference participation
- Regulatory Library; Approvals, AC briefing packages, transcripts, videos, external course notes

Dissemination of RI Info

- Dissemination can take many forms, depending on the company, their culture and if a formal RI depart exists or not
  - E-mail
  - Presentations
  - Databases
  - Newsletters
  - Intranet
  - Lunch meetings (brown bag lunches)
- Needs to be timely!

Archiving and Filing

- Once you do the research, and distribute it, what do you do with it?
  - Keep it hard copy in the filing cabinet
  - Scan it and put it on an electronic shared drive
  - Scan it and include it in an RI database
- If a regulatory strategy or opinion that is stored, how do you insure it is accurate?
- How or where put it so that everyone can access it, if needed?

Acquiring and maintaining Regulatory Intelligence is the most important activity to a successful regulatory department!

Questions, Comments or Compliments:

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