Supporting Post-Approval Biopharmaceutical Changes Through Integrated Pharmacovigilance Activities

*Attaining the Full Value Proposition of ICH Q12*

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Assessing Product Attributes

Does your organization:

- Notify Pharmacovigilance When Major Change Controls are Adopted (Type II Variations)?
- Assess the Product Risk Management Plan (RMP) for Updates in Conjunction with a Change Control?
- Conduct Prospective *Clinical* Risk Assessments for Change Controls, Site Changes, Raw Materials?
Assessing Product Attributes

Does your organization:

• Have a Process in Place to Assess the Potential Efficacy and Safety Implications of Batch-related CQA Variability?
• Perform Batch-Specific AE/PC Surveillance?
• Have a Clinician on the Specification Committee?
Assessing Product Attributes

Four Key Elements:

1. Safety
2. Regulatory
3. Quality/cGMP
4. Brand
Product Safety Review Cycle

A Continuous Review Process at Relevant Decision Points Throughout the Product Lifecycle
Intrinsic sources of potential safety signals based on the manufacturing process and the molecule itself (e.g., impurities, related substances, variants, direct contact packaging materials, stoppers, plungers...)

Environmental sources of safety signals based on the manufacturing environment

"Design Space"
Embedded Medical Opinions in Design Space, Medical Risk Assessment of CQAs; FMEA, HAACP, etc

**Drug Product Safety Assessments**
Manufacturing Process and Safety Surveillance

There's a Hair in My Dirt!

Gary Larson

Creator of THE FAR SIDE
Manufacturing Process and Safety Surveillance

Historical Approach

Manufacturing Investigation

- Deviations
- Product Complaints

Ad Hoc

MEDICAL ASSESSMENT

Manufacturing & QA
Manufacturing Process and Safety Surveillance

QUALITY OVERSIGHT

Manufacturing Investigation

Clinical Relatedness Analysis
(MEDICAL ASSESSMENT REPORT)

Deviations

Product Complaints

Adverse Events

Manufacturing & QA

Product Safety Assessments

GPS/Pharmacovigilance

Medical Complaints
## Impact Ranking

<table>
<thead>
<tr>
<th>Impact Score</th>
<th>Biological Activity</th>
<th>PK</th>
<th>PD/Efficacy</th>
<th>Immunogenicity</th>
<th>Safety &amp; Tolerability</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (9)</td>
<td>&gt; 50 – 100% Change OR No data</td>
<td>Significant change in PK is linked to quality attribute OR Significant change in PK with no connection with quality attribute OR No change in PK detected but metabolism results in significant loss of PD linked to quality attribute OR...</td>
<td>Significant Impact on PD that appears to be attributed to specific quality attribute OR Significant change in PD with no clear link to specific quality attribute OR ....</td>
<td>ADA(^1) detected that appears to be linked to specific quality attribute and has a significant impact on PK/PD/Safety OR ADA detected that has no specific link to the quality attribute but has a significant impact on PK/PD/Safety OR No data available on ADA in relation to specific quality attribute OR...</td>
<td>No Data Available OR No margin of safety OR Cytokine Release Syndrome Grades 3-5 (see Appendix 1) OR....</td>
<td>Data suggests that the attribute affects the conduct/interpretation of the toxicology study (i.e. presence of aggregates). OR The test article has a less than typical margin of safety to clinical doses. OR...</td>
</tr>
</tbody>
</table>

Incorporates attribute’s *impact* to pharmacological properties and the *knowledge basis* used to determine the impact (i.e. uncertainty).
V.B.8.6.2. RMP (Risk Management Plan) module SVI

“Potential for transmission of infectious agents”

- The applicant/marketing authorization holder should discuss the potential for the transmission of an infectious agent. This may be because of the nature of the manufacturing process or the materials involved.

V.B.8.8.3. RMP module SVII

“Details of important identified and potential risks - Advanced therapy medicinal products (ATMPs)”

- The additional risks specific to ATMPs which should be considered for discussion include: *risks to patients related to quality characteristics of the product*, in particular:
  - biologically active substances used in manufacturing (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
  - quality assurance and characteristics of the finished product in terms of defined composition, stability, biological activity, and purity with reference to non-physiologic proteins and fragments thereof;
V.C.3. An RMP or an update, as applicable, may need to be submitted at any time during a product’s life-cycle, i.e. during both the pre- and post-authorization phases.

Article 8(3)(iaa) requires that for all new marketing applications: the risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned shall be submitted, together with a summary thereof.

- Situations, in addition, where a RMP or RMP update will normally be expected include:
  - with an application involving a significant change to an existing marketing authorization
  - new manufacturing process of a biotechnologically-derived product
Factors Impacting Safety Signal Detection

♦ The Drug Product
  • Properly manufactured compound and excipients
  • Related Substances

♦ The Patient
  • Genetic Polymorphisms; Absorption, Distribution & Metabolism Kinetics; Idiosyncratic Issues, etc

♦ Manufacturing Issues
  • Deviations; Process and Product-related Impurity Variability
  • Environmental Impact; Change Controls

♦ The Label and Product Administration
  • How to Administer & What to Watch For
  • Adsorption variability with Infusion sets

♦ Marketing & Promotional Items
  • Dosing Calculators; Travel Coolers

♦ Counterfeit, Substitution (Tampering) & Similares
  • Not Getting the Intended Product
# Discovery of Drug Induced Illness

<table>
<thead>
<tr>
<th>Rate of Suspected Drug Induced Illness</th>
<th>Background Rate</th>
<th>Method(s) of Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>Clinical Observation</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Not discoverable</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Clinical observation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited Formal research</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Formal research</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Formal research</td>
</tr>
</tbody>
</table>

Adapted from Jick H. NEJM. 296(9):481-5 (1977)
Raw Material Source Change

- As a result of the March 2011 earthquake and subsequent tsunami the Japanese fishing industry was unable to operate in their former fishing grounds off Honshu.
- To maintain a protamine supply the fishing grounds for wild Chum salmon were moved northward to Hokkaido Island.

Protamine is an arginine-rich, strongly basic naturally occurring nuclear protein used in insulin to form an insoluble protamine-insulin salt complex and as an antagonist used to reverse heparin’s anticoagulation effects.
The initial analysis of the R-Pro starting material from the new source identified a suspect new peak.

RP-HPLC review also identified the suspected new peak in the R-Pro starting material from the old source.
Suspect New Peak

Why is this important?
• Protamine sulfate can cause severe hypotension, cardiovascular collapse, noncardiogenic pulmonary edema, catastrophic pulmonary vasoconstriction, and pulmonary hypertension.
• Risk factors include high dose or overdose, rapid administration, previous administration of protamine, and current or previous use of protamine-containing drugs (NPH insulin, protamine zinc insulin, and certain beta-blockers), fish allergies, etc.

The Question Was…
• Could the peak represent an innate immune response modulating impurity?
• If so, might this impurity facilitate an enhanced immunogenic response to the protein or increase the potential for hypersensitivity reactions?
The suspected ‘new’ peak was identified in protamine sulfate from both the new source and old source, establishing that the peak was not ‘new.’

A comprehensive assessment of both Hokkaido and Honshu-sourced protamine confirmed the inherent variability characteristic of natural source materials and the historical presence of transient peaks.
Clinical Assessment

- Nine (9) Protamine Sulfate batches were selected from a ten year period with chromatograms showing some peak-profile variability.

- These 9 batches were used to produce a total of 329 insulin suspension drug product (DP) batches.

- The insulin DP batches were grouped as cohorts associated to a single protamine sulfate batch.

- These nine DP cohorts were assessed using disproportionality analyses to determine if any adverse event reports expressed more frequently within any cohort. [A to B; A to C; A to D etc. 45 datasets]

- No discernable differences in adverse event profiles.

- Currently executing on a Quarterly Surveillance Program comparing AE reports from Honshu and Hokkaido-sourced protamine
Automatic Signal Detection

MULTIPLE DATA MINING METHODS

- Proportional Reporting Ratio (PRR)
- Empirical Bayesian Geometric Mean (EBGM)
- Lower-bound of the EBGM’s 90% Confidence Interval (EB05).

## AE and PC Data Mining Outputs

Conditions of increased interest are prioritized in spreadsheet location to facilitate review.
First step: assess single source data over time to eliminate signal drift, changes in MedDRA hierarchy or stack-up from a series of ‘small’ process-related changes.
Surveillance Program Outputs

Concurrent Honshu Batches vs. Hokkaido Sourced Batches
Cases Created Between 01-Jan-2010 and 31-Jan-2016

<table>
<thead>
<tr>
<th></th>
<th>Concurrent Honshu</th>
<th>% Concurrent Honshu Events</th>
<th>Hokkaido Sourced</th>
<th>% Hokkaido Sourced Events</th>
<th>Ratio Concurrent Honshu % / Hokkaido Sourced %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events for All Protamine PT Terms (Used in Calculations)</td>
<td>5,603</td>
<td></td>
<td>7,227</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of Drug Effect PT’s Only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>841</td>
<td>15.01%</td>
<td>976</td>
<td>13.50%</td>
<td>1.11</td>
</tr>
<tr>
<td>Drug ineffective</td>
<td>306</td>
<td>5.58%</td>
<td>329</td>
<td>4.55%</td>
<td>1.20</td>
</tr>
<tr>
<td>Glycosylated haemoglobin increased</td>
<td>30</td>
<td>0.54%</td>
<td>53</td>
<td>0.73%</td>
<td>0.73</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>27</td>
<td>0.48%</td>
<td>57</td>
<td>0.79%</td>
<td>0.61</td>
</tr>
<tr>
<td>Drug effect decreased</td>
<td>17</td>
<td>0.30%</td>
<td>17</td>
<td>0.24%</td>
<td>1.29</td>
</tr>
<tr>
<td>Diabetes mellitus inadequately controlled</td>
<td>8</td>
<td>0.14%</td>
<td>15</td>
<td>0.25%</td>
<td>0.57</td>
</tr>
<tr>
<td>Poor quality drug administered</td>
<td>8</td>
<td>0.14%</td>
<td>1</td>
<td>0.01%</td>
<td>10.32</td>
</tr>
<tr>
<td>Drug effect incomplete</td>
<td>7</td>
<td>0.12%</td>
<td>3</td>
<td>0.04%</td>
<td>3.01</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>3</td>
<td>0.05%</td>
<td>5</td>
<td>0.07%</td>
<td>0.77</td>
</tr>
<tr>
<td>Therapeutic product ineffective</td>
<td>3</td>
<td>0.05%</td>
<td>1</td>
<td>0.01%</td>
<td>3.87</td>
</tr>
<tr>
<td>Drug effect delayed</td>
<td>2</td>
<td>0.04%</td>
<td>2</td>
<td>0.03%</td>
<td>1.29</td>
</tr>
<tr>
<td>Therapeutic response delayed</td>
<td>1</td>
<td>0.02%</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>0</td>
<td>-----</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Drug specific antibody present</td>
<td>0</td>
<td>-----</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Drug tolerance</td>
<td>0</td>
<td>-----</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Drug tolerance increased</td>
<td>0</td>
<td>-----</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>No therapeutic response</td>
<td>0</td>
<td>-----</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Therapeutic reaction time decreased</td>
<td>0</td>
<td>-----</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Therapeutic response decreased</td>
<td>0</td>
<td>-----</td>
<td>1</td>
<td>0.01%</td>
<td>-----</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>0</td>
<td>-----</td>
<td>0</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>All Terms for Lack of Drug Effect</td>
<td>1,253</td>
<td>22.36%</td>
<td>1,463</td>
<td>20.24%</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Then compare the previous material source with the current
Biosynthetic peptide was initially marketed in a prefilled pen injector with 3.0 mL cartridges.

A new presentation using a 2.4 mL cartridge was introduced. The only difference was the position of the plunger.

A trend was noted on the normal condition (2-8°C, 24 month shelf-life) stability studies for the 2.4 mL fill batches.

Atypically high results were observed at the 6-month time-point for the largest other individual related substance.
Molecule has two methionine residues

Extensive analytical and manufacturing investigations concluded that the atypical levels of Met O-18 oxidation occurred in both the 2.4 mL cartridges and the 3.0 mL cartridges produced within an identified date range.

All product produced prior to that date presented a typical analytic profile.

Met O-18 is a well characterized substance always present in low amount

Established TTC well above levels present
A process change at the disc seal vendor was felt to have resulted in weakening the clear lacquer coating on the seal.

Normal washing of the impacted seals produced low level lacquer (possibly with embedded aluminum) deposits on the laminate (product contact) surface.

No lacquer particles were observed during 100% inspection & batch release.

The lacquer/aluminum in the presence of the formulation causes accelerated oxidation of the peptide at Met 18 and to a much lesser extent at Met 8.
Surveillance Program Outputs

- Signals not identified through routine surveillance involving all batches
- Small number of reports but met pre-established signal threshold (PRR ≥ 2, n ≥ 5)
- By having dates and batches associated with the change control and stability data signal clarification and a relatedness assessment could be conducted.
Conclusion

♦ Integrating pharmacovigilance activities and clinician involvement through the product lifecycle provides tangible value

♦ Batch-to-batch surveillance of both product quality and adverse event complaints an important tool to monitor for unanticipated impact to product attributes

♦ Essential to institute processes to notify safety function of manufacturing-related changes
Thank You for Your Attention

Questions?