Raising awareness for Patient Safety in clinical trials and the commercial launch

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Purpose of my talk:

Objective: Raise the level of awareness for Drug Safety in the clinical setting from a mandated process to thoughtful consideration for the patient both during the study and when the drug or therapy is approved.

This is not an educational course for AE reporting, but this talk is meant to be a general discussion about drug safety and considerations from my experience for the clinical setting as well as early stages of the commercial launch

Agenda

- The Why
- The Consequences
- My Experience
- Strategic Considerations
- Clinical Operations
- Post-Approval
- ATMPs – a new Frontier
- To Do List
- APCER's Services

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The WHY – The PATIENT

- What are the risks of the drug alone?
- Can I combine it with other drugs?
- Can I overdose?
- What are the side effects?
- What happens if I take this drug for the rest of my life?

•What is the primary reason that I don't take my medication?

•A) Forget

•B) Cost

•C) Clinical Reason (side effect or inadequate response)

The How - Science

Products withdrawn due to Safety issues:

- Vioxx
- Lipobay
- Seroxat – safety was not a focus
- Intercept – Oclavia

•Why and what failed? Lessons learned.

•Safety today is a partner for product longevity- as much as efficacy and quality

•Focus on the essence and rationale of regulations

•New and advanced therapies- what do the regulators/ethics committees/patient groups want to see.

•Early safety strategy is essential and not just desirable

Stories from the trenches

- We didn't have any SAEs in our clinical trials so we won't have but one or two in the commercial setting, so…We think we can do it all in-house, we just want to have a back up
- We don't think there will be any SAEs so we will just have our CRO report the safety events
- We have a PDUFA date in 3 months, and we don't have a PV system in place yet. It just hasn't been a high priority. Do we have to have a safety database to launch our drug?
- We are a biosimilars company so we don't really have to worry much about Pharmacovigilance. What is signal detection? (same for generics)
- We don't think we should have to provide any aggregate reports to the FDA until we actually launch our product. Is there a problem that we haven't submitted anything for over a year?

Drug Safety Considerations for the C-suite:

•There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

•Donald Rumsfeld

Map out what you know

Be ready for what you know you don't know

What will you do when what you don't know happens?

Have a plan to map out the known unknowns

Thinking on the fly will be difficult

Think about your access to data you might need

Consider ongoing assessments and mock situations

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Drug Safety Considerations for Clinical Trial Managers:

- Protocol should enable safety learnings
- Prepare a safety management plan for each study
- Investigator Brochure
- Consider a Developmental RMP (dRMP)
- Crisis management plan (optional but recommended)
- Learn the possible long term safety issues
- Other considerations:
  - Collect AEs
  - Safety Data Assessments (during the study)
  - Continuous Benefit Risk Evaluation - every 6 months

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What about the Commercial Launch?

- Risk Management Plan (RMP) – Long Term plan to show that safety is not compromised
- RMP/REMS: Based on your Clinical Trials, how will you manage those key risks when your products gets into the market?
- Possible Answers – FOR SAFETY – Not just the commercial team
  - PAP
  - Patient – Doctor communications
  - Follow-up systems
  - Educational programs

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Specific Safety Challenges with Gene Therapies and/or Cellular Therapies

- Long term follow ups (5/15 years)
- Detailed case records from the investigator/prescriber corresponding to long term follow ups
- Unique potential risks associated with gene therapy *(e.g. autoimmune reactions, vector targeting wrong cells, contamination by replication-competent recombinants related to the parental pathogenic virus, insertional mutagenesis leading to cancer etc.)*
- Difficulty in causality assessment due to long latent period between gene therapy and associated side effects. Not all gene therapy products present the same risks of delayed adverse events. Product characteristics to be taken into account.
- Stringent overview by Regulatory authorities and ECs

The above points make it imperative that the safety team personnel involved have high level of expertise and there is medical oversight by an expert in the field……..

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Case Study – Clinical Trial

FDA halts Juno CAR-T trial after three patient deaths

by Stacy Lawrence | Jul 7, 2016 5:5

Investors spooked by Kite CAR-T death, but biotech remains confident

by Ben Adams | May 8, 2017 12:17pm

Deaths in both studies were caused by cerebral edema

Source for both articles: Fierce Biotech

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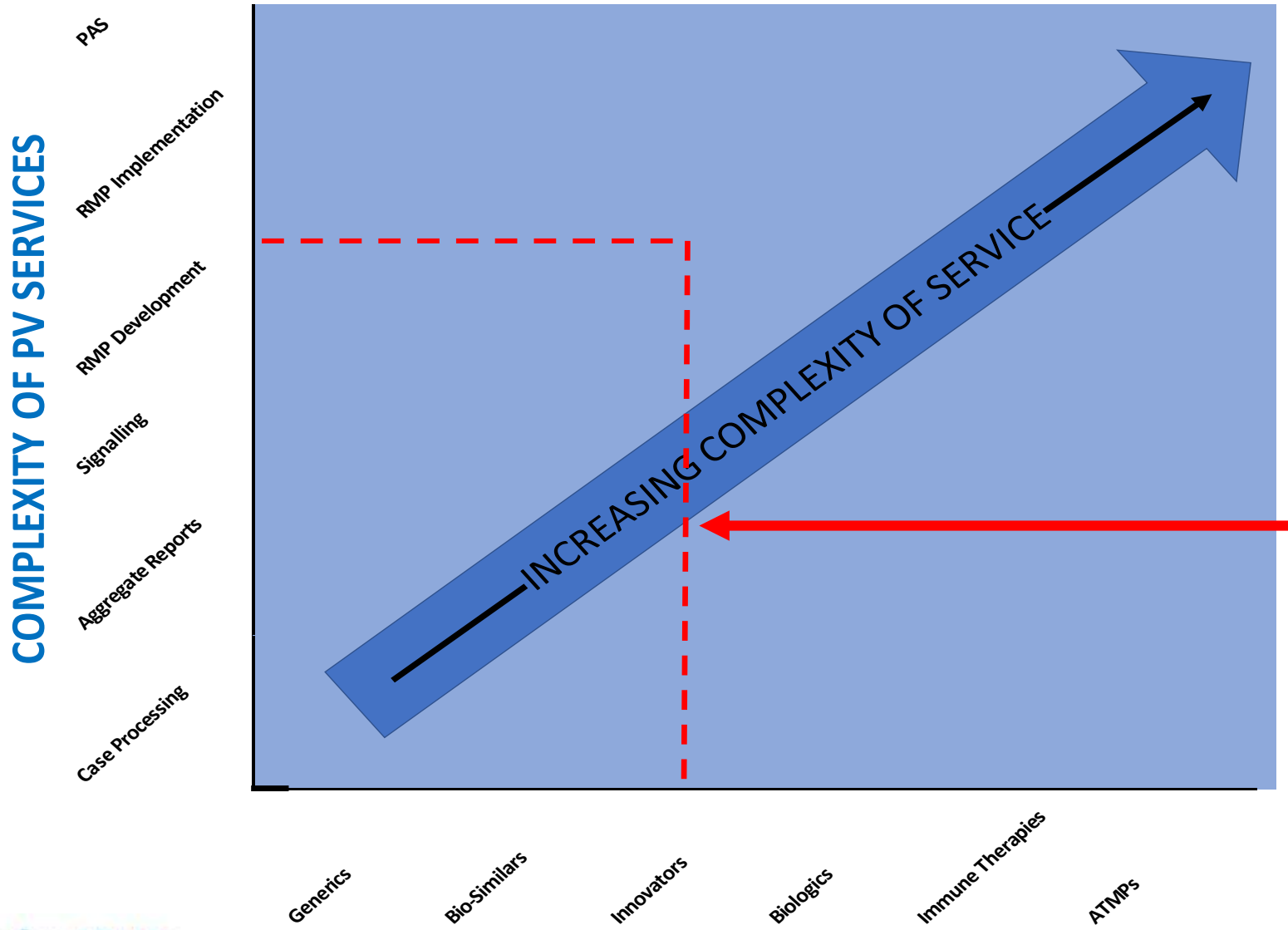
BUSINESS HORIZON



To Do list:

- Start as early as you can….”I wish we would’ve done this sooner”
- Perform a gap analysis for a compliant PV system. Your PV partner should be able to help with this, or hire a 3rd party consultant.
- For your PV RFP, you need to include volumes and timelines for commercial launch(es) and ongoing clinical trials. The PV budget is largely driven by volume of ICSRs. Input from the commercial team as well as your PV partner may help to project AE and SAE volume post-approval. Remember that AEs must be reported and scalability could matter if your AEs could be higher than expected.
- Migration cost estimate will require all different types of source data. Make sure migration costs are inclusive of the entire case with attachments as well as ensure you are in agreement on quality review. (100%).
- Get to know your provider. If you pick the wrong one, you will have a cost of change that could be significant.

About **APCER Life Sciences**

A partner with expertise

- 750+ full-time employees
- **100% of employees involved in PV Operations are HCPs**
- **More than 15% of physicians on staff**

…to deliver solutions

- More than 60 large/mid/small/biopharma clients
- History of long-term, expanding relationships

….globally

- Safety reporting into 100+ countries
- Medical Information coverage in 50+ countries in 30+ languages, scalable to 100+ languages
- Offices in Princeton, London, Hong Kong, New Delhi, Ahmedabad

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Therapeutic experience across product types

- INDs
- Brand
- Generics
- Biologics

- Cardiology/Vascular disease
- CNS - psychology and psychiatry
- Endocrinology
- Gastroenterology
- Gynecology
- Infectious diseases
- Nephrology
- Oncology
- Ophthalmology
- Orthopedics /Rheumatology
- Pediatrics
- Neurology
- Respiratory system
- Dermatology
- Hematology
- Migraine and Pain Management

- Vaccines
- Devices
- Diagnostics
- Advanced Therapies

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Services Portfolio

Pharmacovigilance

- Case Processing
- Literature Search
- Signal Detection
- Safety Reporting
- QPPV
- Risk Management

Medical Writing

- Clinical Writing
- Regulatory Writing
- Commercial Documents

Medical Information

- Integrated response center
- MSL Documents
- Medical Services

Regulatory

- Pre Approval Services
- Submissions
- Life Cycle Management

Quality

- Audits
- Training
- Inspection Readiness
- CAPA Management
- Consulting

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Thank You

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Common Terms and Acronyms:

Adverse Drug Reaction (ADR) and Serious (SADR)

Adverse Event (AE) and Serious Adverse Event (SAE)

Suspected Unexpected Serious Adverse Event Report(SUSAR)

Drug Safety Update Report (DSUR) – submitted annually after the IND has been accepted for unapproved products in the clinical stage

Periodic Safety Update Report (PSUR) – submitted periodically for approved products

PDUFA Date: **PDUFA Date** means the **date** identified in an official communication from the FDA as the target **date** by which the FDA expects to issue an action letter, as required under the Prescription Drug User Free Act of 1992 (P.L. 102-571), as amended and in effect from time to time.

Advanced Therapy Medicinal Products -ATMP

Somatic cell therapy medicinal product (SCTMP)	Tissue engineered product (TEP)	Gene therapy medicinal product (GTMP)	Combined ATMP
contain cells or tissues that have been manipulated to change their biological characteristics. They can be used to cure, diagnose or prevent diseases	contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue	contain genes that lead to a therapeutic, prophylactic or diagnostic effect Inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases.	contain one or more medical devices as an integral part of the medicine, i.e., cells embedded in a biodegradable matrix or scaffold