Unique Challenges and Opportunities in Conducting Pharmacovigilance for Rare Diseases and Orphan Drugs

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Rare Diseases, Orphan Drug, Orphan Drug Designation (ODD)

Regulatory Background - Differences Between the **FDA** and **EMA**:

- The **definition** of rare disease is different between the **FDA** and **EMA**.
  - In the **EU** it is a *rate*: of **5 in 10,000**.
    - Rationale: this can accommodate the changing population and number of member states in the EU.
  - In the **US** it is an *absolute number, and* to be 'rare' the condition must affect **fewer than 200,000 people** in the US
- In the **EU:** the disease has to be not only rare, but also **life-threatening** or **chronically debilitating**. In the **US**, the condition needs to be **rare** and the reason **why** the treatment is needed must be explained in the submission.
- The data required to support the use of the drug in the disease:
  - **EU: EMA** requires data to support the use of the drug in the disease. It is not enough to have a hypothesis for the effect; data, preclinical or clinical, needs to be provided.
  - **US:** the sponsor must append a **discussion on the rationale for the use** of the medicinal product for the rare disease or condition, and whilst all relevant supporting information from non-clinical or clinical studies must be submitted, they are not necessarily required.
- The EMA requires details of whether there are **other methods for treatment available in the EU or not.** Sponsors need to search for all the possible approved treatments in the ODD indication and be aware if there may be an old approved drug in some EU member states. This is **not required for US applicants**.

The Impact of Rare Disease: The Staggering Statistics

AGILITY CLINICAL

More than 350 million people worldwide suffer from rare diseases

Effective treatments are available for only 1% of rare diseases

1/3 of children born with a rare disease are unlikely to see their 5th birthday

Nearly 7,000 rare diseases are recognized

80% of rare diseases are genetic in origin

50% of rare diseases impact children

Only 5% of RD have FDA-approved medicines in US

50% of those with a rare disease spend 3+ years looking for diagnosis and treatment

Sources: “Rare Diseases: Facts and Statistics”. Global Genes. September 2015
“National Organization for Rare Disorders” (NORD); “Every Life foundation”

The Impact of Rare Disease

While at an individual level rare diseases affect very few patients, the collective impact is staggering:

- Globally, the list of rare diseases has grown to approximately 7,000, and 350 million people are living with a rare disease.
- These diseases are serious, progressive, often life-threatening, and have high mortality
- Approximately 50% of those affected are children. ~80% are genetic and majority die before their 5th birthday
- The long time-to-diagnosis (3 + years) and the lack of available treatments (only 5% have approved treatments) leave patients and their families searching for new options and new hope.
- Although Regulatory incentives (such as the Orphan Products Designation and the availability of Pediatric Rare Disease Priority Review Vouchers) have increased the biopharma companies' interest in rare disease research, with each potential new therapy the companies are charting new territories through clinical development, with limited disease knowledge, complex regulatory pathways, few suitable patients, and unknown obstacles ahead.

Sources: "Global Genes"; "National Organization for Rare Disorders" (NORD); "Every Life Foundation"; FDA Rare Disease Program

Regulatory Background - Rare Diseases

USA:

- US Definition of rare disease: the condition affects fewer than 200,000 people in the US
- The Orphan Drug Act 1983
  - Prompted by patient advocacy, the ODA established policy that federal government would assist in product development for rare disease/condition diagnosis, prevention, or treatment
  - FDA's office of Orphan Products Development
- CDER's Rare Disease Program
  - Established February 2010
  - Facilitates and supports the research, development, regulation, and approval of drug and biologic products for the treatment of rare disorders
- FDA Draft Guidance for Industry: *"Rare Diseases: Common Issues in Drug Development - August 2015"*

Regulatory Background - Rare Diseases

European Union (EU):

- Definition of **Orphan Medicinal Product, Rare Disease, and Orphan Designation**
  - Is laid down in Regulation (EC) No 141/2000 of the EU Parliament and of the Council of 16 December 1999 (EC/141/2000)
  - Article 3 summarizes the criteria which a medicine has to fulfill to receive an orphan drug designation in the EU.
  - *"A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:*
    - *a) that it is intended for the diagnosis, prevention or treatment of a life threatening or chronically debilitating condition affecting not more than **5 in 10 thousand persons** in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life threatening, seriously debilitating, or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;* and
    - *b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition."*
    - In both cases, there must also be either no satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorised, or, if such a method does exists, the medicine must be of significant benefit to those affected by the condition.
  - **Committee for Orphan Medicinal Products (COMP)**
    - Responsible for reviewing applications for orphan designation for medicines that are intended for the diagnosis, prevention or treatment of rare diseases.
  - According to the definition above, the number is equivalent to around **250,000 people or less** for each disease. About **30 million people** living in the European Union (EU) suffer from a rare disease.
  - The EU's **Seventh Framework Programme for Research and Technological Development** (FP7): ran between 2007 and 2013, boosting research into rare diseases. Its first phase focused on innovative and multidisciplinary projects investigating non-infectious, non-cancer rare diseases.

Rare Diseases at a Glance

- On average, five new diseases are described every week in the medical literature.
- Symptoms of some rare diseases may appear at birth or in childhood, including spinal muscular atrophy, lysosomal storage disorders, patent ductus arteriosus (PDA), familial adenomatous polyposis (FAP) and cystic fibrosis. More than half of rare diseases appear during adulthood, such as renal-cell carcinoma, glioma and acute myeloid leukaemia
- 80% of rare diseases have identified genetic origins, and affect between 3% and 4% of births. Other rare diseases are due to degenerative and proliferative causes.
- Medical and scientific knowledge about rare diseases is lacking. The number of scientific publications about rare diseases continues to increase, particularly those identifying new syndromes. However, fewer than 1,000 diseases benefit from even minimal amounts of scientific knowledge. These tend to be the rare diseases that occur most frequently.

Source: EMA - Medicines for rare diseases

The Rare Disease Patient's Journey



Clinical Manifestations

Severe / Life-threatening

Challenges in getting to the right doctor

Challenges in getting the right diagnostic (experience with condition, genomic testing availability)

Availability of treatment, funding, time to access



Limited physician knowledge of the signs & symptoms of a rare disease



Rare diseases often hide behind the symptoms of other diseases. Up to 3 ½ yrs time-to-diagnosis.



Only 5% of rare diseases have FDA-approved medicines in US

Conducting Clinical Trials for Rare Diseases and Orphan Drugs: ***The Challenges***



Sources: “National Organization for Rare Disorders” (NORD); “Nature Inside View”; “Rare Diseases: Facts and Statistics”. Global Genes. September 2015

Drug Development **Challenges**

- Limited knowledge about rare conditions, including:
  - disease mechanisms
  - clinical progression
  - potential biomarkers
- Within a disease, there can be many subtypes with different clinical manifestations and progression. They depend on the genotype-phenotype, genetic transmission of disease (dominant/recessive), as well as other factors
- Logistically complex trials:
  - Patient populations are small and geographically dispersed, making site selection and patient recruitment challenging.
  - Patients may need to travel long distances to reach trial sites, making long-term trial engagement difficult from the patient perspective.
- Given these small patient populations, every patient and data point is critically important to the study outcome.
- Safety data difficult to assess and quantify; post-marketing surveillance more commonly requested by regulators for rare diseases (limited disease knowledge, natural history incompletely understood, small numbers of patients and hence AEs)

… and the Opportunities

- Natural history studies and disease registries are often needed *in advance of trials* to understand the natural progression of disease, the patient subpopulations, pathophysiology, and the background incidences
- Patient-centric protocol design: carefully designed trial protocols; look at different endpoints to satisfy regulators and payers, while still being “meaningful” to patients; clinical outcomes assessment
- Biomarker ID and validation support
- Engage Key Opinion Leaders, well recognized in their field, Academic Institutions, National Institutes of Health, and Patient Advocacy Groups
- Patient retention and close monitoring of key data points are very important; home nurses for geographically dispersed patients
- **Innovative methods of safety assessment and signal detection**
  - Natural history studies and disease registries can establish a “baseline” or “background incidence” that can then be compared against the emerging safety data
  - Use graphical display of safety data and patient profiles for individualized review of safety data
  - Analysis of similar events (AOSE) can be used for trending the available data
  - Real-world evidence: post-marketing commitments

Drug Safety Aspects in Rare Diseases

Clinical Development Program:

- The safety evaluation during drug development is intended to characterize and quantify the safety profile of a drug:
  - Timing and magnitude of occurrence of adverse events over a reasonable duration of drug exposure, in an adequate number of patients
- Drug safety and rare diseases:
  - Size of the safety database:
    - Drugs for rare diseases have smaller trial safety population size than those for common diseases, however
    - Rare disease safety database represents a larger proportion of the population with the disease
    - As a result, innovative methodologies need to be developed for safety surveillance of rare diseases
- Assessing safety in small trials of rare diseases
  - Number of patients?
  - Duration of exposure?
  - Should safety assessment focus on the highest dose or the effective dose(s)?
- Risk tolerance (in light of benefit) – what types and/or how much risk might patients and providers be willing to tolerate?

Source: FDA Public Workshop on Complex Issues in Rare Disease Drug Development

Drug Safety Aspects in Rare Diseases

Postmarketing – US perspective

- Postmarketing requirements (PMRs) for studies/trials
  - Approximately 75% of the rare indication drugs have a PMR related to a specific safety issue
  - Of these 9 have a product exposure safety registry ~ one-third of the approved rare disease drugs
- Risk evaluation and mitigation strategies (REMS):
  - Since January 2010, REMS with ETASU (restricted distribution) were approved for 5 rare disease drugs vs. 0 approved for common indication drugs
- Opportunities:
  - Pharmacovigilance strategies
  - Use of patient registries
  - Use of REMS with ETASU (restricted distribution)

Source: FDA Public Workshop on Complex Issues in Rare Disease Drug Development

Safety Assessment for Rare Diseases Learnings from the FDA Guidance for Industry

FDA addresses clinical safety in the “Evidence of Effectiveness and Safety” section.

- Assessment of the safety of the drug should use “**all tests reasonably applicable**” to establish safety for its intended use.
- Clinical trials should include a **monitoring plan** adequate to ensure the safety of clinical trial patients. The elements and procedures of the monitoring plan should be based upon what is known about the drug, including nonclinical toxicology and chemistry, manufacturing, and controls (CMC) information, and, if available, previous human experience.
- There is “**no specific minimum number of patients that should be studied”** to establish effectiveness and safety of a treatment for any rare disease. The number of patients to establish effectiveness and safety is determined on a **case-by-case basis**…
- When conducting a **benefit-risk assessment** for a drug or a **serious or life-threatening illness**, FDA also recognizes that “**greater risks may be accepted for a treatment that is an advantage over available therapy”**. This reflects FDA’s commitment to expediting the availability of **drugs for serious diseases** as soon as it can be concluded that the benefits of the drugs exceed their risks, while preserving appropriate standards for safety and effectiveness, especially when these patients have unmet needs, as is often the case with patients with rare diseases.
- The safety profile may “not be well known” and “greater risks may be accepted.”

Research in Pediatric Populations

- Children, by virtue of their decreased autonomy and still-developing cognition, are considered to be a vulnerable research population needing special protections.

- Cancer may have markedly different pathophysiology, severity and response to treatment in children compared to adults. Historical evidence shows that extrapolation of treatment from adult data can dictate incorrect dosing and in some cases result in severe adverse events in children.

- The variable drug sensitivities of the developing body and brain drive the need to develop therapies specifically tailored to pediatric physiology.

- Specific guidelines for the ethical conduct of drug studies in a pediatric population have been developed over the last decades through collaborative work between the FDA and the AAP. In 1977 the AAP Committee on Drugs issued a report foreshadowing the principles of beneficence, justice and respect for persons that would be published in the Belmont Report the following year.

- ***Federal regulations codifying the protection of children as research subjects*** quickly followed the 1977 AAP report. These regulations, titled “Additional Safeguards (FDA) /Protections (DHHS) for Children Involved as Subjects in Research”, are referred to as **Subpart D**, and are found at 21 CFR 50 (FDA) and 45 CFR 46 (DHHS).

Federal Regulations in the US Designed to Protect Children in Research - Subpart D categories:

- **21 CFR 50.51 (45 CFR 46.404):**
  - **Clinical investigations not involving greater than minimal risk**
    - (a) no greater than minimal risk to the child is presented

- **21 CFR 50. 52 (45 CFR 46.405)**
  - **Clinical investigations involving > than minimal risk but presenting the prospect of direct benefit to individual subjects.**
    - (a) the risk is justified by the anticipated benefit to the subjects
    - (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches

- **21 CFR 50.53 (45 CFR 46. 406)**
  - **Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.**
    - (a) The risk represents a minor increase over minimal risk
      - The regulations define children as "persons who have not attained the legal age for consent to treatments or procedures involved in the clinical investigations, under the applicable law of the jurisdiction in which the clinical investigations will be conducted."
      - The legal age of consent is 18 years old in most states except a few
      - (a) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations
      - (b) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition

- **21 CFR 50.54 (45 CFR 46.407)**
  - **Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.**
    - (a) The investigation presents an opportunity to further understand, prevent or alleviate a serious problem affecting children
    - (b) The FDA in consultation with a panel of experts determine that
      - 1. The conditions of 50.51, 50.52, or 50.53 are satisfied or
      - 2. The following conditions are met: i. (a) above and ii. the investigation will be conducted according to sound ethical principles.

Pharmacovigilance in Pediatric Patient Populations

Here are a few issues that complicate safe medication use in paediatric care, as well as current progress, and provide suggestions for building knowledge within paediatric pharmacovigilance to be used to minimise patient harm.

Intrinsic to the Drug

Children (esp. the youngest) are often excluded from premarketing clinical trials unless the medicine is specifically developed for this population, limiting access to age specific information on dose recommendations, efficacy and risks. Necessary therapy cannot be withheld from children, and medicines are therefore used despite a lack of documented regulatory support. In a recent review of paediatric studies, off-label use ranged between 18 and 65 % of prescriptions in hospital and between 11and 31% in primary care.

The higher proportion of off-label use is found in neonatal hospital care. Off-label/unlicensed use in paediatrics probably increases the risk of ADRs. Given the widespread routine off-label use of some medicines in children, there is still uncertainty around their safe and effective use in routine clinical practice.

If the medicine has been primarily manufactured to be used in adults, child age-suitable formulations might be lacking

Intrinsic to the Child

The continuously developing child puts high demands on healthcare personnel to **adjust doses** and **dose intervals** and **select suitable formulations** for the individual child to achieve optimal benefit and minimal risk. Children are not only **different from adults** but differ vastly within their own age group. A premature infant can weigh 0.5 kg and a teenager more than 100 kg. **Physical growth** during childhood is apparent to the eye but less obvious is the **ongoing maturation of organ function** important for **drug absorption, distribution, metabolism and excretion.**

Young infants have **fewer drug-binding proteins** and **reduced affinity of proteins,** which will affect the **volume of distribution** of medicines as will **changes in the muscle-to-fat ratio.**

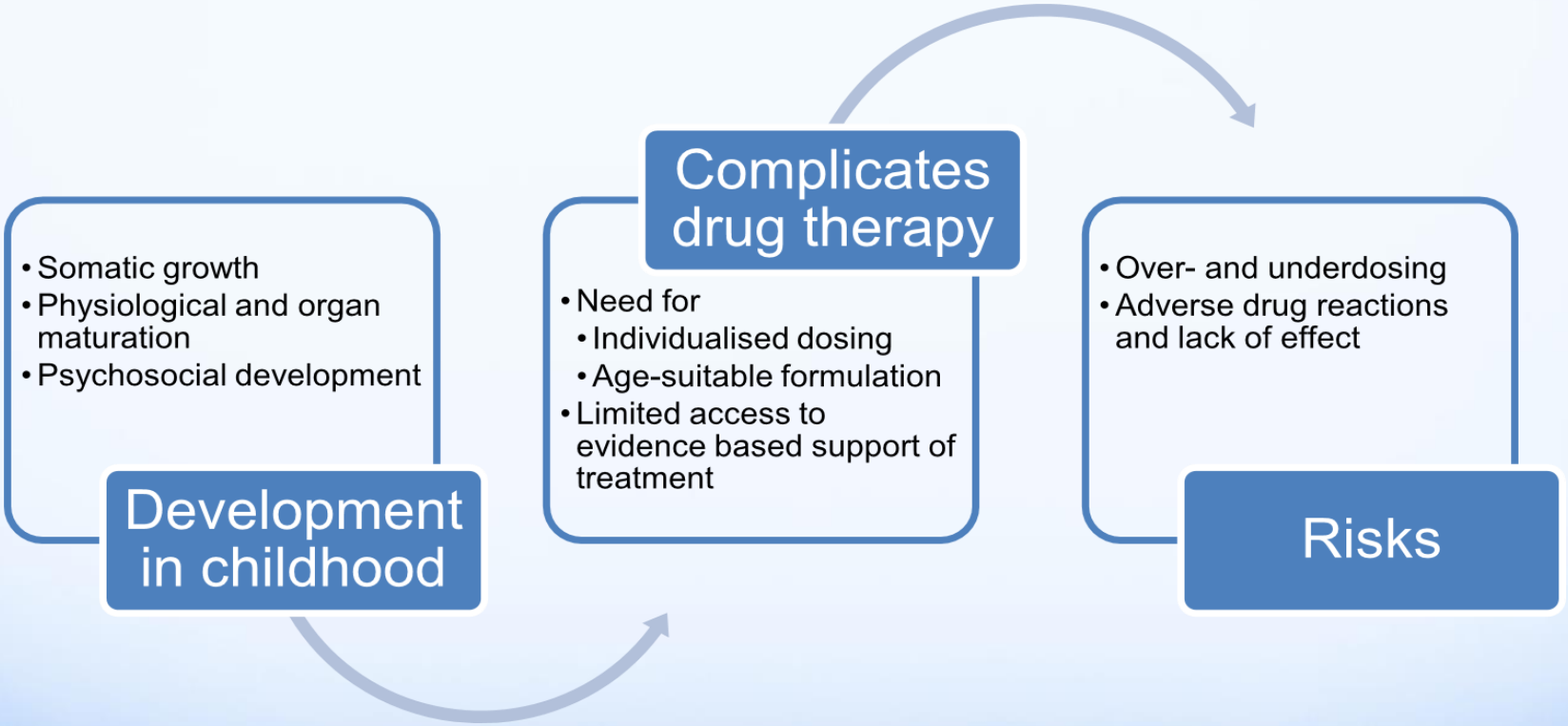
The **hepatic metabolising enzyme activity** is **low in premature infants** and neonates resulting in a **prolonged half-life of some medicines.** Chloramphenicol, for example, can cause “grey baby syndrome” with cardiovascular collapse in newborn infants unless given lower doses of this medicine.

At birth, the activity of the **hepatic metabolising enzymes** begins to increase over time to exceed adult activity in toddlers and older children. The increase in plasma clearance can result in a **reduced therapeutic effect of medicines metabolised in the liver unless dose and dose intervals are adjusted.**

Renal function is **not fully mature until the first year of life**, which needs to be considered when using medicines eliminated via the kidneys.

Source: Pharmacovigilance for Children’s Sake. Kristina Star , I. Ralph Edwards. Drug Safety. February 2014, Volume 37, Issue 2, pp 91-98

Factors that influence medicines and medication safety during childhood



Source: ***Pharmacovigilance for Children's Sake.*** Kristina Star, I. Ralph Edwards. Springer International Publishing Switzerland 2014; Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Box 1051, S-751 40 Uppsala, Sweden

Expediting Rare Diseases Drug Development

- **Fast Track Designation**
  - FDAMA 1997/FDASIA 2012
- **Breakthrough Designation**
  - FD&C Act/FDASIA 2012
- **Priority Review**
  - PDUFA 1992
- **Accelerated Approval**
  - 21CFR314 subpart H, 601 subpart E/FDASIA 2012

Source: FDA Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014

Biomarker Qualification Program - A Drug Development Tool (DDT) Qualification Program

- Provides a framework for scientific development and regulatory acceptance of biomarkers for use in drug development
- Facilitates integration of qualified biomarkers in the regulatory review process
- Encourages the identification of new and emerging biomarkers for evaluation and utilization in regulatory decision-making
- Supports outreach to relevant external stakeholders to foster biomarker development

Source: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm
And Rare Diseases Program/OND/CDER/FDA

Ongoing Safety Assessment

- Objective: show a favorable benefit-risk profile throughout product lifecycle, pre-clinical, premarketing and post-marketing
- In order to do this: identify and confirm/refute safety signals on an ongoing basis
- In the early 2000's: paradigm shift from showing medical products to be "safe and efficacious" → to showing a "**favorable benefit-risk profile**"
- Signal versus Risk
  - A new signal doesn't mean there is a new risk, but that further review and evaluation is required to make these determinations
  - Safety analysis is aimed at making this determination by reviewing all data available

Challenges in Premarketing Signal Identification – Rare Diseases

- Limited exposure
  - Too few patients exposed
  - Limited duration of exposure
  - Study population unlikely to represent the "real world"
- How Many Patients Are Needed to Observe an AE – "The Rule of 3"

Incidence	Exposure
1% (1/100)	300 patients
0.1% (1/1,000)	3,000 patients
0.01% (1/10,000)	30,000 patients

Opportunities for Identification of Premarketing Signals

- Learnings from the natural history studies and disease registries
- Paying attention to preclinical data; add the toxicologist to your safety assessment committee
- Monitoring plan: prospective safety analysis: safety analysis plan; includes review of both AEs and SAEs for trends across the clinical continuum
- SUSARs and Analysis of Similar Events (AOSE): best method of signal detection during clinical trials
- Ongoing safety review by a Signaling Committee
- Graphical display of safety information and patient profiles
- Development Safety Update Report (DSUR) – an opportunity for thought and analysis
- Reference Safety Information Section in the IB – annual updates

Learnings from the Natural History Studies and Disease Registries

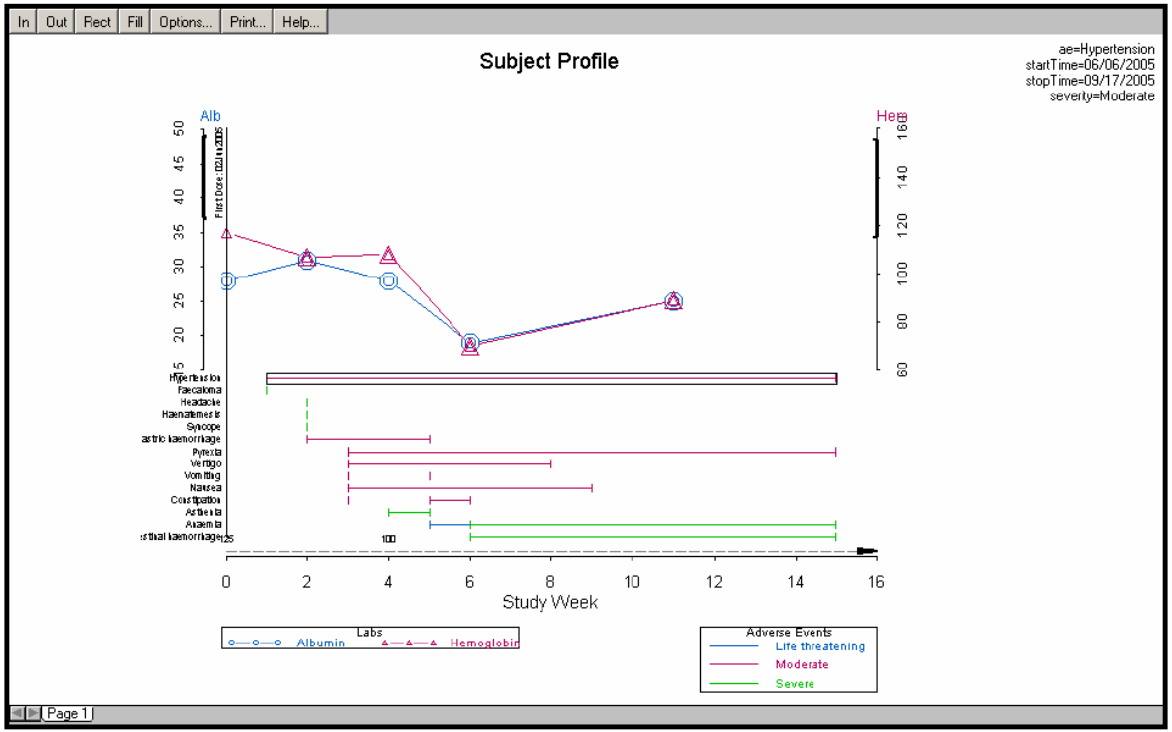
- "Natural history" is the scientific term to describe how a disease would progress with no treatment.
- Since a disease can affect different people differently, scientists must study many cases of a disease to acquire a thorough understanding of its natural history. Well conducted studies of natural history can yield vital information about:
  - Biomarkers, demographic, genetic, and environmental variables that correlate with the course and stages of the disease;
  - Identification of patient subpopulations with different characteristics and effects of the disease;
  - Patient perspectives on what aspects of disease are most important to treat; and,
  - How to quantify those aspects so that they can serve as useful outcome measures for clinical trials.
- In the case of rare diseases, their natural histories frequently are not fully understood because there are simply not enough cases that have been observed and studied. This lack of knowledge limits researchers' ability to study rare diseases and develop new treatments.
- Knowledge of natural history is essential for developing more efficient clinical trial designs. It also could help reduce the length and cost of drug development and, possibly, contribute toward greater predictability of clinical development programs.
- Case Study shared by FDA's Janet Woodcock MD in the FDA blog "FDA Voice" – 2013: http://blogs.fda.gov/fdavoice/index.php/tag/rarediseases/
  - Recently The National Organization for Rare Diseases (NORD), has teamed up with the patient advocacy group that represents people with the rare disease known as Von Hippel Lindau disease. This is a condition with many debilitating symptoms that also predisposes individuals to benign and malignant tumors. The Von Hippel Lindau Alliance and NORD have created an online tool that enables people with this rare disease to enter information about their experiences with the disease, such as the progression of symptoms, and to add to this information at intervals throughout their lives. This tool is now helping researchers compile valuable data about the natural history of Von Hippel Lindau disease. The even better news is that this tool is universal. If it can be used effectively to help researchers better understand Von Hippel Lindau disease, it can do the same for other rare diseases as well! This online tool was developed with direct input from patients, as well as patient organizations, researchers, FDA, and other international drug regulatory agencies.
  - The natural history tool has important features such as these: It protects the security and privacy of personal information, while making valuable information available to a researcher or drug developer interested in creating a new therapy for a rare disease; It can be used by patients or health care professionals; It helps make sure that text and online tools data are accurate.

Analysis of Similar Events (AOSE)

- According to US regulation 21 CFR 312.32:
  - "In each IND safety report (expedited report-premarketing), the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information"
- AOSE is an opportunity for the sponsor to assess the potentially clinically important data in real time with every SUSAR submission
- Use all available safety data: AEs and SAEs
- Complete case information and quality of narratives
- Establish search criteria: PT, SMQ, medical concept
- Estimate exposure and perform a literature search ***if necessary*** to understand background rate of the "event of interest"

Graphical Display of Safety Information and Patient Profiles

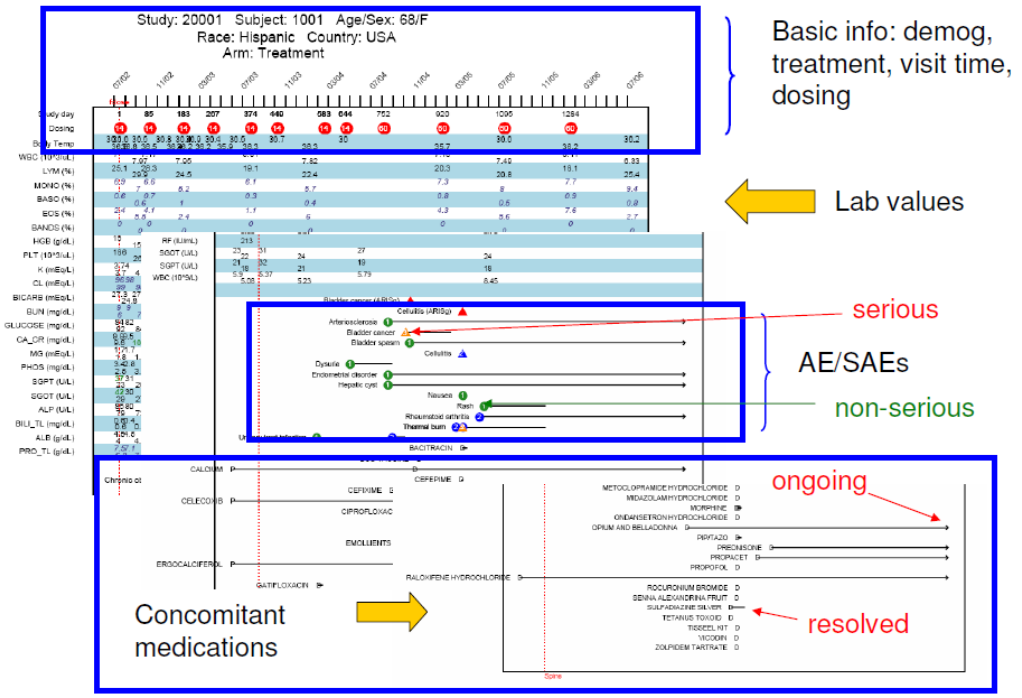
- Patient Profile
  - Simultaneous display of large amount of relevant information of a subject: medical history, con meds, (serious) adverse events, laboratory data, demographics, visit time, therapy, dosing etc.
  - Efficiently establish safety profile of a subject
  - Easier to see drug effect, drug/drug interaction, connections between lab test and adverse events, etc.



Source: Graphical Analyses of Clinical Trial Safety Data
Haijun Ma, Kefei Zhou, Amy Xia, Matt Austin, George Li, Michael O'Connell
GBE Scientific Forum, 2007

Graphical Display of Safety Information and Patient Profiles

- Graphics are powerful in concisely and efficiently conveying multiple pieces of safety information
- Different symbols/colors to distinguish severity, seriousness
- Line versus arrow to indicate whether AE/conMed resolved or not
- Lab values: grade 0-5 CTCAE: color coded (one color per grade)
- Standardized statistical graphical language across industry and regulatory



CTDB AE/SAE Records:

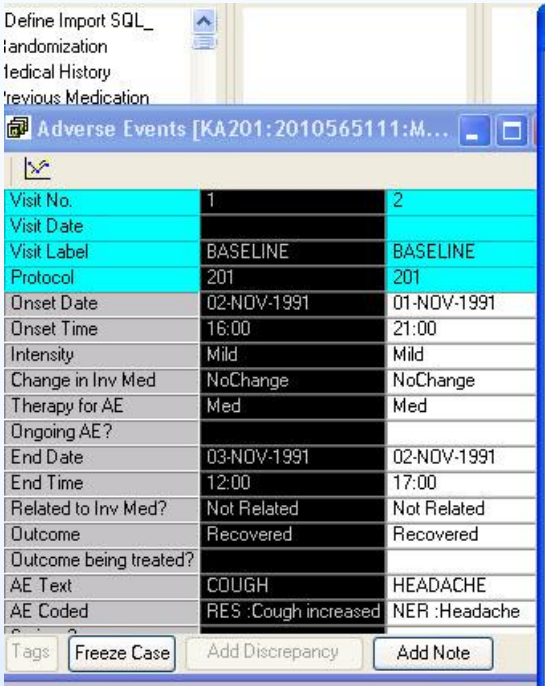
- Mild, non-serious
- Moderate, non-serious
- Severe, non-serious
- Life-threatening, serious
- Not resolved ⟶
- Resolved ═══

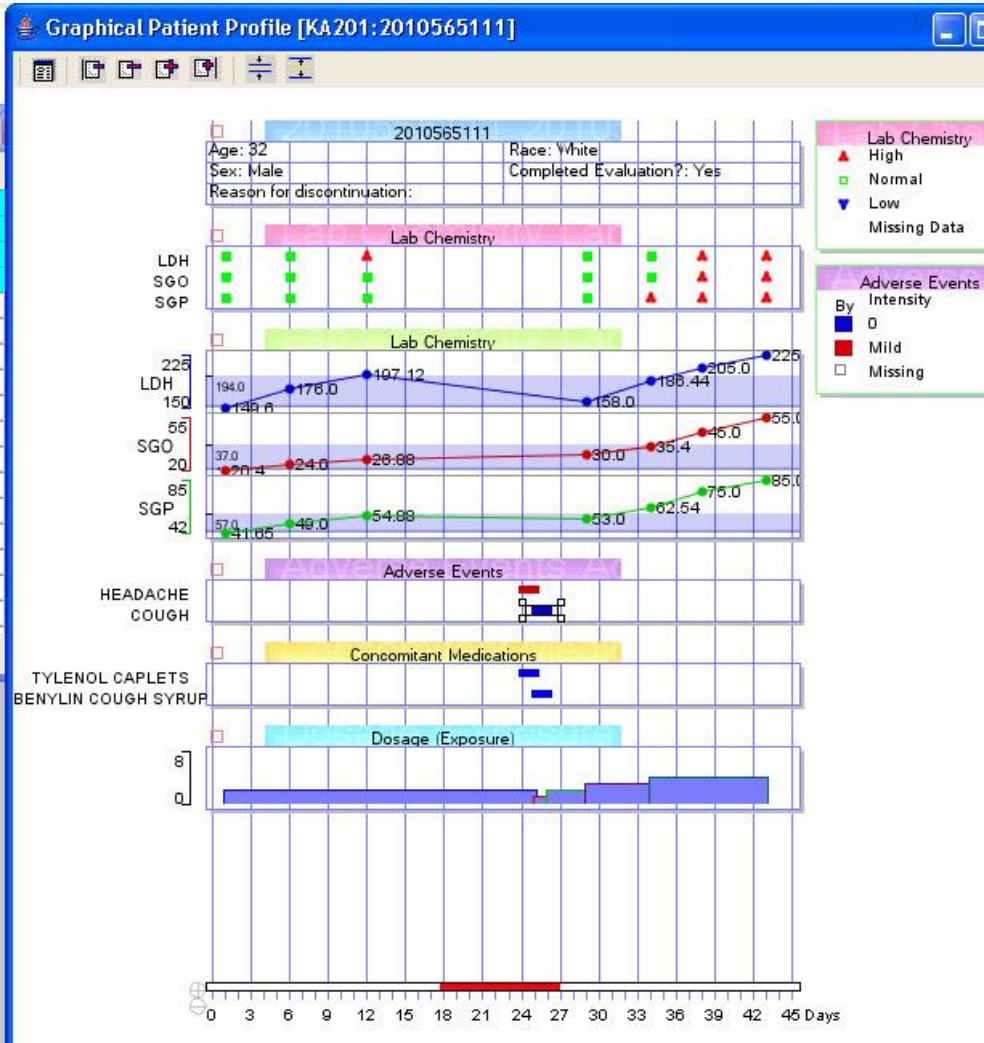
New graphic tools and processes facilitate signal detection and clinical trial safety management

Source: Graphical Analyses of Clinical Trial Safety Data; Haijun Ma, Kefei Zhou, Amy Xia, Matt Austin, George Li, Michael O'Connell
GBE Scientific Forum, 2007

Pattern Recognition is a Key Feature of Effective Graphics

40-60% of the human brain is devoted to visualization
Human visual capability is far ahead of the computer





Graphical Perception

"When a graph is constructed, information is encoded. The visual decoding of this encoded information is graphical perception. The decoding is the vital link … No matter how ingenious the encoding … and no matter how technologically impressive the production, a graph is a failure if the visual decoding fails."

William Cleveland, The Elements of Graphing Data

Customized Approach to Medical Monitoring and Safety Surveillance to Match these Unique Challenges in Rare Diseases Drug Development

- Natural history studies and disease registries
- Subject Eligibility Review: spectrum of clinical features (clinical heterogeneity)
- Real-time, one-on-one data review with Investigators
- Monitoring Plan and Multi-source endpoint review
- Graphical display of safety information and patient profiles
- Analysis of similar events (AOSE)

Thank you

"Knowledge is knowing that a tomato is a fruit, but WISDOM is knowing not to put it in a fruit salad"



Questions?

