Standard Pharmacovigilance Processes

**Collecting**

**Assessing**

**Receiving**

**Monitoring (follow-up)**

**Reporting to Health Agency**

Adverse Reactions

**Pharmacovigilance key areas of action**

- New use findings (finding benefits during use)
- Lack of efficacy
- Medication error (accidental)
- Use in special populations like children, immunosuppressed, etc
- DRP: Drug Related Problems
- Adverse Reactions
- Use in pregnancy and breast-feeding
- Quality claims with clinical impact
- Drug interaction
- Abuse and overdose
- Off-label use
Scope of Pharmacovigilance

- Prevent risks and improve medicine use
- With data from PV
- Discover new drug uses
- Promote creation of health team in drug issues, which improves patient care
- The impact of drugs in special populations can be known

Key Pharmacovigilance stakeholders:

- The State through Health Agencies
- Community and hospital pharmacies
- Pharmaceutical industry
- Medical associations
- Health institutions, like clinics
- Health institution managers
- Patients and/or relatives
- Off-label use
- Health care professionals
Risk / Benefit Ratio
The Risk of Adverse Drug Reactions

Risk analysis
Decision making
Risk management

Generate work hypotheses, project more studies to identify new risks

Anticipate knowledge-based risk

Data
Actions

Drug development phases: PV participates in each phase

Development phases

Pre-clinical

Phase I

Phase II

Phase III

Phase IV

Marketing

Healthy volunteers
Preliminary data

Reduced number of patients (sick people)

Post-approval studies

Intensive PV

Spontaneous report

Registry approval by Health Agency

Experiments with animals or tissue

Multicenter clinical studies, large number of patients
Drug life cycle: safety data in each stage

- Proposal of research strategy for new indications
- Changes in label
- Changes in production
- Change in dosage form

Risk Management Plan

Health Authority Requirements (according to each country)

For new medicines, new indications, biotherapeutics or high-risk labeled medicines, you must submit a

Risk Management Plan

Some countries request it during the drug approval process

PV Intensive Program:

Systematic safety monitoring throughout the prescription stage
Research, Development and Marketing of Biotherapeutics

Characterize: establish the qualities or characteristic features of a molecule

Physical-chemical characterization

Studies in animals or tissue.

Pre-clinical studies

Clinical studies

Approval

Marketing

Use in the population. In addition, clinical studies are continued (e.g., clinical studies on safety)

Approval requirements will depend on each Health Agency’s resolutions

Biotherapeutics: characteristics and impact.

What are proteins of biotherapeutics?

They are macromolecules (large molecules)

They have a very unstable chemical structure (they may change during the production process)

They are almost identical to body molecules

Their 3D structure is very complex

Slight changes in these molecules may cause:

Changes in efficacy

Safety alterations
Differences you must know between Chemically-synthesized and Biotherapeutics from design to production

**Chemically-synthesized**
- Produced by chemical synthesis
- Analyzed by standardized chemical methods
- Bioequivalence

**Biotherapeutics**
- Produced by complex biotechnological processes
- Subject to complex analytical methods
- Clinical trials
- Patient follow-up plan obligatory throughout the marketing process.

Biosimilars: the key to be similar is comparability

Comparability that determines similarity with the reference product must be shown in all the biosimilar development stages.

When Comparability is not convincing, a special clinical trial called "equivalence design controlled" must be conducted.

**Safety and Efficacy**
Confirm comparability (BIOCOMPARABILITY)

**Establishing comparability**

<table>
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<th>Clinical Phases</th>
<th>First objective:</th>
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<td>Pre clinical</td>
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<td>Comparability of the biological activity</td>
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<td>Define reference product</td>
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<td>Characterization It is the process to know the reference drug components in detail</td>
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<td>Physical-chemical comparability</td>
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The greatest concern is the risk of an unwanted immune response where the patient reacts against drug proteins, which limits drug efficacy or affects safety.

The immune system can identify very small differences between two molecules, imperceptible or negligible among molecules of a chemical origin! 

Risk Management Programs: the sole guarantee for prevention of adverse reactions in patients.

Traceability of the product administered to the patient is the key.

Reporting of a suspected Adverse Reaction against an innovative biotherapeutic or a biosimilar must always contain the information of the product’s trademark and, whenever possible, lot number and expiration date.

Interchange an innovative biotherapeutic with a biosimilar: a complex decision.

Interchangeability

It is a medical practice consisting in exchanging one drug for another from which the same clinical effect is expected as when the patient was already receiving an active ingredient.

Substitution

It is a pharmaceutical practice consisting in dispensing a drug in lieu of an equivalent pharmaceutical without asking the prescribing physician.
Strictly speaking, substitution or interchangeability can only be guaranteed if medicines are bioequivalent for chemically synthesized products and “similar” for biotherapeutics (with all clinical tests proving equivalence).

Sometimes, the doctor’s decision to interchange with a biosimilar is made evident to the patient because of the emergence of an immunological adverse reaction.

In addition to clinical safety, this may result in a negative perception of the treatment.

It is important for the patient to know the reasons and terms of the interchange of a biological drug with another.

Notas: