Adverse Drug Events to Biomedicines

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Adverse Drug Events (ADEs) are commonly differentiated in two classes: **Type A**, as predictable reactions related to the pharmacological properties of the drug in study; **Type B**, as unpredictable events in predisposed individuals. The former group includes side effects, toxicity of overdose, secondary effects, and drug interactions. Overall, they contribute for about 80–90 % of ADEs. The latter group includes hypersensitivity (immunological) reactions, and non-specific reactions, such as pseudo-allergic (anaphylactoid) reactions and idiosyncrasy, all contributing for the remaining 10–20 % of events [1, 2].

Type A reactions are typically related to the *pharmacological action* of the agent, expressed by its known or presumed mechanism(s) of action, while Type B events are usually unwanted and sometimes unexpected accessory phenomena derived from the interaction of the agent with the recipient's environment.

Hypersensitivity may derive from all the known four types of immune-specific reactions, namely the three antibody-mediated, Type I (IgE-mediated, or allergy), Type II (IgG and/or IgM-mediated cell cytotoxicity), Type III (immune complex deposition), and the cell-mediated Type IV reaction induced by T cells (delayed hypersensitivity).

Non-specific reactions may derive from a variety of mechanisms, including defective enzyme functioning, aspecific mast cell degranulation and, in the present view, as a consequence of a cytokine network imbalance causing mild to serious, local or systemic syndromes with potential life threatening outcomes (see Chap. 3).

Two additional types of reaction less frequently used consist in Type C events associated with long-term therapy, and Type D events referred to carcinogenic and mutagenic drug with long-term effects.

While Type A reactions are preferably dose-related, Type B events usually are not; in fact, the latter type may be triggered by extremely low doses of the causative agent.

Alternatively, they all may induce *Tachyphylaxis*, defined as an acute decrease of drug response and reactivity related to both dose and rate of administration, leading to desensitization, and to rebound phenomena following treatment.

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Idiosyncratic reactions are usually referred to non-immune, unexpected, abnormal events not related to the peculiar pharmacologic action of the responsible agent.

Drug metabolism dysfunction may cause ADEs, mostly due to accumulation of detoxified metabolites expressing direct cell and tissue damage, or indirect induction of immune responses by binding to macromolecular (proteic) endogenous components.

Therefore, a number of unexpected, unpredictable AEs are difficult to classify, since most of the responsible mechanisms are not known, or more parameters are involved in a single reaction, thus leading to their grouping according to the mentioned SOC or Frequency classification criteria.

Recently, a different approach considered not only the intrinsic properties of the agent as the leading criterion for classification of AEs, but also other concomitant properties, such as time, dose, severity, and individual peculiarities (genetic, biopathological conditions) conferring different susceptibility. In particular, the addition of individual susceptibility to the more familiar dose-timing conditions widely experienced in the evaluation of adverse events to vaccines, takes in proper consideration important variants such as the genetic background, age, sex, physiological (pregnancy) and underlying pathological conditions, and exogenous factors (**Dose-Time-Susceptibility -DoTS- classification**). Although such tridimensional approach is more realistic and appropriate for biomedicines as well, it has not gained much diffusion in the field [3]. On this basis, ADEs can be identified by a number of clinical syndromes which appear more frequent and relevant than others. Among them, there are *CNS toxicities* (acute toxic confusion), *respiratory disorders* (asthma, pulmonary fibrosis), *cardiovascular events* (tachycardia—torsade de points—), *hemopoietic toxicity* (aplasia, agranulocytosis, aplastic anemia), and *neuropsychiatric disorders* [4].

However, the spectrum of adverse *cutaneous drug eruptions*, not considered in the previous report, is also fundamental for the ADEs evaluation of old and new drugs, including biomedicines [5]. Elevated sensitivity, prompt detectability, and potential gravity of some skin lesions, together with the possibility of discriminating distinct ADEs on the basis of easily performable histopathological analyses, make the dermatological observation crucial for the understanding, prevention, and control of drug-induced reactions. Unfortunately, most of the cutaneous expressions of drug harm are not followed by dermatologists during this kind of studies.

An additional and relevant problem relates to the assessment of *ADEs in pediatric age*. In fact, experience on this age setting with biomedicines is even more limited and is associated with additional risks. Over-dosing, the absence of pharmacokinetic studies performed in premarketing stages, the influence on growth and development, and of long-term exposure in chronic diseases are among them. There is no ADE classification that takes into consideration such aspects. In fact, most of the premarketing trials either exclude pediatric subjects, or enroll quite small groups, even when the disease in study pertains to this age (i.e., genetic disorders such as autoinflammatory diseases); in most cases the efficacy profile analysis prevails on the safety profile [6]. In consideration of the expanding use of

Table 2.1 Criteria for adverse drug events classification

Criterion		Typology		Manifestation
Class	Type A	Predictable	Dose Toxicity	Hepatic failure
		Common	Side Effects	Collateral pharmacoactivity
		Drug-related	Drug interactions	Synergistic toxicity
			Secondary Effects	Diarrhea (xenobiotic imbalance)
	Type B	Unpredictable	Intolerance	Low threshold pharmacoactivity
		Uncommon	Hypersensitivity	Anaphylaxis, Arthralgia
		Drug-unrelated	Pseudoallergic	Radiocontrast reaction
			Idiosyncratic	Anemia (enzymatic deficiency)
Dose	Dose–response	Dependent	Independent	
		Related	Time change	Increasing toxicity
		Unrelated		Decreasing/paradoxical toxicity
Time	Time-response	Dependent	Independent	
		Injection rapidity	Dose change	Acute toxicity
		First Dose	Accumulation	Toxicity
		Peaking Dose	Drug interaction	Synergistic, unexpected
Frequency		Type	Range	
		Very common	> 10 %	Injection site reaction
		Common	1–10 %	Pyrexia, diarrhea
		Uncommon	0.1–10 %	Vasculitis
		Rare	0.01–0.1 %	Anaphylaxis
		Very rare	< 0.01 %	Leucoencephalitis
SOC		System Organ Groups	Subgroups	Blood/Anemia/Grade (1-5)
Combined		SOC	Frequency	Bidimensional AEs comparison
		Group	Range	

(continued)

Table 2.1 (continued)

Criterion		Typology		Manifestation
DoTS		Mechanism of action	Clinical evidence	Tridimensional AEs comparison
	Dose	Yes/No	Yes/No	
	Time	Yes/No	Yes/No	
	Susceptibility	Yes/No	Yes/No	

new therapies in *off-label conditions*, the relevance of the problem is even more concerning for these young patients. In an interesting, yet not very recent study on 1419 children, 45 % of them was exposed to off-label treatments, associated to a significant increased risk to develop ADEs [7].

Tables 2.1 and 2.2 summarize the criteria for ADEs' classification more frequently adopted.

Is the mentioned conventional approach of AEs evaluation feasible also for biomedicines? Probably not. These agents are a relatively new class of therapeutics carrying specific risks. They are derived from living sources; production and purification result in more complex procedures; and minor modifications can result in major differences, both in efficacy and safety. A few changes in the glycosylation of a monoclonal antibody or a fusion protein, may modify its binding capacity and immunogenicity. With this respect they are more comparable to vaccines and allergenic products. Moreover, they have an extraordinary capacity of influencing the complex network of cytokines, directly interfering with their receptors and ligands. In fact, application requirements for biomedicines' approval were soon adapted as ad hoc Biological License Applications (BLA) or similar, but the body of pre- and postmarketing safety regulatory actions remained practically the same. Moreover, due to their promising expectancies in lethal diseases lacking efficient therapy, accelerated approvals were released and important safety problems could be individuated only in the postmarketing experience. Between 1995 and 2007, a total of 174 biological products were approved (136 in US; 105 in EU; 67 in both). Up to 2008, 81 regulatory actions/alerts were issued on 41 biomedicines (24 %), along with 46 letter to health care professionals, 17 direct healthcare communications, and 19 BBWs [8]. First in drug class approvals were exposed to more safety regulatory actions, while last issued biomedicines, such as mAbs, fusion proteins, and cytokines, that are primarily considered in this volume, had a higher risk of ADEs induction compared to early issued hormones, such as recombinant insulin, somatotropin, and immunoglobulins.

Even the simple Type A and Type B distinction of ADEs appears questionable for biomedicines. For example, typical hypersensitivity reactions could be triggered by direct stimulation of cytokine receptors or by non-covalent interactions with

Table 2.2 System organ classification categories (°)

Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial, and genetic disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General disorders and administration site disorders
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning, and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Nervous system disorders
Pregnancy, puerperium, and perinatal conditions
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic, and mediastinal disorders
Skin and subcutaneous tissue disorders
Social circumstances
Surgical and medical procedures
Vascular disorders

(°) evs.nci.gov/ftp1/CTCAE v 4.03

immune receptors, without triggering a conventional immune response. This peculiarity was observed also for smaller therapeutic molecules acting as haptens when bound to endogenous protein carriers [9]. In fact, the homeostatic alteration produced by biomedicines bypassing immune-mediated mechanisms, may explain the higher frequency of hypersensitivity-like reactions observed during treatment, in the absence of a significant induction of sensitization signs and of antibody production [10].

Consequently, **new classificative criteria** are needed and are being proposed, which selectively consider AEs encountered during administration of mAbs, fusion proteins, and cytokines.

In particular, one classification identifies five groups of ADRs to biomedicines: (α) *Immunostimulation* (infusion reactions, direct substance-dependent effects, cytokine release); (β) *Immunogenicity* (Type I-IV hypersensitivity reactions; anti-drug antibody formation); (γ) *Immunodeviation* (immunosuppression, autoimmunity); (δ) *Cross-reactivity*; (ε) *Non-immune adverse reactions* [11].

The major novelty in such classification relates to the attention dedicated to immunogenic substance-specific reactions, as referred to the three fundamental classes of new biomedicines, namely monoclonal antibodies, fusion proteins, and cytokines. Therefore, in analogy to the known CTCAE grading, a severity I-V scale has been put aside for Type α and Type β reactions.

On this basis, Table 2.3 reports a modified version of the proposed ADRs classification, with the aim of underlining the necessity of pursuing a better approach to the peculiarities of biomedicines. The reported approach is rather preliminary and too complex to be routinely applied to prospective investigations, and even more to retrospective analyses.

Recently, a mechanistic approach to "**Biological Adverse Events**" (BAE) has been proposed [12]. Two pathogenetic mechanisms are identified, *Pharmacological* and *Non-Pharmacological,* including two subgroups, respectively. The former identifies reactions derived from the intended interaction of the biomedicine with its target. They are distinct in "expected biology" and "new biology" events. Non-pharmacological events basically identifies "immune-mediated" responses and "non-immune mediated" reactions. Examples of pharmacologically mediated toxicity include infections subsequent to immunosuppression, inhibition of vascularization, cardiotoxicity, and massive cytokine release. Non-pharmacological immune events relate to all hypersensitivity reactions and to autoimmune diseases, while non-immune reactions are referred to Fc-mediated acute phase reactions. Table 2.4 reports a modified version of BAE classification.

Although this approach also appears preliminary, it clearly indicates that a better characterization of BAE with respect to ADEs may become feasible, and ensure a more precise identification of the pathogenetic routes of biomedicines.

In conclusion, while waiting for more stringent classifications and possibly differentiated procedures of pharmacovigilance for biomedicines, the evaluation of their ADEs still remains in the general framework of the **System organ classification** (SOC) of the **Frequency classification**. In fact, they allow collection of any encountered AEs under a unified terminology identified in the MedDRA hierarchy, where anatomical, physiological, etiological, and investigational interventions are grouped. Within each category AEs are graded in terms of severity on 1–4 or 1–5 scale, according to the typology of the observed event. In fact, not all grades are appropriate for all AEs, and therefore some are grouped in fewer grades. For example, stroke is graded from 1–5, while generalized muscle, ataxia, and some investigational events are graded from 1–3, syncope is only grade 3, and cerebral edema is only grade 4.

Table 2.3 Classification of adverse drug reactions to biomedicines (a)

Class	Mechanism of action	Type	Effectors	Manifestation
Alpha	Immunostimulation	Infusion reactions	Cytokine release and Complement activation	CRS, FLS
		Injection reactions		Erythema, Dyspnea, Hypotension,
				Arthralgia, Systemic signs
Beta	Immunogenicity	I	IgE	Anaphylaxis, Rash, Urticaria
		II, III	IgG, IgM	Serum Sickness, Arthralgia
		IV	T cells	Cytotoxicity, Exanthema
				Autoimmunity
Gamma	Immune deviation	Immunosuppression	Receptor/Ligand blockage	Infections Tumors
				Virus-associated tumors
		Immune imbalance	Th1,Th2, Treg	Autoimmunity
				Hypersensitivity induction
				Disease exacerbation
Delta	Cross antigenicity	Bystander aggression	Cross-reactive Abs, T cells	Exanthema, Skin toxicity
				Autoimmunity
Epsilon	Non-immune	CYP 450 inhibition	Cytokine release	Cardiovascular, ATE, VTE
		Anaphylactoid reactions		Xeroderma

(a) Modified from Sherer K et al. (2010) JDDG 8:411–426
Type I–IV hypersensitivity (Gell and Coombs classification); CRS: cytokine release syndrome; FLS: flu-like syndrome; ATE,VTE: arterial, venous thromboembolic events

The frequency parameter is a practical and simple evaluation, and includes the following categories: Very common events (>10 %); Common events (1–10 %); Uncommon events (0.1–1 %); Rare events (0.01–0.1 %), and Very rare events (<0.01 %).

The combination of the two criteria is still the basis for all types of AEs classification in all sorts of clinical situations, and has been adopted for data

Table 2.4 Biologic adverse events (BAE)[a]

Pharmacological			
Expected biology		**New biology**	
Type	**Target**	**Type**	**Target**
Inhibition of wound healing	VEGF	CRS	Massive T cell activation
Hypoglycemia	Insulin	Cardiotoxicity	HER2
Infections	Immunosuppression	Thrombosis	VEGF
Non-pharmacological			
Immune response mediated		**Non-immune response mediated**	
Type	**Target**	**Type**	**Target**
Hypersensitivity	Non-self epitopes	TLS	CD20
Autoimmunity	Self epitopes	Inflammation	Acute phase proteins

[a] Modified from Clarke JH, Adverse Drug Reactions. Handbook Exp Pharmacol,Uetrecht J(ed) Springer 2010, pp 453–474
CRS: cytokine release syndrome; TLS: tumor lysis syndrome. See Chap. 3

collection in the electronic data sheets annexed to this volume. On this basis, the analysis of the safety profile has focused on three drug classes, **Monoclonal Antibodies**, **Fusion proteins**, and **Cytokines**, representing the core of the new biological therapeutics in oncology, autoimmune and autoinflammatory diseases, and hemopoietic stimulation.

In this monograph, such data have been arranged in distinct *Sections*, and in *Downloadable Associated Files* provided for the most relevant examined biomedicines. In the first section, data of each product include a short *History* on basic safety studies leading to approval. Such data setting is fundamental to understand the amount of experience accumulated in the premarketing phase, and the subsequent evolution and evaluation of safety profiles during the postmarketing expansion.

A short, albeit detailed, section on the *Mechanism(s) of Action* follows, since many pathogenetic roots of ADEs are linked to their expression. A brief analysis of the *Immunogenicity* of the drug in study follows. These two aspects are instructive not only for the understanding of therapeutic risks, but also as useful guidelines for the development of better medicines. Interestingly, by following the progressive modulation of immunogenicity during the development of new monoclonal antibodies, the overall progress in the safety of biomedicines becomes tangible and educational. However, lessons have also been learned from unexpected reactions due to minimal underestimated molecular variations, such as in the glycosylation of antibodies or of fusion proteins. The *Adverse Events* main section is dedicated to the *safety general profile* of each agent, depicted in relation to its officially approved indications. Whenever applied in different pathological situations, attention has been given to substantial differences and *specificities with respect to the standard profile*, usually assessed on the major disease representative of the group (e.g.

Rheumatoid Arthritis for rheumatic diseases, etc.). Subsequently, *additional experiences*, mainly concerning long-term studies, subpopulation differential reactivities, and studies of particular relevance in confirming initial safety trends, or the appearance of new signals, are reported. When available, particular attention has been given to experiences from the clinical practice, in unselected groups of patients, where the background pathology and the presence of comorbidities make a great difference with the cohorts of patients selected for clinical trials, thus offering to evaluate safety aspects closer to the reality of clinical care.

The following section is dedicated to *Off-label experience*, including controlled studies conducted in clinical trials, as well as in clinical care and in case reports, whenever indicative of relevant safety concern. These individual/small group studies on off-label conditions are often of more concern than utility. However, in some circumstances they may show potential alert signals or suggest new therapeutic indications, requesting immediate attention and proper confirmation in controlled studies.

With a similar aim, data from the *Postmarketing surveillance* databases, in particular the FAERS and the EUV database, have been consulted and reported. When considered of particular interest for safety understanding, information on developing drugs strictly related to the biomedicine in study are reported (e.g., the unsuccessful evolution of palivizumab into motavizumab). In fact, attempts to improve efficacy, such as by increasing the affinity of the product for the respective target, are not necessarily independent from a relevant modification of the safety profile, making the acquired clinical improvement unacceptable. Finally, some *Remarks* on most relevant safety peculiarities of the agent, including peculiarities within the same drug class, are provided.

The downloadable *Electronic Sheet Dataset* includes additional safety information, organized according to SOC and frequency classifications.

In the upper part of the downloadable sheet, *general data* on brand name(s), typology, target(s), class (Anatomical Therapeutic Chemical—ATC) and function, therapeutic indications, and major approval dates are reported, followed by essential product information and the major involved *Mechanism(s) of Action*. *Excipients* present in each commercial product have also been reported due to their known potential role in AE reactivity, and with the aim of providing all the useful information to help in understanding and evaluating the documented AEs reported in the same file.

In the second part, *safety information* has been reported according to SOC classification, and has been slightly modified to better fit the purpose of this volume. For example, the "Immune system disorders" SOC group has been divided into "allergy"/"immunology" "immunogenicity", and "autoimmune" subgroups. *Pre- and postmarketing data acquisition* from studies and reports has been considered separately, and major sources of information have been reported. In particular, data have been collected from scientific papers and reviews, official reports, case studies, clinical studies, trials—mainly of Phase II and III—AE alerts and documents from official producers, when available. The reported AEs have also been classified according to their frequency (common, uncommon, rare, etc.)

in order to allow a quick representation of the whole spectrum of detected reactions. *Spontaneous Reports* from the two major *postmarketing surveillance* databases (FAERS, EUV) have been separately reported, and organized according to the same frequency grading.

Finally, *BBWs and additional relevant warnings* along with most common and most serious events have been inserted in the last section, followed by essential information on *Drug interactions* and *Associations,* and some *Comments* completing the whole safety profile of each biomedicine.

The information provided in the electronic data sheets may help in quick searching for specific AEs and in comparing drug classes. Being such data sheets provided in the excel format, users may integrate the downloaded file with their personal experience.

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