

---

# Contents

## Part I General Aspects

<b>1</b>	<b>Introduction</b>	<b>3</b>
1.1	Definitions	4
1.1.1	Drugs as Biological Derivative: Biomedicines	5
1.2	Adverse Events	6
1.2.1	Typology of Adverse Events	7
1.2.2	Classification of Adverse Events	9
1.2.3	Adverse Drug Events	10
1.2.4	Off-Label Observations	11
1.2.5	Postmarketing Surveillance	11
1.2.6	Adverse Events Analysis	12
	References	14
<b>2</b>	<b>Adverse Drug Events to Biomedicines</b>	<b>15</b>
	References	24
<b>3</b>	<b>Systemic Syndromes with Biomedicines</b>	<b>25</b>
3.1	Capillary/Vascular Leak Syndrome (CLS/VLS)	25
3.2	Cytokine Release Syndrome (CRS)	31
3.3	Infusion Reaction Syndrome (IRS)	34
3.4	Tumor Lysis Syndrome (TLS)	34
3.5	Systemic Inflammatory Response Syndrome (SIRS)	36
3.6	Macrophage Activating Syndrome (MAS)	37
3.7	Immune Reconstitution Inflammatory Syndrome (IRIS)	38
	References	45

## Part II Monoclonal Antibodies

<b>4</b>	<b>Monoclonal Antibodies</b>	<b>51</b>
4.1	Structure and Typology	52
4.2	Chimeric and Humanized mAb	54
4.3	Fully Humanized mAb	54

4.4	Nomenclature . . . . .	56
4.5	Basic Structure, Targets and Mechanism of Action . . . . .	56
4.6	Therapeutic Indications . . . . .	60
	References . . . . .	63
<b>5</b>	<b>Abciximab . . . . .</b>	<b>65</b>
5.1	Mechanism of Action . . . . .	65
5.2	Adverse Events. . . . .	66
5.3	Immunogenicity and Immune Thrombocytopenia . . . . .	67
5.4	Off-Label Experience . . . . .	69
5.5	Postmarketing Surveillance . . . . .	69
5.6	Remarks . . . . .	70
	References . . . . .	70
<b>6</b>	<b>Adalimumab . . . . .</b>	<b>71</b>
6.1	Mechanism of Action . . . . .	72
6.2	Immunogenicity . . . . .	74
6.3	Adverse Events. . . . .	74
6.4	Off-Label Experience . . . . .	78
6.5	Postmarketing Surveillance . . . . .	79
6.6	Remarks . . . . .	79
	References . . . . .	80
<b>7</b>	<b>Alemtuzumab . . . . .</b>	<b>81</b>
7.1	Mechanism of Action . . . . .	82
7.2	Immunogenicity . . . . .	83
7.3	Adverse Events. . . . .	83
7.4	Off-Label Experience . . . . .	86
	7.4.1 Neoplastic Off-Label Experience . . . . .	86
	7.4.2 Non-Neoplastic Off-Label Experience . . . . .	88
7.5	Postmarketing Surveillance . . . . .	92
7.6	Remarks . . . . .	92
	References . . . . .	93
<b>8</b>	<b>Basiliximab . . . . .</b>	<b>97</b>
8.1	Mechanism of Action . . . . .	97
8.2	Immunogenicity . . . . .	98
8.3	Adverse Events. . . . .	99
8.4	Off-Label Experience . . . . .	100
8.5	Postmarketing Surveillance . . . . .	102
8.6	Remarks . . . . .	102
	References . . . . .	103

<b>9</b>	<b>Belimumab</b> . . . . .	105
9.1	Mechanism of Action . . . . .	106
9.2	Immunogenicity . . . . .	107
9.3	Adverse Events. . . . .	107
9.4	Off-Label Experience . . . . .	108
9.5	Postmarketing Surveillance . . . . .	110
9.6	Remarks . . . . .	110
	References . . . . .	111
<b>10</b>	<b>Bevacizumab</b> . . . . .	113
10.1	Mechanism of Action . . . . .	114
10.2	Immunogenicity . . . . .	116
10.3	Adverse Events. . . . .	116
10.4	Off-Label Experience . . . . .	120
10.5	AEs and Tumor Typology . . . . .	121
10.6	The AMD Experience . . . . .	121
10.7	Postmarketing Surveillance . . . . .	122
10.8	Remarks . . . . .	123
	References . . . . .	124
<b>11</b>	<b>Brentuximab</b> . . . . .	127
11.1	Mechanism of Action . . . . .	128
11.2	Immunogenicity . . . . .	129
11.3	Adverse Events. . . . .	129
11.4	Off-Label Experience . . . . .	130
11.5	Postmarketing Surveillance . . . . .	131
11.6	Remarks . . . . .	131
	References . . . . .	132
<b>12</b>	<b>Canakinumab</b> . . . . .	135
12.1	Mechanism of Action . . . . .	136
12.2	Immunogenicity . . . . .	137
12.3	Adverse Events. . . . .	137
12.4	Off-Label Experience . . . . .	138
12.5	Postmarketing Surveillance . . . . .	140
12.6	Remarks . . . . .	140
	References . . . . .	141
<b>13</b>	<b>Catumaxomab</b> . . . . .	143
13.1	Mechanism of Action . . . . .	144
13.2	Immunogenicity . . . . .	145
13.3	Adverse Events. . . . .	145
13.4	Postmarketing Surveillance . . . . .	146
13.5	Remarks . . . . .	146
	References . . . . .	147

<b>14 Certolizumab</b>	149
14.1 Mechanism of Action	150
14.2 Immunogenicity and Immunity	151
14.3 Adverse Events	152
14.4 Off-Label Experience	154
14.5 Postmarketing Surveillance	155
14.6 Remarks	156
References	157
<b>15 Cetuximab</b>	159
15.1 Mechanism of Action	161
15.2 Immunogenicity	163
15.3 Adverse Events	164
15.3.1 AEs in SCCHN	165
15.3.2 AEs in mCRC	166
15.4 Off-Label Experience	168
15.5 Postmarketing Surveillance	169
15.6 Remarks	170
References	171
<b>16 Daclizumab</b>	173
16.1 Mechanism of Action	174
16.2 Immunogenicity	174
16.3 Adverse Events	175
16.4 Off-Label Experience	176
16.5 Postmarketing Surveillance	180
16.6 Remarks	180
References	181
<b>17 Denosumab</b>	183
17.1 Mechanism of Action	184
17.2 Immunogenicity	185
17.3 Adverse Events	186
17.4 Off-Label Experience	189
17.5 Postmarketing Surveillance	189
17.6 Remarks	190
References	192
<b>18 Eculizumab</b>	193
18.1 Mechanism of Action	194
18.2 Immunogenicity	195
18.3 Adverse Events	195
18.4 Off-Label Experience	196
18.5 Postmarketing Surveillance	198
18.6 Remarks	198
References	199

<b>19</b>	<b>Edrecolomab</b> . . . . .	201
	References . . . . .	202
<b>20</b>	<b>Efalizumab</b> . . . . .	203
	20.1 Mechanism of Action . . . . .	204
	20.2 Immunogenicity . . . . .	205
	20.3 Adverse Events. . . . .	206
	20.4 The PML Case and Postmarketing Surveillance . . . . .	208
	20.5 Remarks . . . . .	209
	References . . . . .	210
<b>21</b>	<b>Gemtuzumab</b> . . . . .	211
	21.1 Mechanism of Action . . . . .	212
	21.2 Immunogenicity . . . . .	213
	21.3 Adverse Events. . . . .	213
	21.4 Postmarketing Surveillance . . . . .	215
	21.5 Remarks . . . . .	216
	References . . . . .	216
<b>22</b>	<b>Golimumab</b> . . . . .	219
	22.1 Mechanism of Action . . . . .	220
	22.2 Immunogenicity . . . . .	221
	22.3 Adverse Events. . . . .	221
	22.4 Off-Label Experience . . . . .	224
	22.5 Postmarketing Surveillance . . . . .	225
	22.6 Remarks . . . . .	226
	References . . . . .	227
<b>23</b>	<b>Ibritumomab</b> . . . . .	229
	23.1 Mechanism of Action . . . . .	230
	23.2 Immunogenicity . . . . .	231
	23.3 Adverse Events. . . . .	231
	23.4 Off-Label Experience . . . . .	233
	23.5 Postmarketing Surveillance . . . . .	234
	23.6 Remarks . . . . .	235
	References . . . . .	235
<b>24</b>	<b>Infliximab</b> . . . . .	237
	24.1 Mechanism of Action . . . . .	238
	24.2 Immunogenicity and Related Events . . . . .	240
	24.3 Adverse Events. . . . .	241
	24.3.1 AEs Peculiarities . . . . .	243
	24.4 Off-Label Experience . . . . .	244
	24.5 Postmarketing Surveillance . . . . .	246
	24.6 Remarks . . . . .	246
	References . . . . .	248

<b>25</b>	<b>Ipilimumab</b> . . . . .	251
25.1	Mechanism of Action . . . . .	252
25.2	Immunogenicity . . . . .	253
25.3	Adverse Events. . . . .	254
25.4	Off-Label Experience . . . . .	257
25.5	Postmarketing Surveillance . . . . .	259
25.6	Remarks . . . . .	259
	References . . . . .	260
<b>26</b>	<b>Muromonab</b> . . . . .	263
	References . . . . .	265
<b>27</b>	<b>Natalizumab</b> . . . . .	267
27.1	Mechanism of Action . . . . .	268
27.2	Immunogenicity . . . . .	269
27.3	Adverse Events. . . . .	269
27.4	Postmarketing Surveillance . . . . .	273
27.5	Remarks . . . . .	273
	References . . . . .	274
<b>28</b>	<b>Nimotuzumab</b> . . . . .	277
28.1	Mechanism of Action . . . . .	278
28.2	Adverse Events. . . . .	278
28.3	Remarks . . . . .	279
	References . . . . .	280
<b>29</b>	<b>Ofatumumab</b> . . . . .	281
29.1	Mechanism of Action . . . . .	281
29.2	Immunogenicity . . . . .	282
29.3	Adverse Events. . . . .	283
29.4	Off-Label Experience . . . . .	285
29.5	Postmarketing Surveillance . . . . .	286
29.6	Remarks . . . . .	287
	References . . . . .	288
<b>30</b>	<b>Omalizumab</b> . . . . .	291
30.1	Mechanism of Action . . . . .	292
30.2	Immunogenicity . . . . .	293
30.3	Adverse Events. . . . .	294
30.4	Off-Label Experience . . . . .	295
30.5	Unexpected Adverse Events. . . . .	297
30.6	Postmarketing Surveillance . . . . .	297
30.7	Remarks . . . . .	298
	References . . . . .	299

<b>31</b>	<b>Palivizumab</b>	301
31.1	Mechanism of Action	302
31.2	Immunogenicity	303
31.3	Adverse Events.	304
31.4	Off-Label Experience	306
31.5	Postmarketing Surveillance	307
31.6	The Motavizumab Experience	308
31.7	Remarks	310
	References	311
<b>32</b>	<b>Panitumumab</b>	313
32.1	Mechanism of Action	314
32.2	Immunogenicity	315
32.3	Adverse Events.	316
32.4	Off-Label Experience	320
32.5	Postmarketing Surveillance	322
32.6	Remarks	322
	References	324
<b>33</b>	<b>Pertuzumab</b>	327
33.1	Mechanism of Action	327
33.2	Immunogenicity	329
33.3	Adverse Events.	329
33.4	Off-Label Experience	331
33.5	Postmarketing Surveillance	332
33.6	Remarks	333
	References	333
<b>34</b>	<b>Ranibizumab</b>	335
34.1	Mechanism of Action	336
34.2	Immunogenicity	338
34.3	Adverse Events.	339
	34.3.1 Ocular Adverse Events	339
	34.3.2 Systemic Adverse Events.	340
34.4	Off-Label Experience	345
34.5	Postmarketing Surveillance	346
34.6	Remarks	346
	References	348
<b>35</b>	<b>Rituximab</b>	351
35.1	Mechanism of Action	353
35.2	Immunogenicity	355
35.3	Adverse Events.	355
35.4	Off-Label Experience	360

35.5	Postmarketing Surveillance . . . . .	365
35.6	Remarks . . . . .	365
	References . . . . .	367
<b>36</b>	<b>Tocilizumab . . . . .</b>	<b>369</b>
36.1	Mechanism of Action . . . . .	370
36.2	Immunogenicity . . . . .	372
36.3	Adverse Events. . . . .	373
36.4	Off-Label Experience . . . . .	377
36.5	Postmarketing Surveillance . . . . .	378
36.6	Remarks . . . . .	379
	References . . . . .	380
<b>37</b>	<b>Tositumomab . . . . .</b>	<b>383</b>
37.1	Mechanism of Action . . . . .	384
37.2	Immunogenicity . . . . .	386
37.3	Adverse Events. . . . .	386
37.4	Off-Label Experience . . . . .	389
37.5	Postmarketing Surveillance . . . . .	389
37.6	Remarks . . . . .	390
	References . . . . .	390
<b>38</b>	<b>Trastuzumab . . . . .</b>	<b>393</b>
38.1	Mechanism of Action . . . . .	394
38.2	Immunogenicity . . . . .	397
38.3	Adverse Events. . . . .	397
38.4	Off-Label Experience . . . . .	402
38.5	Postmarketing Surveillance . . . . .	403
38.6	Remarks . . . . .	404
	References . . . . .	405
<b>39</b>	<b>Ustekinumab . . . . .</b>	<b>409</b>
39.1	Mechanism of Action . . . . .	410
39.2	Immunogenicity . . . . .	411
39.3	Adverse Events. . . . .	411
39.4	Off-Label Experience . . . . .	417
39.5	Postmarketing Surveillance . . . . .	418
39.6	Remarks . . . . .	419
	References . . . . .	420
 <b>Part III Fusion Proteins</b>		
<b>40</b>	<b>Fusion Proteins . . . . .</b>	<b>425</b>
	References . . . . .	428



<b>41</b>	<b>Abatacept</b> . . . . .	429
41.1	Mechanism of Action . . . . .	431
41.2	Immunogenicity . . . . .	432
41.3	Adverse Events. . . . .	433
41.4	Off-Label Experience . . . . .	438
41.5	Postmarketing Surveillance . . . . .	440
41.6	Remarks . . . . .	440
	References . . . . .	442
<b>42</b>	<b>Aflibercept</b> . . . . .	445
42.1	Mechanism of Action . . . . .	447
42.2	Immunogenicity . . . . .	449
42.3	Adverse Events. . . . .	449
	42.3.1 Aflibercept (Eylea) . . . . .	450
	42.3.2 Aflibercept (Zaltrap; Ziv-Aflibercept) . . . . .	452
42.4	Off-Label Experience . . . . .	453
	42.4.1 Aflibercept (Eylea) . . . . .	454
	42.4.2 Aflibercept (Zaltrap; Ziv-Aflibercept) . . . . .	455
42.5	Postmarketing Surveillance . . . . .	458
42.6	Remarks . . . . .	458
	References . . . . .	459
<b>43</b>	<b>Alefacept</b> . . . . .	463
	References . . . . .	464
<b>44</b>	<b>Belatacept</b> . . . . .	465
44.1	Mechanism of Action . . . . .	466
44.2	Immunogenicity . . . . .	467
44.3	Adverse Events. . . . .	468
44.4	Off-Label Experience and Postmarketing Surveillance. . . . .	470
44.5	Remarks . . . . .	471
	References . . . . .	472
<b>45</b>	<b>Etanercept</b> . . . . .	473
45.1	Mechanism of Action . . . . .	475
45.2	Immunogenicity . . . . .	478
45.3	Adverse Events. . . . .	478
	45.3.1 Additional Adult Safety Profiles (Ps, PsA, AS) . . . . .	481
	45.3.2 Pediatric Additional Profiles (JIA, Ps, PsA) . . . . .	482
	45.3.3 Safety Profiles in Other Studies . . . . .	484
45.4	Off-Label Experience . . . . .	487
45.5	Postmarketing Surveillance . . . . .	489
45.6	Remarks . . . . .	489
	References . . . . .	491

<b>46</b>	<b>Rilonacept</b> . . . . .	495
46.1	Mechanism of Action . . . . .	496
46.2	Immunogenicity . . . . .	498
46.3	Adverse Events. . . . .	498
46.4	Experience in Gout Studies . . . . .	499
46.5	Off-Label Experience . . . . .	500
46.6	Postmarketing Surveillance . . . . .	501
46.7	Remarks . . . . .	501
	References . . . . .	501
<b>47</b>	<b>Romiplostim</b> . . . . .	503
47.1	Mechanism of Action . . . . .	504
47.2	Immunogenicity . . . . .	504
47.3	Adverse Events. . . . .	505
47.4	Off-Label Experience . . . . .	507
47.5	Postmarketing Surveillance . . . . .	509
47.6	Remarks . . . . .	510
	References . . . . .	511
 <b>Part IV Cytokines</b>		
<b>48</b>	<b>Cytokines</b> . . . . .	515
	References . . . . .	521
<b>49</b>	<b>Interleukins</b> . . . . .	523
49.1	Interleukin-1 (IL-1). . . . .	524
49.2	Interleukin-2 (IL-2). . . . .	526
	References . . . . .	529
<b>50</b>	<b>Denileukin-Diftitox</b> . . . . .	531
50.1	Mechanism of Action . . . . .	531
50.2	Immunogenicity . . . . .	532
50.3	Adverse Events. . . . .	533
50.4	Off-Label Experience . . . . .	534
50.5	Postmarketing Surveillance . . . . .	536
50.6	Remarks . . . . .	536
	References . . . . .	537
<b>51</b>	<b>Anakinra</b> . . . . .	539
51.1	Mechanism of Action . . . . .	540
51.2	Immunogenicity . . . . .	542
51.3	Adverse Events. . . . .	542
51.4	Off-Label Experience . . . . .	544
51.5	Postmarketing Surveillance . . . . .	547
51.6	Remarks . . . . .	547
	References . . . . .	549

<b>52</b>	<b>Interferons</b> . . . . .	551
52.1	Alpha Interferons . . . . .	552
52.2	Beta Interferons . . . . .	555
52.3	Gamma Interferon. . . . .	559
52.4	Remarks . . . . .	560
	References . . . . .	562
<b>53</b>	<b>Hemopoietic Stimulatory Factors</b> . . . . .	563
53.1	Erythropoietins and Epoetins . . . . .	563
53.2	Remarks . . . . .	569
	References . . . . .	570
<b>54</b>	<b>Myelopoietic Stimulatory Factors</b> . . . . .	573
54.1	Filgrastim, Pegfilgrastim, Sargramostim . . . . .	574
54.2	Remarks . . . . .	578
	References . . . . .	578
<b>55</b>	<b>Thrombopoietic Stimulatory Factor</b> . . . . .	579
55.1	Interleukin-11. . . . .	579
55.2	Remarks . . . . .	581
	References . . . . .	581
<b>56</b>	<b>Pluripotent Growth Factors</b> . . . . .	583
56.1	Ancestim . . . . .	584
	References . . . . .	585
<b>57</b>	<b>Epidermal Growth Factors</b> . . . . .	587
57.1	Palifermin and Becaplermin. . . . .	588
	References . . . . .	590

## Part V Overview

<b>58</b>	<b>Biomedicines as Adverse Event Inducers</b> . . . . .	593
58.1	General Safety Profile . . . . .	603
58.1.1	Infusion Reactions and Injection Site Reactions . . . . .	603
58.1.2	Infections. . . . .	604
58.1.3	Hematological Events . . . . .	606
58.1.4	Anti-Drug Antibody Response . . . . .	606
58.1.5	Autoimmune Events . . . . .	607
58.1.6	Cutaneous Reactions . . . . .	608
58.1.7	Cardiotoxicity. . . . .	610
58.1.8	Systemic Syndromes . . . . .	610
58.1.9	Malignancies . . . . .	611
58.1.10	Other AEs Typologies . . . . .	612

---

58.2	Drug Class Analysis . . . . .	613
58.2.1	TNF Inhibitors . . . . .	613
58.2.2	T Lymphocyte Inhibitors . . . . .	614
58.2.3	B Lymphocyte Inhibitors . . . . .	616
58.2.4	VEGF Inhibitors . . . . .	617
58.2.5	Cytokines . . . . .	617
58.2.6	Interferons . . . . .	619
58.2.7	Hemopoietic Stimulatory Factors . . . . .	619
58.2.8	Epidermal Growth Factors . . . . .	620
	References . . . . .	622
<b>59</b>	<b>Conclusion and Perspectives . . . . .</b>	<b>625</b>
	References . . . . .	632



<http://www.springer.com/978-88-470-5312-0>

Adverse Events with Biomedicines  
Prevention Through Understanding

Tridente, G.

2014, XXX, 633 p., Hardcover

ISBN: 978-88-470-5312-0