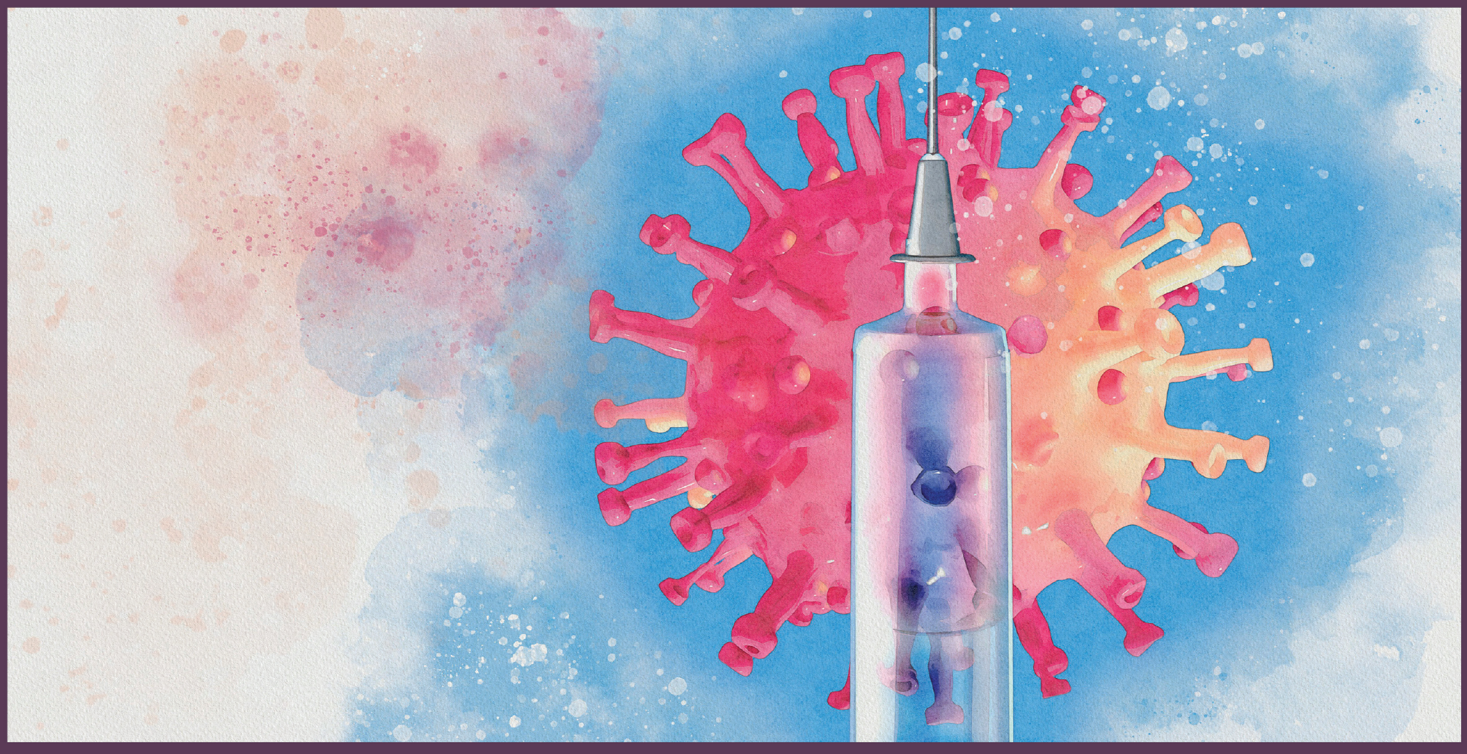
Drug Safety Evaluation

Fourth Edition

Shayne Cox Gad and Dexter W. Sullivan, Jr.



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To my beloved Novie Beth, for years of love and support, and to my aunt Ernestine, who is our matron and always a firecracker.

—Shayne Cox Gad

To Adrienne and Ayden, for your patience and support, and to my mother, Debby Mandeville, who never fails to inspire me with her courage.

—Dexter W. Sullivan, Jr.

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PREFACE

This fourth edition of *Drug Safety Evaluation* is a revision of the third edition that maintains the central objective of presenting an all-inclusive practical guide for those who are responsible for ensuring the safety of drugs and biologics to patients and shepherding valuable candidates to market, healthcare providers, those involved in the manufacture of medicinal products, and all those who need to understand how the safety of these products is evaluated. The many changes in regulatory requirements, pharmaceutical development, technology, and the effects of Covid on our society and science have required both extensive revision to every chapter and the addition of four new chapters.

This practical guide presents a road map for safety assessment as an integral part of the development of new drugs and therapeutics. Individual chapters also address specific approaches to evaluation hazards, including problems that are encountered and their solutions. Also covered are the scientific and philosophical bases for evaluation of specific concerns (e.g. carcinogenicity and development toxicity) to provide both understanding and guidance for approaching the new problems that have come to face both our society and the new challenges they brought. *Drug Safety Evaluation* specifically aims at the pharmaceutical and biotechnology industries. It addresses not only the general cases for safety evaluation of small and large molecules but also all of the significant major subcases: imaging agents, dermal and inhalation route drugs, vaccines, and gene therapy products. It is hoped that the approaches and methodologies presented here will show a utilitarian yet scientifically valid path to the everyday challenges of safety evaluation and the problem solving that is required in drug discovery and development.

Shayne Cox Gad
Raleigh, North Carolina

ABOUT THE AUTHORS

Shayne Cox Gad, B.S. (Whittier College, Chemistry and Biology, 1971) and Ph.D. in Pharmacology/Toxicology (Texas, 1977) DABT, ATS, is the principal of Gad Consulting Services, a 24-year-old consulting firm with 7 employees and more than 450 clients (including 200 pharmaceutical companies in the United States and 50 overseas). Before this, he served in the director level and in the abovementioned positions at Searle, Synergen, and Becton Dickinson. He has published 48 books and more than 350 chapters, articles, and abstracts in the fields of toxicology, statistics, pharmacology, drug development, and safety assessment. He has more than 39 years of broad-based experience in toxicology, drug and device development, statistics, and risk assessment. He has specific expertise in neurotoxicology, *in vitro* methods, cardiovascular toxicology, inhalation toxicology, immunotoxicology, and genotoxicology. He was the past president of the American College of Toxicology (ACT), the Roundtable of Toxicology Consultants, and three of Society of Toxicology (SOT's) specialty sections. He has direct involvement in the preparation of Investigational New Drugs (INDs) (110 successfully to date), New Drug Application (NDA), Product License Application (PLA), Abbreviated New Drug Application (ANDA), 501(k), Investigational Device Exemption (IDE), Common Technical Document (CTD), clinical databases for phase 1 and 2 studies, and PMAs. He has consulted for Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and National Institutes of Health (NIH) and has trained reviewers and been an expert witness for FDA. He has also conducted the triennial toxicology salary survey as a service to the profession for the past 27 years.

Dr. Shayne Cox Gad is also a retired line officer in Navy.

Dexter W. Sullivan Jr., MS, DABT, is the senior toxicologist of Gad Consulting Services where he consults on issues related to toxicology, pharmaceutical and medical device development, regulatory affairs, and human health risk assessment. He has authored and co-authored over 40 peer-reviewed publications, journal articles, book chapters, and abstracts in the abovementioned fields. Dexter is a Diplomate of the American Board of Toxicology and a member of the SOT as well as a member of the ACT. As an active member of the ACT, he has served as a member of the ACT Social Media Subcommittee and currently chairs the ACT Webinar Subcommittee. As a service to the scientific community, he has co-authored the toxicology salary survey for the past 10 years. As a consultant, Dexter has supported the successful preparation and filings for countless INDs as well as NDAs. He has consulted for EPA and performed thousands of human health risk assessments, including assessments for the EPA National Center for Environmental Assessment (NCEA) and the EPA Office of Water (OW). Dexter received his BS in Toxicology from the University of Louisiana at Monroe and his MS in Biology from Western Kentucky University.

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THE DRUG DEVELOPMENT PROCESS AND THE GLOBAL PHARMACEUTICAL MARKETPLACE

1.1 INTRODUCTION

Pharmaceuticals are a global industry, grossing $1.25 trillion (US dollars) in 2019. They are developed to benefit (and sell to) individuals and societies worldwide. Their effectiveness and costs affect, directly or indirectly, all of us.

This fourth edition focuses (as its predecessors did) on the assessment of the safety of new drugs. In the broadest sense, this means it must address not only the traditional "small molecules" that have dominated the field for the last century and the large therapeutic molecules derived from biotechnology sources but also vaccines, biologics such as blood and blood products, cell therapies, and excipients. The globalization of the regulation of the safety, efficacy, and manufacture of pharmaceutical products comes from the success of the International Conference on Harmonization (ICH) process. But, as will be seen, the same globalization of the industry and continuous advances of science have also led to market diversification of the types and uses of drugs, and with this, regulatory drug safety evaluation requirements continue to fragment, which has made things more complex rather than simpler (Alder and Zbinden, 1988; Gad, 2018; Norman 2016a, 2016b).

1.2 THE MARKETPLACE

The world marketplace for drugs is large, although the majority of sales are in three regions: in 2019 about 35% of the pharmaceutical market (by sales) resided in the United States, 24% in Europe, 12% in Japan, with the remaining 29% in emerging markets (Christel, 2019). This does not mean, however, that marketing applicants can or should ignore the requirements of other countries, for example, China and Indonesia. Approval processes in these countries can at times be as rigorous as in any other regulatory authority's domain.

Pharmaceuticals in all their forms compete today as part of a global market, though one which serves (and is available to) different parts of the world's population to varying extents.

The term "pharmaceuticals" is here used in the broadest sense of man-made therapeutics: small molecules, large protein moieties, vaccines, blood products, and as must be, their attendant components (excipients, impurities, and all) to different degrees and in different types of products.

According to the Statista (2019) global pharmaceutical market and therapy report, the global market for regulated drugs (as differentiated from dietary supplements, herbal products, and nutraceuticals) is estimated to have been some $1.25 trillion in 2019 (US dollars) (Drugs.com, 2014). In 2015, there were 143 individual products with annual sales in excess of $1 billion (i.e., "blockbusters") which have tended to be the focus of pharmaceutical development until recently and the impending demise of patents on which is changing the industry (Table 1.1). It remains to be seen how the Covid-19 pandemic influences 2020 and 2021 statistics.

This concentration of total sales in a limited number of products (e.g., there are currently more than 22 000 approved prescription drugs in the United States) is widely held to have distorted the therapeutic aspects of new drug development but is now starting to undergo change (back to) a paradigm that looks at a decreased emphasis on the billion dollar "blockbuster" drugs.

Widely misunderstood is the extent and diversity of the pharmaceutical R&D sector. While precise numbers are unavailable (and meaningless, as companies are continuously being started, merged, or going out of business, though the overall trend is to increased numbers), best estimates place the number of companies directly involved in discovering

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TABLE 1.1 Top 20 Selling Pharmaceuticals (2019) (Sharma, 2020)

Rank	Drug	Current manufacturer	Total sales 2019	Total sales 2018	Total sales 2017	Primary disease/ medical use	Route(s)
			In billions, USD				
1	Humira (adalimumab)	AbbVie, Inc. and Elsai	19.16	20.3	Not available	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, adult, and pediatric Crohn's disease, plaque psoriasis, juvenile idiopathic arthritis, ulcerative colitis, axial spondyloarthropathy (EU only), hidradenitis suppurativa, pediatric enthesitis-related arthritis (EU only), panuveitis, Behcet's disease (Japan only)	Injection
2	Keytruda (pembrolizumab)	Merck & Co.	11.08	7.17	3.8	Nonsmall cell lung cancer, melanoma, head, and neck squamous cell cancer, urothelial bladder cancer, kidney cancer, microsatellite instability-high cancer, classical Hodgkin lymphoma, gastric cancer, cervical cancer, primary mediastinal B-cell lymphoma, hepatocellular carcinoma, Merkel cell carcinoma	Injection
3	Revlimid (lenalidomide)	Bristol-Myers Squibb and Ono Pharmaceutical	9.37	9.69	8.19	Anemia, multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma, follicular lymphoma	Oral
4	Elquis (apixaban)	Bristol-Myers Squibb	7.92	9.87	7.4	Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; deep vein thrombosis and pulmonary embolism	Oral
5	Eylea (aflibercept)	Regeneron Pharmaceutical, Bayer, Saten Pharmaceutical	7.54	7.16	6.39	Neovascular (wet) age-related macular degeneration, macular edema following central retinal vein occlusion, diabetic macular edema, diabetic retinopathy	Intraocular

(Continued)

TABLE 1.1 (Continued)

Rank	Drug	Current manufacturer	Total sales 2019	Total sales 2018	Total sales 2017	Primary disease/ medical use	Route(s)
			In billions, USD				
6	Avastin (bevacizumab)	Roche, Chugai Pharmaceutical	7.3	7	6.8	Anti-angiogenic, brain tumor, certain types of cancers of the kidney, lung, colon, rectum, cervix, ovary, or fallopian tube. Cancer of the membrane lining the internal organs in the abdomen	IV
7	Opdivo (nivolumab)	Bristol-Myers Squibb, Ono Pharmaceutical	7.2	7.55	5.76	Melanoma, nonsmall cell lung cancer, small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma	IV
8	Rituxan/MabThera (Rituximab)	Roche, Chungai Pharmaceutical, Zenyaku Kogyo	6.9	6.9	7.55	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, pemphigus vulgaris, B-cell lymphoproliferative disorders (Japan), pediatric nephrotic syndrome (Japan)	IV
9	Stelara (ustekinumab)	Johnson & Johnson	6.36	5.16	4	Plaque psoriasis, Crohn's disease, psoriatic arthritis	Injection
10	Herceptin (trastuzumab)	Roche, Chugai Pharmaceutical	6.23	7.14	7.17	Breast cancer	IV
11	Prevnar 13/Prevenar 13 (pneumococcal conjugate vaccine)	Pfizer, Daewoong Pharmaceutical	5.84	5.8	5.69	Vaccine, pneumococcal disease, and pneumococcal pneumonia	Injection
12	Enbrel (etanercept)	Amgen, Pfizer, Takeda Pharmaceutical	5.22	7.13	8.23	Arthritis, or ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and polyarticular juvenile idiopathic arthritis	Injection
13	Ibrance (Palbociclib)	Pfizer	4.96	4.12	3.13	Breast cancer	IV
14	Remicade (Infliximab)	Johnson & Johnson, Merck, Mitsubishi Tanabe Pharma	4.36	6.44	7.73	Arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, plaque psoriasis	IV

(Continued)

TABLE 1.1 (Continued)

Rank	Drug	Current manufacturer	Total sales 2019	Total sales 2018	Total sales 2017	Primary disease/ medical use	Route(s)
			In billions, USD				
15	Genvoya (elvitegravir 150 mg/cobicstat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg)	Gilead Sciences, Torii Pharmaceutical	3.93	4.69	3.73	HIV-1 infection	Oral
16	Imbruvica (ibrutinib)	Johnson & Johnson, AbbVie	3.4	5.58	4.04	Mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, chronic graft versus host disease	Oral
17	Lyrica (pregabalin)	Pfizer Inc.	3.32	4.97	5.07	Control of seizures, fibromyalgia, diabetic neuropathy, herpes zoster, post-herpetic neuralgia, or neuropathic pain associated with spinal cord injury.	Oral
18	Victoza (liraglutide injection)	Novo Nordisk	3.29	3.85	3.67	Glycemic control in type 2 diabetes mellitus patients, reduce adverse cardiovascular events in adults with T2 diabetes mellitus	Injection
19	Neulasta/ Peglasta/G-Lasta (pegfilgrastim injection)	Amgen, Kyowa Hakko Kirin	3.22	4.69	4.72	Neutropenia caused by receiving chemotherapy, febrile neutropenia	Injection
20	Truvada	Gilead Sciences, Torii Pharmaceutical	2.81	3.01	3.17	HIV-1	Oral

Source: pharmashots.com (2020).

and developing new drugs in the United States and Canada at about 3800, 10% of which are publicly traded. There are an equal number in Europe and significant numbers in many other parts of the world (Japan, China, Australia, India, and Israel, to name just a few other countries). While most of the public focuses on very large companies, such as those in Table 1.2, there are many more midsize and small companies.

Starting in 1984 with the Drug Price Competition and Patent Term Restoration Act (better known as the Hatch–Waxman Act), members of small-molecule drugs leaving the period of patent protection could be introduced into the marketplace by an ANDA-approved route—a much simpler and quicker route to market approval. Such generics constituted 81% of the prescriptions in the United States by 2019, though their market share by sales ($260 billion in 2012) is only 21% of revenues (Statista, 2019).

One factor to consider in the regulatory requirements for early development of new therapeutic entities is the higher degree to which costs may present barriers to smaller, innovative companies. This is commonly overlooked by many