Chapter 2
Pharmaceutical Development

The process by which a new therapeutic entity is discovered and developed to the point that it is available to patients in the marketplace is complex, expensive, and long. We will not pretend to present or analyze this process in any detail here, but rather to give a basic understanding of the process and of the components that may be outsourced to a contract organization. There are no current or comprehensive volumes describing this process, though there are some volumes on the area (Guarino 1987; Mathieu 2000; Smith 1992; Sneader 1986; Spilker 1994).

As explained at the beginning of this volume, the pharmaceutical development process is a long (13–16 years from drug inception to market approval) and costly ($250–$800 million, depending on how one allocates costs) process, even when successful. It is shaped by medical needs, regulatory requirements, economics, finances, ethics, legal considerations, our understanding of sciences and diseases, and limitations of technology. All of these interact to shape a process that serves to iteratively reduce risks (to both economic and human safety), with the probability of failure being reduced in a stepwise fashion (Matoren 1984; Zbinden 1992). Figure 2.1 briefly summarizes this process, while Fig. 2.2 presents a more detailed summary of the process and activities up to the filing of an INDA (Investigational New Drug Application) and Fig. 2.3 is an alternative presentation. We will use the six categories of activities in Fig. 2.2 (Safety, Pharmaceutical Development, Pharmacology, Analytical, Clinical, and Regulatory) as a framework to discuss activities throughout the development process. The major pharmaceutical companies have their research and development expenses well documented (Tables 2.1 and 2.2). These figures are impressive, as are the sales of their products (Table 2.3). It should be kept in mind, however, that there are more than 2,500 smaller pharmaceutical development companies (both "small molecule" and biotech) in the United States, which have an even higher proportion of their budgets invested annually in research and development.

For our purposes (i.e., from the development to market perspective), the purpose of all nonclinical (animal and in vitro) development is to reduce the risks and probability of adverse events while optimizing the potential for therapeutic efficiency in humans.

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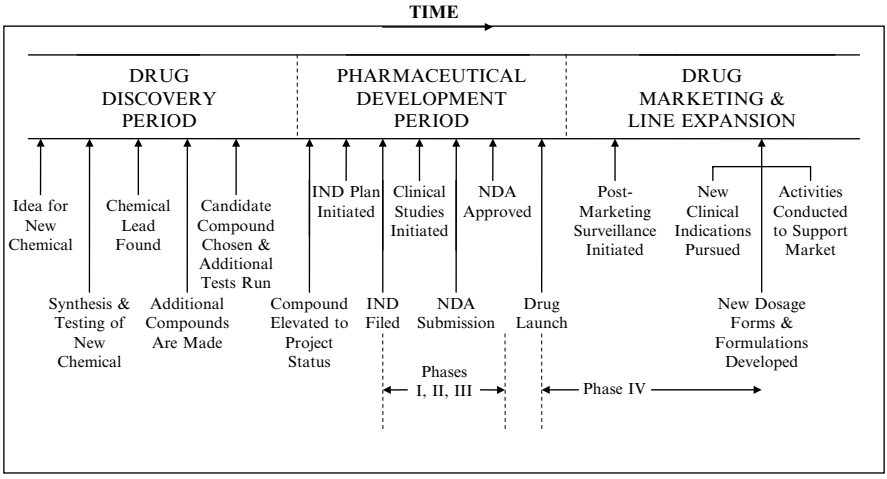

Fig. 2.1 Generalized flow of pharmaceutical development

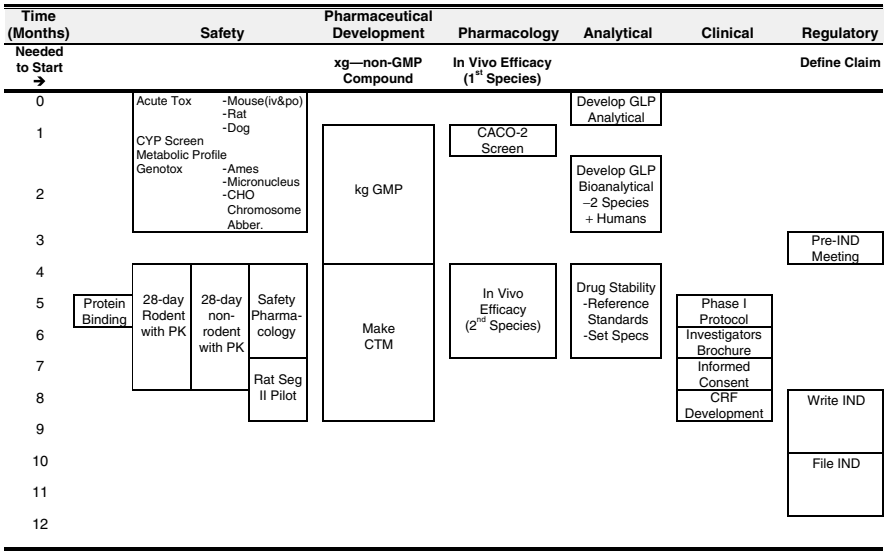

Fig. 2.2 Components of development to the filing and opening of an IND

But between initial nonclinical testing (and concurrent with additional animal testing) and a drug reaching the marketplace, the potential for having adverse effects in the general patient population, it is intended for is further guarded against by a scheme of increasingly more powerful human ("clinical") trials (Piantadosi 1997; Nylen 2000). How a drug is moved through this process is the subject of this chapter.

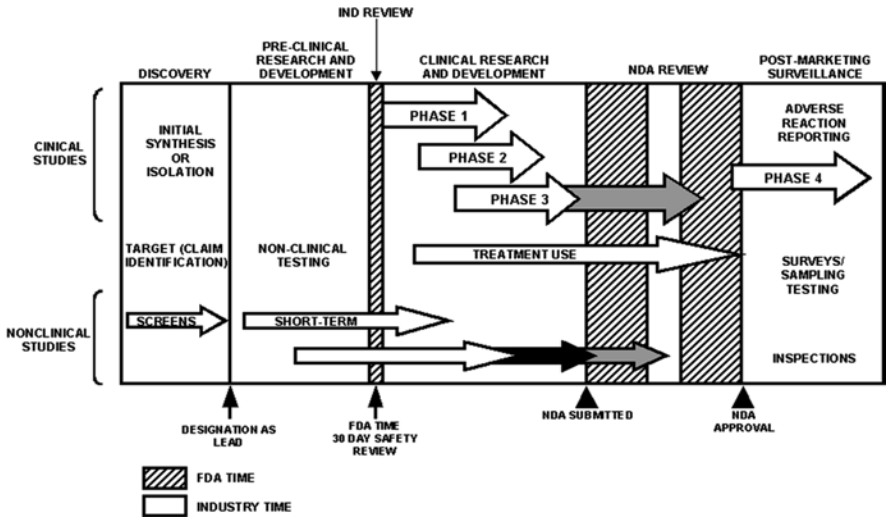

Fig. 2.3 The pharmaceutical development process, viewed as four stages (discovery, preclinical development, clinical development, and NDA review) as well as the important postmarket surveillance phase

Table 2.1 R&D, PhRMA member companies growth in domestic R&D and R&D abroad, ethical pharmaceuticals, PhRMA member companies, 1970–2009

Year	Domestic R&D ($)	Annual percentage change (%)	R&D abroad[a] ($)	Annual percentage change (%)	Total R&D ($)	Annual percentage change (%)
2009[b]	34,806.0	–2.2	10,976.1	–7.1	45,782.1	–3.4
2008	35,571.1	–2.8	11,812.0	4.6	47,383.1	–1.1
2007	36,608.4	7.8	11,294.8	25.4	47,903.1	11.5
2006	33,967.9	9.7	9,005.6	1.3	42,973.5	7.8
2005	30,969.0	4.8	8,888.9	19.1	39,857.9	7.7
2004	29,555.5	9.2	7,462.6	1.0	37,018.1	7.4
2003	27,064.9	5.5	7,388.4	37.9	34,453.3	11.1
2002	25,655.1	9.2	5,357.2	–13.9	31,012.2	4.2
2001	23,502.0	10.0	6,220.6	33.3	29,772.7	14.4
2000	21,363.7	15.7	4,667.1	10.6	26,030.8	14.7
1999	18,471.1	7.4	4,219.6	9.9	22,690.7	8.2
1998	17,127.9	11.0	3,839.0	9.9	20,966.9	10.8
1997	15,466.0	13.9	3,492.1	6.5	18,958.1	12.4
1996	13,627.1	14.8	3,278.5	–1.6	16,905.6	11.2
1995	11,874.0	7.0	3,333.5	[b]	15,207.4	[b]
1994	11,101.6	6.0	2,347.8	3.8	13,449.4	5.6
1993	10,477.1	12.5	2,262.9	5.0	12,740.0	11.1
1992	9,312.1	17.4	2,155.8	21.3	11,467.9	18.2
1991	7,928.6	16.5	1,776.8	9.9	9,705.4	15.3

(continued)

Table 2.1 (continued)

Year	Domestic R&D ($)	Annual percentage change (%)	R&D abroad[a] ($)	Annual percentage change (%)	Total R&D ($)	Annual percentage change (%)
1990	6,802.9	13.0	1,617.4	23.6	8,420.3	14.9
1989	6,021.4	15.0	1,308.6	0.4	7,330.0	12.1
1988	5,233.9	16.2	1,303.6	30.6	6,537.5	18.8
1987	4,504.1	16.2	998.1	15.4	5,502.2	16.1
1986	3,875.0	14.7	865.1	23.8	4,740.1	16.2
1985	3,378.7	13.3	698.9	17.2	4,077.6	13.9
1984	2,982.4	11.6	596.4	9.2	3,578.8	11.2
1983	2,671.3	17.7	546.3	8.2	3,217.6	16.0
1982	2,268.7	21.3	505.0	7.7	2,773.7	18.6
1981	1,870.4	20.7	469.1	9.7	2,339.5	18.4
1980	1,549.2	16.7	427.5	42.8	1,976.7	21.5
1979	1,327.4	13.8	299.4	25.9	1,626.8	15.9
1978	1,166.1	9.7	237.9	11.6	1,404.0	10.0
1977	1,063.0	8.1	213.1	18.2	1,276.1	9.7
1976	983.4	8.8	180.3	14.1	1,163.7	9.6
1975	903.5	13.9	158.0	7.0	1,061.5	12.8
1974	793.1	12.0	147.7	26.3	940.8	14.0
1973	708.1	8.1	116.9	64.0	825.0	13.6
1972	654.8	4.5	71.3	24.9	726.1	6.2
1971	626.7	10.7	57.1	9.2	683.8	10.6
1970	566.2	–	52.3	–	618.5	–
Average		*11.6%*		*15.5%*		*12.2%*

[a]Estimated

[b]R&D abroad affected by merger and acquisition activity

Notes: (1) R&D expenditures for ethical pharmaceuticals only. (2) Domestic R&D includes expenditures within the United States by PhRMA member companies. (3) R&D abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by U.S. divisions of foreign-owned PhRMA member companies. (4) Increases in R&D expenditures are likely due to a more rigorous data collection methodology

Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2009

Safety

The safety component of the development of a new drug has both a nonclinical (i.e., not in human beings) and a clinical component. Until an IND is opened, all safety evaluation is classified as nonclinical (also properly called, to this point, preclinical). After an IND is opened, both clinical and nonclinical components of safety evaluation are required. The timing of the nonclinical components, particularly after an IND is opened, is susceptible to a fair degree of judgment. The details of the components of this process are beyond the scope of this volume (see Gad 2009 for such details).

Table 2.2 Domestic R&D by function, ethical pharmaceuticals, PhRMA member companies, 1998–2000 (dollar figures in millions)

	1998		1999		2000	
Function	Dollars	Share (%)	Dollars	Share (%)	Dollars	Share (%)
Synthesis and extraction	2,066.7	12.07	1,763.1	10.0	987.7	9.3
Biological screening and pharmacological testing	2,600.5	15.1	2,508.1	14.2	2,582.9	12.1
Toxicology and safety testing pharmaceutical dosage	895.5	5.2	802.1	4.5	872.1	4.1
Formulation and stability testing	1,550.0	9.0	1,290.6	7.3	1,081.3	5.1
Clinical evaluation: phase I, II, and III	4,873.9	28.3	5,139.5	29.1	5,464.6	25.6
Clinical evaluation: phase IV	998.9	5.8	2,060.5	11.7	1,882.3	8.8
Process development for manufacturing and quality control	1,705.0	9.9	1,463.4	8.3	1,4999.9	7.0
Regulatory: IND and NDA	757.7	4.4	730.3	4.1	644.2	3.0
Bioavailability	413.4	2.4	321.6	1.8	327.8	1.5
Other R&D	1,265.9	7.9	1,594.3	9.0	2,693.7	12.6
Uncategorized ethical pharmaceutical R&D[a]	0.4	0.0	797.6	4.3	2,327.2	10.9
Total	*$17,127.9*	*100%*	*$18,471.1*	*100%*	*$21,363.7*	*100%*

[a]Represents companies that provided total R&D expenditure figures, but not individual details

Notes: (1) Company-financed R&D expenditures for ethical pharmaceuticals only. (2) Domestic R&D includes expenditures within the Unites States by PhRMA member companies

Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2002

Table 2.3 Top pharmaceutical companies

Company	Annual revenue (2009 global pharma sales) ($)	R&D expenditures (2009) ($)
Pfizer	44.2 Billion	7.9 Billion
GlaxoSmithKline	43.0 Billion	5.2 Billion
Sanofi-Aventis	38.7 Billion	6.5 Billion
Novartis	36.0 Billion	7.2 Billion
AstraZeneca	31.6 Billion	5.1 Billion
Johnson&Johnson	24.6 Billion	5.1 Billion
Merck	23.6 Billion	4.8 Billion
Roche	21.0 Billion	7.2 Billion
Eli Lilly	19.3 Billion	3.8 Billion
Wyeth	19.0 Billion	3.4 Billion
Bristol-Myers Squibb	17.7 Billion	3.6 Billion
Abbott	16.7 Billion	2.7 Billion
Bayer	15.1 Billion	2.5 Billion
Amgen[a]	14.7 Billion	3.0 Billion
Schering-Plough	14.2 Billion	3.5 Billion
Boehringer Ingelheim	13.6 Billion	2.9 Billion
Takeda	12.2 Billion	2.7 Billion
Teva	11.1 Billion	786 Million
Genentech[a]	10.5 Billion	2.8 Billion
Astellas	9.7 Billion	1.3 Billion
Daiichi Sankyo	8.8 Billion	1.6 Billion
Novo Nordisk	8.6 Billion	1.5 Billion
Merk KGaA	7.6 Billion	1.5 Billion
Eisai	7.2 Billion	2.2 Billion
Otsuka	6.5 Billion	1.0 Billion
Baxter International	5.3 Billion	868 Million
Servier	5.2 Billion	N/A
Gilead Sciences	5.1 Billion	722 Million
Mylan	4.3 Billion	317 Million
UCB	4.3 Billion	1.1 Billion

[a]Indicates biopharmaceutical companies

All the safety evaluation components have in common that they are heavily regulated and subjected to either GLPs (Good Laboratory Practices) or GCPs (Good Clinical Practices). The nonclinical components include genotoxicity (a minimum of three studies, usually an *Ames* assay (in vitro) and CHO chromosome aberration or unscheduled DNA synthesis in vitro and a mouse micronucleus in vivo), safety pharmacology (with evaluations of cardiovascular, central nervous system, and respiratory pharmacologic activities being required prior to the filing of the IND (pre-IND) and others before large clinical trials in patients are initiated), immunotoxicology (just now coming into being specifically required), systemic toxicity (single and multiple dose studies in two or more species with a pharmacokinetic (PK) component or arm to the multi-dose pre-IND, then longer multiple dose studies in concert with clinical development), developmental and reproductive toxicities,

carcinogenicity evaluations (if the drug is intended to be for chronic use), and any special studies that may be of interest to the reviewing agency or specific to the class of drugs or the intended use of the potential drug. Also generally required are determinations of degree of protein binding, the pharmacokinetics and disposition of the drug in animals and man, metabolic activation and inhibition, and the nature and level of significant metabolites in man (Ozdemir et al. 2001).

Pharmaceutical Development

The chemical development process also stretches through most of the length of the pharmaceutical development process. The needs to be met include the following:

- Manufacture of increasing amounts of quantities of active pharmaceutical ingredient of suitable purity and stability. Early lots are in gram (or tens of grams) quantities for small molecules. Such are produced under GLPs but not GMPs. Frequently, the first upscale produces lots of hundreds of grams. Finally, lots of kilo or greater sizes are produced. Keep in mind that the purities of these different lots are important. There are no specific guidelines written with regard to the levels of purity of test article material for nonclinical studies. Under any circumstances, do not produce material that is of extremely high purity for nonclinical studies. You can back yourself into a corner. If the material that is used in preclinical studies is of higher purity than that used in clinical studies, then the preclinical studies will have to repeated, because of the unfavorable impurity difference. This does not mean that the purities of preclinical and clinical lots have to be the same or identical. Typically the purity of any preclinical material should be about 95% or within 5% of the intended purity of the clinical trial material (CTM). It is acceptable and desirable to use material in nonclinical studies that is of lesser purity than the CTM. As synthetic scale up proceeds, the impurity profile of the test article will more than likely adversely change as a direct result of the scale up and the kinetic qualities of side reactions. Although such problems can be addressed, such activity consumes money, time, and resources and can readily be avoided with proper planning. Somewhere in here (typically late in the process), the most stable (and possibly soluble) form (frequently a salt) is produced under GMP's. Later efforts still may seek to identify and optimize the most economical production process.
- Human dosage form(s) must be developed and produced. When used in clinical trials, these are labeled CTM (Clinical Trials Materials). If for an oral drug, a simple formulation (such as a stable, simple capsule) may be used for phase I studies, but more elegant formulations are produced for later studies. If the route is parenteral, simple sterile, stable, and isotonic solutions are explored.
- Formulations must be developed, first for preclinical studies and then for clinical studies. Lots of considerations come into such formulations including bioavailability, stability, use of allowed excipients, and patient acceptability.

Swarbrick and Boylan (2002) provide an excellent overview of the range of skills and technology involve here.

Pharmacology

Pharmacology studies (other than safety pharmacology) initially serve to identify candidate compounds for development that is to identify and optimize "leads." Such studies (particularly in appropriate "gold standard" models of the specific disease to be treated – or predictive of efficacy) are essential both in making decisions to go forward with development of a compound and in helping estimate or model the dose to be used in the clinic. Dose selection or "target identification" for clinical trials is best performed based on achieving an effective concentration of therapeutic entity at the target site (receptors or organs in vivo), but should also at least have achieved plasma levels at efficient doses driving the target concentration for clinical studies.

Additionally, it is important to evaluate the specificity of action at the target sites. This means that activity and or binding at other receptor sites must be characterized quantitatively (e.g., K_i, K_d, K_a, etc.), as such may limit the actual target concentration and potential utility of a drug.

Since 2006, the FDA has started to require formal laboratory evaluation (with formal reports) to support the claims and/or assumptions of pertinent pharmacodynamics – that is desired therapeutic activity in a suitable animal model.

Analytical

It is clearly essential to be able to both identify and quantitate the actual drug entity itself in a range of biological and nonbiological milieu. These include the lots of drug produced (where purity and the identity of any accompanying impurities also is important), stability study samples, dosage preparations for preclinical studies, and fluid and tissue samples from in vivo studies.

The last of these tasks usually mean being able to accurately and sensitively quantitate the levels of the drug entity in serum, blood or plasma, and urine, and possibly in target tissues. Such methods need to be developed and validated not only for humans but also for the principal species used in nonclinical studies (usually rats and either dogs or nonhuman primates (NHP), plus in rabbits to verify exposure in developmental toxicology studies).

It also becomes important at some point to be able to identify and quantitate the levels of significant metabolites, particularly if they are pharmacologically active. The limit of detection (LOD) needs to be in the picogram (pg/mL) range to satisfy regulatory agencies. This LOD is not documented in any guideline, but has slowly evolved over the recent years as analytical technology has increased to permit such a level of detection. What exactly does a pictogram level of detection mean? Well certainly 1 pg/mL is a highly desirable level, and 1,000 pg/mL is not ideal. In method development, try to get as close as one can to the 1 pg/mL level, but if the final result is 495 pg/mL, it will be acceptable to the agency. A level such as 500 ng/mL will not be acceptable, providing that there is not sufficient documentation to PROVE and support that number as a methodological endpoint.

Clinical

Generally, the single most expensive (and time consuming) portion of any pharmaceutical development timeline is the clinical evaluation portion (Spilker 1994). Initially these studies (Phase I) are intended primarily to evaluate the safety (tolerance) and pharmacokinetics of a drug, and unless the drug is intended to treat life threatening conditions, such studies are performed in healthy volunteers and not patients. Patients can be used in life-threatening conditions. Although it should generally be possible to perform such work with just three (single dose escalating, multi-dose tolerance and a single dose escalating) or four studies (validation of achieved dose by an optimized formulation/dosage form), many more may need to be performed.

Subsequent to the completion of the Phase I studies, a series of phase II studies are generally performed in patients, first and very importantly to give confidence in efficacy. Finally, it should be noted that regulatory approval generally requires the completion of two successful "pivotal" studies. These are generally phase III studies, but may be phase II studies. The requirements are as follows: adequate numbers of patients to achieve unequivocal statistical proof of efficacy of an accepted a priori endpoint, and adequate numbers and exposure of a representative patient population to identify the potential occurrence of any significant safety concerns when the drug is on the market. All this is done while protecting trial subject safety and confidentiality to the fullest extent possible (Willman 2000; Wechsler 2001).

The phase III testing phase is almost always both the longest and the most expensive segment of the drug development process. From the earliest point, sponsors/investigators seek to gain first any reliable hint that the drug works (see Biomarkers Definitions Working Group 2001) while also worrying about previously undetected safety concerns such as hepatic damage (Kaplowilz 2001).

Regulatory

In parallel with (Gad 2010) all of the technical activities in the pharmaceutical development process, there is an accompanying string of activities which must be conducted to fulfill the regulatory requirements for successfully completing the market approval (NDA) process. Such usually start with bringing about a successful pre-IND meeting with FDA. Subsequent to this interaction, the following generally must occur:

- An INDA must be assembled, paginated, and submitted. Any resulting questions raised by the FDA must be answered effectively and in a very timely manner.
- The "opening" of the IND (Investigational New Drug (Application)) must be verified (the FDA does not usually provide any such verification).
- Necessary IND amendments (documenting changes in formulation; significant findings as to safety; changes in clinical study protocols, facilities or personnel, or new protocols) must be to the FDA submitted in a timely manner.
- An end of phase II meeting with FDA should be effectively executed.

- Assembly and submission of an NDA, with effective and timely response to any subsequent FDA queries.
- An effective quality monitoring and auditing program of vendors performing GLP, GMP, and/or GCP regulated tasks.

Except for those cases where there is substantial potential to save or extend lives (such as anticancer and anti-AIDS drugs) or where the intended target diseases are chronic and severe (e.g., Parkinson's or MS) or the routes of administration are invasive (e.g., intrathecal), the initial evaluations in humans are performed in "normal," healthy volunteer with the primary objective being limited to defining the limits of tolerance (safety) of the potential drug and its pharmacokinetic characteristics. These trials may also seek to detect limited (usually surrogate or indirect) indicators of efficacy, but are severely limited in doing so (Biomarkers Definitions Working Group 2001). Later trials look at the drug's actions on carefully defined and selected groups of patients.

With the number of drugs withdrawn from the marketplace since 1990 (or, perhaps, the degree of media coverage of such withdrawals), public concern with and media coverage of the workings of the drug safety evaluation aspects of the development process have risen sharply (Granter 1999; Wechsler 2001). It is currently estimated that in the United States, adverse drug reactions (ADRs) rank between the fourth and sixth leading cause of death (Eikelbom et al. 2001). Although improvements in the nonclinical procedures of drug safety assessments are possible and even likely, clearly the clinical aspects are likely to be where the most relevant improvements in trials and a better understanding of individual or subpopulation differences in human responses to drugs are to be found.

Although there is much press about the concern that the "increased pace of drug approval" has caused the release onto the market of less safe drugs (Willman 2000), the causes are more mundane and of much longer standing. The most common "unexpected" (from nonclinical trial results) safety findings in initial trials involve the skin (dermatitis of one form or another) and the liver (Kaplowilz 2001).

An important reason for the high incidence of serious and fatal ADRs is that the existing drug development paradigms do not generate adequate information on the mechanistic sources of marked variability in pharmacokinetics and pharmacodynamics of new therapeutic candidates, precluding treatments from being tailored for individual patients with their physiologic, biochemical, and genetic idiosyncrasies (Ozdemir et al. 2001).

Pharmacogenetics is the study of the hereditary basis of person-to-person variation in drug response. The initial focus of pharmacogenetic investigations has traditionally been unusual and extreme drug responses resulting from a single gene effect. The Human Genome Project and recent advancements in molecular genetics now present an unprecedented opportunity to study all genes in the human genome, including genes for drug metabolism, drug targets, and postreceptor second messenger mechanisms, in relation to variability in drug safety and efficacy. In addition to sequence variations in the genome, high throughput and genome-wide transcript profiling for differentially regulated mRNA species before and during drug treatment

will serve as important tools to uncover novel mechanisms of drug action. Pharmacogenetic-guided drug discovery and development represent a departure for the conventional approach, which markets drugs for broad patient populations, rather than smaller specifically targeted groups of patients in whom drugs may work more effectively and optimally. To date, these new tools have not brought a product to market. But their use is in demand, as are the older receptor-binding screening services intended to determine the specificity of action of a potential drug.

Putting It All Together

While integrative project management is not a separate or distinct segment of pharmaceutical development, its proper use and incorporation in the development pathway is essential to ensure that in the end all of the steps and pieces fit together in a coherent fashion. Extensive options are available in contract research are available to ensure that this happens. In the large pharmaceutical companies (Table 2.3), these skills historically have been to a large part internal. For the vast majority of the smaller 3,500 pharmaceutical/biotech companies (in the US and Canada), this is not the case and the services must be contracted at least in part or more commonly in the whole from either a large ("meta") CRO, a smaller CRO, a provider specializing in niche services, or a "fatigue" organization, which serves only a few clients at a time. Keep in mind that there are about an equal number of drug companies located all over the world that are not located in the US or Canada.

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