

INDUSTRY TRENDS—CLINICAL

The 2007 Pharmaceutical and Biotech Pipeline Year-End Summary:

What it Says About the State of the Art of Discovery & Development

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The BioPharm Insight 2007 pipeline data summary (see Tables) accentuates a theme that has been repetitively voiced within the research and clinical development community for a number of years:

- Basic science is the engine of innovation in drug discovery
- There is a return to “deep science” within the pharmaceutical community with a commitment to characterizing both normal and pathophysiological processes at the molecular level in order to develop potential therapeutics
- The more permissive and informative the science the more compounds within discovery that can transition into clinical trials (see cancer, infectious disease, and central nervous system disorders for example)
- Drug discovery and early phase clinical development are increasingly enmeshed phases conceptually, with “discovery *within* development” used as a vehicle to select compounds for registration programs

NDA/BLA Filed	858
Phase 3	1,962
Phase 2	4,231
Phase 1/IND Filed	4,577
Preclinical/Discovery	11,553
No. of Products Launched	4,017
Status Unclear	306
Total	27,504

BLA indicates biologic license application; IND, investigational new drug application; NDA, new drug application.

There is no economy of scale regarding innovation. Novel therapeutics may be derived from academic institutions, and small and medium-sized pharmaceutical companies, as often as from the larger research organizations. Given an increasingly prolific process, competitive drug discovery demands an ability to eliminate compounds as early in discovery as possible, in a fashion that

does not stifle creativity. Across the industry, “potential hits” are triaged using virtual and actual biodisposition and toxicity paradigms with criteria consistent with potential as a drug candidate. Additionally, enhanced screening is introduced earlier in the discovery/development algorithm, ie, more upstream (closer) to the primary and secondary biological assays leading to candidate selection for clinical testing. In an entirely analogous fashion, integration of early phase clinical research into the drug discovery process requires an ability to efficiently evaluate different compounds simultaneously, rather than sequentially. The objective of this integrated stratagem is to maximize the value of the early phase portfolio considered in aggregate, rather than the value of individual projects contained within the portfolio, minimizing resource utilization and expenditures until program risk is significantly reduced.

A comparison of the attrition pattern for compounds from preclinical/discovery to registration programs (phase 3) is illustrative. Innovative science permits identification of an increasingly large array of novel new molecular entities. Given the uncertain homology that may exist in some therapeutic areas between animal models and biological effects in man even for basic attributes such as pharmacokinetics and safety, the need to render an early decision about a compound’s potential utility in man, as opposed to extensive testing in animals, is increasingly recognized as key. Therefore, there is an impetus to begin limited human experimental evaluation as expeditiously as possible in phase 1 (including first in man studies) then phase 2 studies (dose ranging, proof of concept trials) placing considerable emphasis upon decision-making paradigms with an efficient allocation of resources. The more compounds within the discovery portfolio (see cancer for example), the more innovative the clinical and biostatistical methodology employed. This process is accelerating.

For example, no therapeutic area has contributed more to the development of clinical trial methodology, broadly defined, than has oncology. This phenomenon is in part due to an explosion in basic science that has facilitated the identification of very innovative therapeutics for which traditional trial methodology in a “proof of concept” study might be inappropriate. In oncology, and increasingly in other therapeutic areas, an ability to update and modify trial design as new clinical data are accrued, can allow a trialist to “prune” uninformative dosage groups from multi-arm dose-ranging trials prior to trial conclusion, terminate research on a clinical candidate as “futile” within constraints defined at study inception, and continuously update the information supporting the rationale for a study (ie, the hypothesis) as data

Therapeutic Area	Total No. of Investigational Drugs	NDA/BLA Filed	Phase 3	Phase 2	Phase 1/IND Filed	Preclinical/Discovery	No. of Products Launched	Status Unclear
Cancer	7,020	104	527	1,540	1,473	2,859	437	80
Infectious Diseases	2,957	89	196	348	423	1,327	542	32
Central Nervous System	2,900	155	211	394	397	1,217	507	19
Cardiovascular	2,135	75	219	300	287	740	480	34
Hormonal Systems	1,515	72	124	222	265	513	309	10
Miscellaneous	1,490	8	8	18	168	1,232	44	12
Immune System	1,434	48	93	126	214	732	214	7
Gastrointestinal	1,096	48	98	208	176	347	212	7
Musculoskeletal	1,089	38	84	177	161	388	222	19
Pain	956	58	99	172	147	236	231	13
HIV Infections	874	17	43	99	171	454	70	20
Respiratory	870	27	56	167	163	310	135	12
Diagnostic/ Imaging Agents/Delivery	832	17	23	47	125	508	106	6
Genitourinary	670	32	57	134	90	165	186	6
Dermatology	660	27	43	140	109	173	151	17
Hematological	579	24	39	78	124	198	111	5
Eye and Ear	427	19	42	61	84	154	60	7
Total	27,504	858	1,962	4,231	4,577	11,553	4,017	306

accumulates. Utilization of biomarkers including imaging technology rather than clinical endpoints, and enrolling a highly “leveraged” patient sample (patients with characteristics likely to enhance signal detection based upon genotypic or phenotypic information) additionally maximizes sensitivity in a proof of concept motif. All of these complementary approaches provide a conduit for early phase translational research supporting an active drug discovery process.

Indeed, innovative trial design methodology is facilitated by the existence of relatively new regulatory guidance both in the United States and Europe that will permit compound evaluation in man, with certain restrictions, following submission of a comparatively limited portfolio of preclinical studies. Limited “exploratory IND investigations” in humans can be initiated with less, or different preclinical support than would be required for a traditional application as these studies present fewer potential risks to subjects or patients than traditional trials that specifically look for dose limiting toxicities. An exploratory IND program may permit an understanding of a compound’s mechanism of action relevant to a particular disease state, characterize the pharmacokinetic or biodisposition profile of a candidate drug, or enable the selection of promising lead products from a group of candidates that interact with a therapeutic target in humans. Should a compound prove “interesting” in small elegant

clinical trials, traditional safety and toxicological studies in animals that enable large-scale clinical trial testing are completed. This concept is closely related to a “fail fast” thematic that places considerable valence on the *elimination* of compounds early in development, prior to the allocation of the resources required to obtain regulatory approval. Parenthetically, this strategy is far more appropriately utilized in those pharmaceutical companies with a robust pipeline as opposed to organizations with limited resources and potential therapeutic agents.

The implications for the healthcare environment are considerable.

- First, of necessity, the system continues to place considerable emphasis upon novelty, not potential clinical *value* during the discovery process and the early phases of clinical research. By definition, it is the chemical and biological novelty of the compound, and a confirmation of activity in man that provides the catalyst for a decision to transition from “discovery in development” to a prototypical development program. For example, it is an unusual company, perhaps only one with a cornucopia of compounds for potential evaluation, that will heavily weight reimbursement decisions late in discovery or very early in clinical research.

- Secondly, in the ultimate expression of the art, the clinical trial methodology upon which early development decisions can be based increasingly uses experimental

paradigms and endpoints that are not transparent to the non-trialist and non-scientist. This process essentially precludes the informed observation and participation of many consumers of this research until peri-approval studies are launched.

- Thirdly, the database that enables health technologies assessments can be increasingly populated by patients and physicians who may not be representative of those ultimately utilizing the product. Although poor “generalizability” has always plagued the drug development process, the current development environment frequently does not encourage evaluation of patients in the “deep end of the swimming pool” until very late in the process; ie, those less than optimal patients from a research perspective with the co-morbidities, diverse concomitant medications, and complicated medical management requirements that ultimately drive healthcare utilization. Given that many discovery programs focus upon indications where “chronicity” is characteristic, where physicians and patients must form a dyadic relationship for healthcare decisions, the inability for many healthcare professionals and patients to participate in the evaluation of a potential therapeutic until its commercialization is notable.

- Finally, given that rare but clinically important safety observations are a reflection of the extent of patient exposure, duration of therapy and disease characteristics, accelerated development efforts particularly for serious or life-threatening illnesses virtually assure the submission of a database with highly circumscribed implications regarding safety and other pragmatic applications in a more relevant healthcare environment. Accelerated clinical development processes therefore provide an impetus for the initiation of post approval studies (post marketing, phase 4 commitments) that are designed to detect safety signals, characterize optimal use, and generate other hypotheses for definitive prospective testing. An emerging “science of safety” will facilitate an ability to target a specific drug to an appropriate population, maximizing its potential as a therapeutic at every phase of testing. As important as translational medicine has become for first in man investigations, a complementary concept also recognizes that “translational medicine” is mandated at the interface of a development program with its commercial transition.

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Dr. Murphy is an Editorial Board member of American Health & Drug Benefits™.

INDUSTRY TRENDS—BUSINESS

UNITED HEALTHCARE BECOMES FIRST COMPANY TO BASE CHEMOTHERAPY DRUG COVERAGE ON NATIONAL COMPREHENSIVE CANCER NETWORK COMPENDIUM

- *NCCN Compendium provides independent source for chemotherapy coverage decisions*
- *Reflects United HealthCare’s commitment to evidence-based medicine by partnering with leading medical societies and physician organizations*

MINNEAPOLIS—(Jan. 16, 2008)—United HealthCare, a UnitedHealth Group (NYSE: UNH) company, announced that, effective March 15, it will base its benefit coverage for chemotherapy drugs used in outpatient settings on the *National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium*.

The NCCN, an alliance of 21 of the nation’s leading cancer centers, is an authoritative source of information to help patients and health professionals make informed decisions about cancer care. The NCCN’s compendium recommends drugs and biologics for the major types of FDA-approved disease indications and specific NCCN panel recommendations.

The development of NCCN information is based on the independent evaluation of available scientific evidence integrated with the expert judgment of leading clinicians. Compendium recommendations are derived from the *NCCN Guidelines™*, a widely-used source of information recognized as the standard of care for oncology in the United States.

Bill McGivney, PhD, NCCN CEO, said: “We are pleased that United HealthCare is the first company to choose the NCCN’s compendium as the basis for its guidelines in reimbursing for chemotherapy drugs administered in an outpatient setting. The compendium is developed based on the explicit evaluation of available scientific evidence integrated with the expert judgment of multidisciplinary panels of expert physicians from NCCN member institutions. The breadth and scope of this collaborative effort represents a significant advance beyond any previously developed guidelines. As a result, the NCCN guidelines have become the most widely used in oncology practice.”

Previously, United HealthCare based its chemotherapy-drug policies on a range of medical literature resources, which, according to Lee Newcomer, MD, United HealthCare’s senior vice president, oncology, has been standard in the industry.

The *NCCN Drugs & Biologics Compendium* guidelines recommend the most appropriate therapy based on clinical

INDUSTRY TRENDS—BUSINESS (continued)

evidence and the consensus of leading academic cancer centers. They suggest the correct diagnostic evaluation, such as scans, x-rays and lab tests, optimal therapy—drug, x-ray or surgery—as well as appropriate follow-up tests.

“United HealthCare is the first national health plan to incorporate National Comprehensive Cancer Network guidelines into our chemotherapy-drug benefit,” said Dr. Newcomer. “Our collaboration with NCCN reflects United HealthCare’s commitment to partner closely with the nation’s leading independent medical societies and physician organizations in order to ensure our members receive quality, evidence-based care.

“This new policy provides clinicians, patients and our customers with a respected, independent reference

source for use in making chemotherapy coverage decisions,” Dr. Newcomer added. “It is one of several programs launched after United HealthCare established a dedicated oncology team in 2005 to improve the quality of oncology care for our members. NCCN guidelines are a trusted source of treatment recommendations, and we value the fact that they are publicly available for both physicians and patients.”

United HealthCare will update its chemotherapy-drug policies in conjunction with monthly updates made by the NCCN to its compendium. United HealthCare is currently communicating this change in drug policy regarding use of the compendium to its network of physicians. Complete information is available on the company’s physician portal at www.unitedhealthcareonline.com. ■

INDUSTRY TRENDS—POLICY

Healthcare Cost Concerns

The Kaiser Health Security Watch reports that more Americans are personally worried about healthcare costs than about paying their rent or mortgage, being a victim of a terrorist attack or a violent crime, losing their job, or losing money in the stock market.

Nearly half of adults (46%) say they are very worried about their income not keeping up with rising prices, and nearly as many say the same about having to pay more for their healthcare or health insurance (41%). In our 3 years of tracking, income not keeping up with rising prices and having to pay more for healthcare and insurance have always been the top 2 worries; in some months, the concern about income has been slightly higher, and in others, healthcare cost worries have been slightly higher.

Among other specific healthcare worries, 35% say they are very worried about not being able to afford healthcare services they think they need, and 29% of those with health insurance say they are very worried about losing their health insurance coverage.

Healthcare worries rank ahead of other nonhealth concerns for the public, including not being able to pay their rent or mortgage (27%), losing a job (23% of those who are employed), being the victim of a terrorist attack (22%) or a violent crime (21%), or losing money in the stock market (21%). ■

Kaiser Health Security Watch—December 2007, The Henry J. Kaiser Family Foundation, December 2007. <http://www.kff.org/healthpollreport/CurrentEdition/security/upload/HSW1207.pdf>.

Kaiser Health Tracking Poll: Election 2008 - December 2007

This December 2007 tracking poll finds that Iraq continues to top the list of issues that the public wants to hear presidential candidates talk about, with more than a third (35%) naming the war as one of the top 2 issues in an open-ended question. Healthcare (30%) ranks second, followed by the economy (21%) and immigration (17%).

Healthcare ranks second behind Iraq for Republicans, Democrats, and Independents alike; however, although health ranks clearly ahead of the economy and immigration for Democrats, it is more tightly packed with these issues for Republicans.

When asked about the issues that will affect their vote for president in 2008, the list of issues is similar to those the public wants to hear candidates discuss—Iraq (29%), followed by healthcare and the economy (tied at 21%), with immigration (12%) somewhat further behind. Iraq is the top voting issue for Republicans, Democrats, and Independents alike.

The poll also examines the specific aspects of healthcare that the public wants candidates to address, as well as their perceptions of the presidential candidates on health issues.

This latest Kaiser Health Tracking Poll: Election 2008, the fifth in a series, was designed and analyzed by public opinion researchers at the Kaiser Family Foundation. A nationally representative random sample of 1,221 adults was interviewed by telephone between November 28 and December 9, 2007. The margin of sampling error for the survey is plus or minus 3 percentage points; for results based on subgroups, the sampling error is higher.

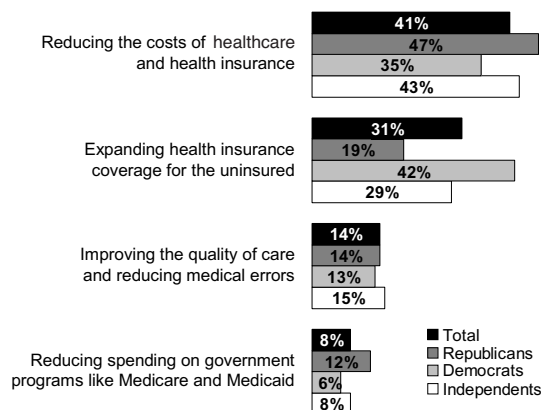
Thinking about the campaign for the presidential election in 2008, what 2 issues would you most like to hear the presidential candidates talk about? (open-ended)

Issue Rank	Total	Republicans	Democrats	Independents
1	Iraq (29%)	Iraq (25%)	Iraq (35%)	Iraq (30%)
2	Healthcare (21%)	Economy (18%)	Healthcare (28%)	Economy (22%)
3	Economy (21%)*	Healthcare (16%)	Economy (23%)	Healthcare (20%)
4	Immigration (12%)	Terrorism (15%)	Immigration (10%)	Immigration (16%)
5	Frustration w/gov't (11%)	Morality issues (14%)	Frustration w/gov't (9%)	Frustration w/gov't (10%)
6	Terrorism (8%)	Frustration w/gov't (14%)*	Gas prices/energy (6%)	Terrorism (9%)
7	Taxes (6%)	Immigration (13%)	Education (5%)	Taxes (9%)*

*Indicates a tie with item directly above.

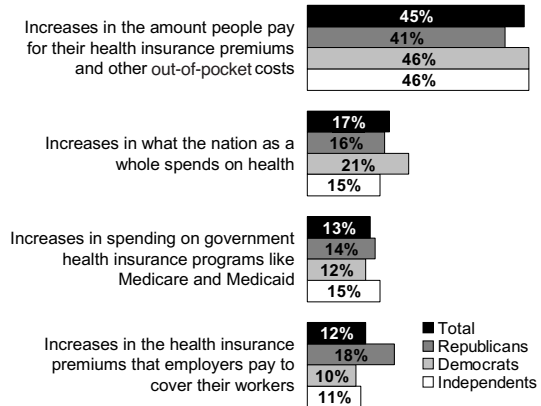
Kaiser Health Tracking Poll—Election 2008: Key Findings (#7728), The Henry J. Kaiser Family Foundation, December 2007.

Which ONE of the following healthcare issues would you most like to hear the presidential candidates talk about? (Dec. 2007)



Kaiser Health Tracking Poll—Election 2008: Key Findings (#7728), The Henry J. Kaiser Family Foundation, December 2007.

When thinking about rising healthcare costs, which ONE of the following concerns you most...? (Dec. 2007)



Kaiser Health Tracking Poll—Election 2008: Key Findings (#7728), The Henry J. Kaiser Family Foundation, December 2007.

We asked people what concerns them most when thinking about rising healthcare costs. For nearly half the public, their biggest healthcare cost-related concern has to do with increases in the amount people pay out of their own pockets for healthcare and insurance (45%, up from 38% in June, the last time the question was asked). This is true for Republicans, Democrats, and Independents alike. Behind out-of-pocket costs, smaller shares say they are most concerned about increases in what the nation as a whole spends on health (17%), increased spending on government health insurance programs (13%), and increases in insurance premiums paid by employers (12%). ■

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