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*Life Sciences Reports*

# A New Paradigm for Clinical Development: The Clinical Trial in 2015

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*By Hermann A.M. Mucke, PhD*

## About the Author

*Hermann A.M. Mucke, PhD*, spent 17 years in academia and industry before he founded H.M. Pharma Consultancy ([www.hmpharmacon.com](http://www.hmpharmacon.com)) in 2000 to become an independent pharmaceutical consultant, analyst, and science author. His last industry position was Vice President R&D in a European pharmaceutical company, which he helped to take public on the Frankfurt Stock Exchange in 1999. Since then, Dr. Mucke, who holds a Ph.D. in biochemistry from the University of Vienna (Austria) became a consultant and advisory board member for several European and American pharmaceutical companies, and a regular reviewer of drugs and patents for Thomson Current Drugs and Ashley Publications. He has been writing reports for CHA since 2004, when he became an Affiliated Author. Dr. Mucke is based in Vienna and can be reached at [h.mucke@hmpharmacon.com](mailto:h.mucke@hmpharmacon.com), or by fax at +43 1 494 9989.

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# Executive Summary

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The pharmaceutical industry is trapped in a deepening productivity crisis: The years 2003 and 2004 marked a 25-year low point in worldwide market launches for new active compounds. On the other hand, the number of investigational drug applications to the Food and Drug Administration (FDA) reached a new high in 2004, passing a record mark that had been held since 1998. Evidently, the discovery and preclinical development process is highly productive, but the fraction of candidates that make it through the subsequent clinical evaluation process is steadily decreasing. Currently, approximately 30% of new molecular entities fail in Phase I clinical testing, and, although a 20% failure rate in Phase III trials was common in the early 1990s, this figure is now closer to 50%. Of all compounds that begin human clinical testing, more than 80% fail, because of either efficacy or safety issues. For those candidates that made it to U.S. pharmacy shelves as prescription drugs, no fewer than 10% faced market withdrawal or severe use restrictions between 1975 and 2000.

Although the changing characteristics of early-stage compounds that emerge from the discovery process and marginally adequate animal models certainly represent one part of the problem, the way that human trials are presently designed and conducted makes greater contributions to the delays, failures, and exploding costs that are the current hallmarks of the clinical process. So far, the industry has reacted to these problems essentially only by “streamlining” the existing processes and by introducing information technology in a cautious and evolutionary fashion. No fundamental changes were attempted, in large part because the FDA and other regulatory authorities worldwide tended to rely on tried and tested study designs, clinical endpoints, and modes of documentation. However, the FDA’s Critical Path Initiative of 2004 has shown that the agency is now not only willing to work toward a remedy with representatives from industry and academia but to take the lead in this process.

We believe that a bidirectional approach is needed to accelerate the clinical process and make it more effective. These two avenues—revamping of trial design and truly pervasive modeling and monitoring driven by information technology—are fundamentally different from each other but need to be implemented in a closely linked fashion. Although radical in effect, none of these changes would involve concepts or technologies that are unknown today.

On the design level, Phase I will assume a new role as a brief confirmatory testing stage for the model for drug–human interactions that the sponsor has proposed. Phases II and III will merge into a single, advanced-stage human testing phase that involves fewer patients than today, relying on relatively small populations that are highly homogenous with respect to key criteria of pharmacologic response. Likewise, systematic postmarketing studies and a significantly improved and extended postmarketing surveillance system that goes far beyond adverse event reporting will be integrated into a postmarketing monitoring phase that documents real-life use of the newly licensed drug.

These new processes will be made possible through holistic mathematical models, such as the “virtual patient” (representing not the “average human” but variants of target patients of both sexes, different ethnicities, and various ages, with medical conditions that typically coexist in this target population), extensive biomarker monitoring, and “pervasive computing.” The last-mentioned omnipresent information technology will rely not so much on vastly improved software algorithms or hardware (although both will be needed) but more on the concept of seamless capture of every elementary act (driven by radiofrequency identity tags [RFIDs] and distributed processors) and equally seamless worldwide data exchange, driven by global standards.

With full implementation of all envisaged changes by the year 2015, the stage would be set for a new world of drug development. The pre-approval clinical trial phase might be shortened to approximately 3 years, and 40% to 50% of all candidate compounds that enter this stage could complete it, with the majority of the failures occurring in the early human validation phase. Instead of being plagued by safety issues, as is the case today, the crucial function of advanced-stage human testing phase will be to determine whether efficacy is sufficiently superior over the established standard of therapy to warrant the cost of launch and the mandated postmarketing monitoring. Although this will allow developers to recoup development costs earlier and to enjoy

a longer life cycle under patent protection, it will also require that more and closer attention be paid to real-life use of the newly licensed drug.

Although implementation of such a reinvented clinical process by 2015 is feasible from a conceptual, technical, and logistical point of view, it might face delays stemming from deficiencies in international cooperation between regulatory authorities. However, such political resistance will not be a permanent hurdle in an increasingly globalized economic environment because, in the author's view, no alternative option exists for reinvigorating pharmaceutical productivity.

# Table of Contents

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**CHAPTER 1**

- CLINICAL TRIALS TODAY.....1
- 1.1. More Targets, More Research and Development Spending,  
More Candidate Drugs—and Fewer New Products.....1
- 1.2. The Clinical Trial Process: From Phase I to Phase IV .....2
- 1.3. A Strategic Problem Analysis .....7
  - Why Do Phase III Trials Fail So Frequently?.....9
  - High-Profile Market Recalls: The Worst-Case Scenario  
Enacted .....13
  - Approved but Not Effective in All Eligible Patients.....14

**CHAPTER 2**

- CURRENT STRATEGIES FOR CLINICAL STREAMLINING .....15
- 2.1. Cost-Effective Solutions for Clinical Go/No-Go Decisions.....16
  - Better Disease Models that Are Predictive of Human  
Exposure .....16
  - Human Microdosing: “Phase Zero” .....17
- 2.2. Optimized Project Planning .....21
- 2.3. Recruiting the “Right” Patients More Quickly—and  
Keeping Them .....24
  - Maximizing Outpatient Compliance .....25
  - “Offshoring” Clinical Trials .....28
- 2.4. “Information-Rich” Trial Design and Biomarkers .....30
  - Pharmacogenomics .....30
  - Biomarkers for Clinical Monitoring .....31
- 2.5. Electronic Data Capture: Heading for the “E Trial” .....32
  - Digitizing the Case Report Form .....33
  - Interactive Voice Response Systems and Web-Supported  
Trials .....34
  - The E Trial: A “Revolutionary Evolution” .....36
- 2.6. Mining Clinical Databases.....38

**CHAPTER 3**

FORCES SHAPING FUTURE CLINICAL TRIALS.....	41
3.1. The Confounding Mega-Trends .....	41
3.2. Paradigm Changes Rather than Technological Leaps at the Clinical Inflection Point.....	43
IBM's Vision: "Pharma 2010: Silicon Reality" .....	44
3.3. Systems Biology as a Key to Understanding Disease and Patients' Reactions to Drugs .....	45
The Virtual Patient: A "Crash Dummy" for the Pharmaceutical Industry .....	46
3.4. Beyond Today's Biomarkers .....	48
Molecular Fingerprinting and Metabolomics.....	48
Functional Endpoints Defined by Molecular Imaging.....	50
Theranostics: The Co-Evolution of Drugs and Diagnostics.....	51
3.5. Pervasive Computing: Can a New Type of Information Technology Bring Trials to New Shores? .....	52
Clinical Data Management Systems (CDMS).....	52
The Omnipresent Radiofrequency Identity Tags .....	53
Grid Computing, Virtual Trial Organizations, and Data Interchange .....	53

**CHAPTER 4**

REGULATORY AGENCIES IN AN ERA OF CHANGE.....	57
4.1. The FDA Takes the Initiative .....	58
The FDA's "Exploratory Investigational New Drug Application" Guideline .....	58
The FDA's Critical Path Document .....	60
The Biomarker Bootstrap Situation .....	62
The FDA and the Emerging E-Trial Modalities.....	63
4.2. The Thorough QT Trial: An Example for International Coordination of Clinical Study Reform .....	64
4.3. The Dwindling Role of the Placebo .....	64
4.4. Focused Postmarketing Surveillance Instead of Megatrials .....	65

**CHAPTER 5**

A SCENARIO FOR CLINICAL TRIALS IN THE YEAR 2015 .....	67
---	----

**CHAPTER 6**

<b>CORPORATE PROFILES</b> .....	71
ClinPhone Group.....	71
Compugen .....	74
Entelos, Inc. ....	76
etrial Worldwide, Inc.....	79
Gene Network Sciences.....	81
IBM Healthcare and Life Sciences .....	82
LifeTree Technology LLC .....	84
Pharsight Corporation .....	86
Quintiles Transnational Corporation .....	88
Xceleron Ltd. ....	90
<b>References</b> .....	93
<b>Index</b> .....	95

**FIGURES**

Figure 1.1. New Active Substances (NASs) Launched Worldwide, 1995 to 2004 .....2

Figure 1.2. The Drug Development Process .....5

Figure 1.3. Investment Escalation per Successful Compound.....6

Figure 1.4. Attrition during the Clinical Development Process .....8

Figure 2.1. Comparison of the Conventional and the Microdose Approach to Candidate Selection .....20

Figure 2.2. The Radiofrequency Identifier–Based Med-ic ECM Smart Package for Clinical Supplies and Output from Med-ic Certi-Scan Software .....27

Figure 2.3. Data Flow and Processing in a Typical E-Clinical Trial .....37

Figure 3.1. Projected Schematic Development of Medicine and Healthcare toward Personalized Medicine .....43

Figure 3.2. Representation of Raw Data from a Clinical Trial that Allows Patients to be Clustered Based on Drug Response .....49

Figure 3.3. Schematic Representation of the VOTES Clinical Trial Grid Computing Study .....55

Figure 4.1. The FDA’s Concept of the Three Dimensions of the “Critical Path” in Drug Development .....61

**TABLES**

Table 2.1. Features of Typical Electronic Patient-Reported Outcome Information Technology Tools.....35

# CHAPTER 2

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## CURRENT STRATEGIES FOR CLINICAL STREAMLINING

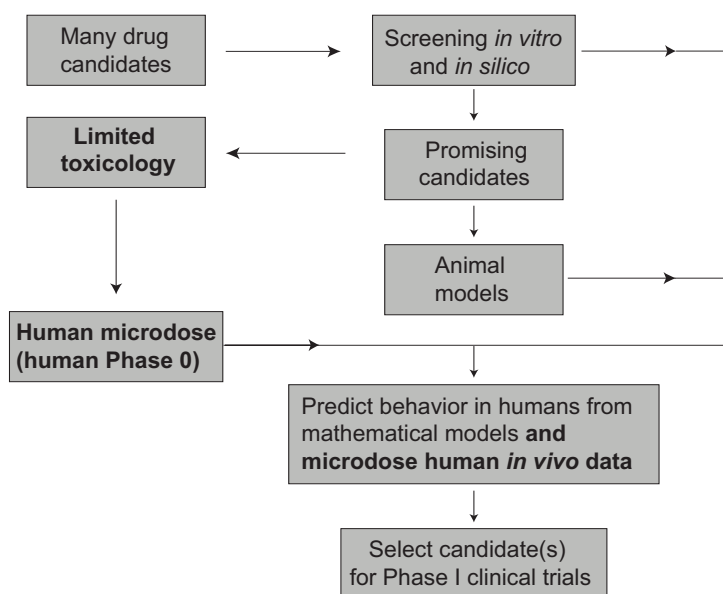
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The facts that we have presented so far will certainly not come as a revelation to anybody in the pharmaceutical industry. They have been a long time in the making, and industry players and observers have been commenting on the pharmaceutical productivity crisis, its causes, and conceivable solutions for many years, mostly more or less along the lines laid out in the previous chapter.

Drug development is a contiguous process, and even under otherwise optimal conditions the success rate of the clinical phase will be strongly influenced by the characteristics of the candidate compounds that reach human testing. Although clinical testing as it is conducted today offers much room for improvement, any truly meaningful attempt at “re-inventing” the drug development process (*i.e.*, making it quicker, more predictable, and more predictive of a drug’s performance after approval) must not limit itself to the clinical trial stage. Instead, it must also scrutinize the preclinical selection and characterization process.

The attempts at process improvements that have been proposed and implemented so far have not been revolutionary ones but have largely relied on incremental (and often obvious) improvements that do not question the current system of clinical development on a fundamental level. This can be attributed to the conservatism that is inherent in the complex interplay between the industry, its stakeholders and analysts, and regulatory agencies. As the figures and facts presented in Chapter 1 clearly show, these conservative process improvement measures have largely failed to provide a real remedy to the pharmaceutical productivity problem, although, arguably, they might have prevented an even more profound decline in the efficacy and speed of drug development.

**Figure 2.1. Comparison of the Conventional and the Microdose Approach to Candidate Selection**



Additional steps that are required for a microdose approach to drug selection are depicted in bold.

*Source: Wilding IR, Bell JA. Improved early clinical development through human microdosing studies. Drug Discov Today 2005;10:890–894.*

The Consortium for Resourcing and Evaluating AMS Microdosing (CREAM) was a collaborative industry-sponsored method validation trial that was undertaken using several drugs for which human pharmacokinetic characteristics at pharmacologic dose levels were known and that were expected to strongly challenge the microdosing concept. These drugs included several that have been in widespread use for a long time (the anticoagulant warfarin, the antibiotic erythromycin, and the benzodiazepines diazepam and midazolam), but also ZK-253, a drug candidate that Schering AG had dropped after Phase I. Each compound was administered to subjects at a microdose level and at a therapeutic dose level in an appropriate crossover design. In this study, midazolam (a compound with extensive first-pass metabolism and a well-known substrate for the polymorphic cytochrome CYP2C9 gene) gave excellent correlation with the pharmacologic dose, although microdosing would not have been expected to succeed in this case. ZK-253 exhibited extremely low bioavailability by microdosing, which correlated well with the low

## 2.5. Electronic Data Capture: Heading for the “E Trial”

Information technology has made huge inroads into the clinical trial process since the 1960s, when physicians first began to experiment with gathering inpatient medical information on their computers. However, it was not before the 1990s that software (and, most significantly, its user interfaces) became sufficiently comprehensive and user-friendly to be integrated into the design and management of clinical trials.

### *Digitizing the Case Report Form*

In conventional paper-based trials, data for each trial participant are entered in a CRF that has been pre-approved by the regulatory authority sanctioning the clinical trial. In most cases these CRF entries would not constitute the original bedside records but would rather be assembled from various primary data sources in the investigator’s hospital office. The CRF sheets would then be passed to a clinical research associate to be checked. At regular intervals (with small trials, after their conclusion) these data frames would be entered into an electronic clinical database (twice by different operators, with a software intercept layer that accepts the entry only if all data points are identical, so that transcription errors are minimized). The trial monitor would then follow up on any discrepancies and attempt solving them by querying the clinical investigators. Should this “data cleaning” prove impossible for a particular logical unit, the data frame is partially or completely lost for data analysis, depending on the structure of the CRF and the nature of the predefined outcome analysis.

*Information technology has made huge inroads into the clinical trial process since the 1960s.*

Electronic data capture (EDC) attempts to streamline this process by capturing all relevant data into electronic CRFs (eCRFs) on the spot of their generation, by creating a series of electronic source documents that eventually build the “electronic casebook” for each patient in the trial. Every investigator (or nurse) is equipped with a handheld device (usually a tablet or pocket PC, or a customized device) and appropriate preconfigured software for entering data manually or capturing from digital recording sources, or both. This allows the elimination of obvious errors (typographical and out-of-range data) immediately on entry. Pull-down menus could present options for answering questions where such a list would not be available on paper, which might be helpful for category-driven decisions such as clinical symptom coding. At predefined intervals (ideally, on a daily basis), the data frames are downloaded directly to the central clinical database. Secured phone lines or Internet connections are employed for this transfer process, unless the handheld devices are already networked to a secure clinical site server that takes care of this job, optionally after performing some elementary additional consistency checks on the data.

# CHAPTER 3

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## FORCES SHAPING FUTURE CLINICAL TRIALS

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### 3.1. The Confounding Mega-Trends

The overarching trends that will shape the pharmaceutical industry between now and 2015 can be extrapolated by looking at the pressures that the industry faces today and at the developments—technological and others—that this same industry adopts or fosters. Three major groups of such powerful sociological, political, and technological trends will have a decisive influence on the ways that clinical trials will change within the next 10 years:

- *Continuing globalization and individualization.* The countries that constitute the major pharmaceutical markets are becoming more ethnically diverse, and humankind as a whole is becoming increasingly more mobile geographically. This results in increasing exposure to environmental conditions and agents (infectious and other) that residents of these important markets have not encountered before, played out against an increasing diversity of genetic backgrounds. At the same time, citizens of these developed markets tend to express their individuality and what they believe to be their rights more than ever before. They are increasingly unwilling to accept being given drugs that, although proven effective in general, might not work in them as individuals. The pharmaceutical industry has to adapt to increasing levels of consumerism and demands for individualized healthcare among the social middle classes. Acting against the background of demographics and lifestyle, these secular developments might seem commonplace and unsurprising today but will soon begin to erode the conventional “blockbuster model” to which large companies have catered for such a long time.

- *Increased pressure on corporate margins and shareholder returns.* The current business model of the pharmaceutical industry emerged in the 1960s, brought an era of unprecedented growth and prosperity that culminated in the 1970s and early 1980s, and in the 1990s showed increasing signs of an emerging crisis that has deepened during the new millennium. The fact that shareholder returns fell 25% between 1998 and 2003, and have since continued their slide, reflects an interplay of three crucial economic factors: decisive moves for healthcare cost containment, increasing R&D costs with diminishing returns even in the long term, and loss of revenue and profit caused by patent expirations and market recalls for major drugs. In addition to this, clinical trials are becoming increasingly complex, and with drug combinations studying every drug alone, together, and in every permutation with possibly interacting drugs, they will soon be close to impossible if today's practices are continued. The pharmaceutical industry can return on the growth path and restore its lost position as a top-ranker in shareholder value only if it re-invents itself by creating more effective drugs more quickly, and in a more predictable fashion, than today.
- *The ongoing merger between life science and information technology.* The continuing advances in our molecular concepts of health and disease will make entirely new and unconventional approaches to treatment possible within the next 10 years. During the same period information technology will not only create faster computers and more powerful software that will exploit data and algorithms from these advances in life science but will also move into a totally new field, embedded and pervasive computing based on low-level linkage, communication, and information processing and storage, which will allow unprecedented developments in process management. The pharmaceutical industry contributes to several of these developments by assuming the role of a co-development and testing ground for IT companies, but it also assumes the driving role in hardware and software developments for life science.

In summary, nonbiologic factors are powerful shaping influences for the path that the pharmaceutical industry has to follow, although biologic factors remain extremely important.

#### **4.1. The FDA Takes the Initiative**

The United States Food and Drug Administration is uniquely positioned to help identify the challenges to drug development. Agency reviewers not only see the complete spectrum of successes and best practices during all clinical trials that are conducted under its investigational new drug applications (INDs) in the United States and elsewhere in the world, but also the failures, slowdowns, barriers, and missed opportunities (most of which are never fully published by the sponsors) that occur during clinical trial programs.

As a result of this excellent starting point, but also because of its generally positive attitude toward the industry, the agency has built a track record of reform initiatives during the last quarter-century. Elements that indicate a willingness to embrace change in the drug development process, either on behalf of the FDA itself or U.S. lawmakers, can be found in the Orphan Drug Act of 1983, the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments), and the FDA Modernization Act of 1997 (FDAMA).

##### ***The FDA's "Exploratory Investigational New Drug Application" Guideline***

The FDA's classic "Screening IND" concept, which has subsequently determined the format of preclinical development worldwide, calls for single-dose toxicology in two species, using multiple dose levels to define toxicity and "no observed effect level" (NOEL) and a full safety pharmacology and routine genotoxicity testing program to support initial single-dose testing for a candidate compound in humans. In accordance with the M3 Guideline of the International Conference on Harmonization (ICH), the FDA has proposed to adopt an additional "exploratory IND" approach (Food and Drug Administration 2005).

The philosophy of safety testing under an exploratory IND would be a pragmatic one: It should be sufficient to identify real risks from exposure in the subsequent human studies, not theoretical or extrapolated risks. The primary enabling animal study for each compound is a 2-week, multiple-dose-level toxicology study in both sexes of single sensitive species (usually a rodent species based on metabolic and target receptor sensitivity) accompanied by toxicokinetic information. Organ toxicity and "no observed adverse effect level" (NOAEL) dose must be determined. A toxicology study in a second (nonrodent) species then has to justify the use of the primary species from a general toxicology perspective by proving that the secondary

species is not significantly more sensitive to the compound than the primary species based on dose normalization. The number of animals used in the confirmatory study can be fewer than normally used to attain statistically meaningful comparisons, but of sufficient number to meaningfully identify a toxic response.

Subsequent clinical testing under exploratory IND does not attempt to determine a maximum tolerated dose as in conventional first-time-in-man studies. The endpoints are exploratory and may include biomarkers or pharmacokinetic criteria intended for candidate selection. The following Phase I clinical study designs are permissible:

- Subpharmacologic dosing (“microdosing” up to near nonclinical NOAEL), with the starting dose up to 1/50 the rodent NOAEL on an mg/m<sup>2</sup> basis
- Up to seven sequential doses (days) with a given compound for proof of concept
- Sequential testing within the same subjects with up to five different test articles (or formulations) for a maximum of 10 dosing days with appropriate washout periods
- Normal volunteers and minimally diseased subjects allowed

*FDA-  
recommended  
CMC data do not  
differ much  
between  
exploratory and  
Phase I INDs.*

Industry representatives note that this guideline indicates increased flexibility of the FDA with regard to the requirement for studies to have been conducted using Good Laboratory Practices (GLPs). However, the chemistry, manufacturing, and controls (CMC) data that the FDA recommends for exploratory INDs are not much different from those for traditional Phase I INDs.

The European Federation of Pharmaceutical Industries (EFPIA) is in very similar discussions with the Committee for Medicinal Products for Human Use (CHMP) Safety Working Party to try to identify a reduced preclinical package to support exploratory clinical investigations in humans. The main difference in the EFPIA approach from that of the FDA is that conducting toxicology has been recommended.

# CHAPTER 5

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## A SCENARIO FOR CLINICAL TRIALS IN THE YEAR 2015

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Ten years from now, the reality of clinical drug development will already be fundamentally different from the unsatisfactory situation of today. Forced by the reality of diminishing returns on increasing drug development costs, pharmaceutical companies are even now working with regulatory agencies to redesign the process.

Two factors will be important here. The conceptual framework of trial design will be the primary driver of change, but the emerging opportunity of proteomics-driven, truly pervasive modeling of biologic responses and deep-level monitoring of patient responses will make these changes possible. Applied information technology will constitute the fundamental matrix and modulator of both. In addition, candidates that reach the clinical stage will be much better tailored toward clinical success in distinct populations, giving the entire human testing phase a different role.

In its 1999 treatise, “Pharma 2005 Silicon Rally: The Race to e-R&D,” PricewaterhouseCoopers expressed its belief that extensive use of *in silico* technologies could reduce the overall cost of drug development by as much as 50%. Today such statements cannot amount to much more than educated guesses, but we see the important point elsewhere: The overall environment of the pharmaceutical industry is such that the bulk of any achievable savings do not relate to per-patient investment in clinical trials but rather to failure risk, time-to-launch, and ex-factory prices in the major markets. To increase return on investment over the life cycle of a drug, the industry has to aim primarily for making the clinical process quicker and more reliable; almost any investment that can be reasonably expected to make a significant contribution to this goal is justified from the cost side.

# CHAPTER 6

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## CORPORATE PROFILES

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In this chapter, 10 companies are discussed that represent today's corporate involvement in the changing perception of the clinical trial process. Their innovative contributions are likely to play significant roles in the clinical trial environment to 2015.

### **ClinPhone Group**

**Vital Statistics:**

**Location:**

**Headquarters:**

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Lady Bay House, Meadow Grove, Nottingham NG2 3HF, United Kingdom

**Phone Number/Fax Number:** +44-115-955-7333/+44-115-955-7555

**U.S. Subsidiary:**

ClinPhone, Inc.

7 Roszel Road, 3rd Floor, Princeton, NJ 08540

**Phone Number/Fax Number:** 609-524 4100/609-520-0633

**Web Site:** [www.clinphone.com](http://www.clinphone.com)

**E-Mail:** [info@clinphone.com](mailto:info@clinphone.com)

**Year Founded:** 1993

**Selected Management:** Edwin Moses, Chairman; Steve Kent, Managing Director; Kevin Bishop, Chief Operating Officer; Howard Goldberg, Vice President of Business Development; Patrick Hughes, Director of Marketing and Business Development

**Number of Employees:** 400 (estimated)

**2004 Sales (millions):** \$69.6

**Partners:** ALMEDICA International, Cognitive Drug Research, Healthcare Technology Systems, InfoPro Solutions, Phase Forward

ClinPhone, global leader in clinical technology solutions, was founded in 1993 to improve the clinical trial process by providing centralized support services. The company's current business mostly involves the integration of Internet- and telephone-based services (accessed via local, toll-free numbers in 88 countries and 71 languages) that are constantly available to clinical investigators and sponsors as well as contract research organization (CRO) partners. This includes IVR and interactive Web response (IWR) services to exchange data in real time with electronic data capture (EDC) software. This is most important with trials that use disparate technologies and where it is correspondingly difficult to integrate seamlessly with various third-party and inhouse systems and software.

ClinPhone Connect, an integrative Oracle-based platform for IVR/IWR, EDC, and clinical trial management software (CTMS) applications, can capture self-reported patient data from any of these systems. ClinPhone Connect eliminates the need for duplicate records and discrepancy resolution, thereby reducing the potential for confusing information and time wastage. For instance, Eli Lilly used IVR-collected patient data for its drug Cymbalta based on improvement by day one in shoulder and back pain when compared with a lower dose of the same drug. Patients also reported reduced pain while awake by day three, improved overall pain by day two, global emotional improvement by day three, and global physical improvement by day seven. These IVR data would have been difficult, if not impossible, to collect reliably at the study site or via paper. This may also lead to a faster database lock.