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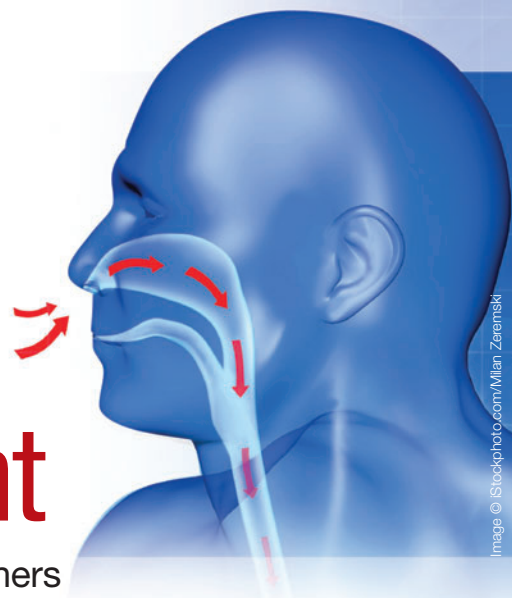
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Taming the Cost of Respiratory Drug Development



Computer modeling and simulation help researchers to better visualize pulmonary functions for faster, less expensive clinical testing of innovative respiratory drugs.

By Jan De Backer, CEO, FluidDA nv, Kontich, Belgium
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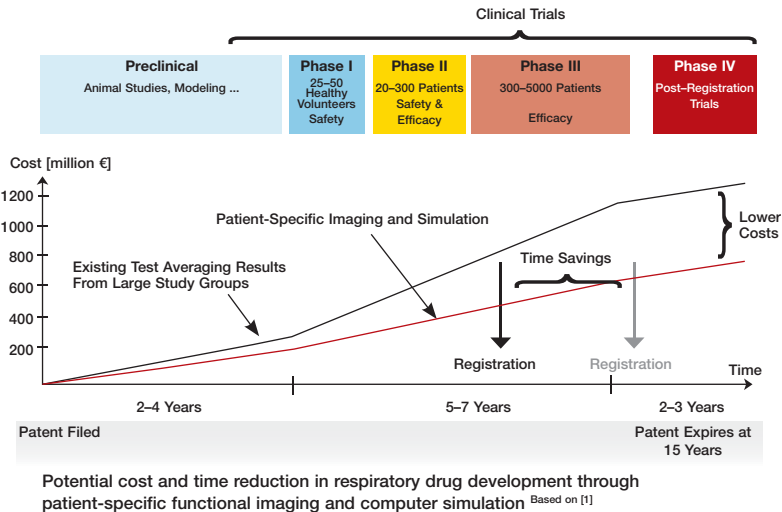
The cost of developing a new inhalation therapy drug for respiratory diseases such as asthma, emphysema and cystic fibrosis is estimated at more than \$1 billion — the highest in the pharmaceutical industry. This figure is considerably more than for developing medications to treat cancer or neurological disorders.^[1]

The main cause of this extremely high cost is that current testing methods of evaluating respiratory drug effectiveness are only coarse measures of patient long-term outcome. Even so, such methods are extremely time-consuming and expensive, as many patients must be tested over a long period of time. Researchers are addressing these issues with the emerging field of *in silico* modeling, which uses computer simulation to speed up medical studies and to provide greater detail than is otherwise practical with extensive lab work and wide-scale clinical trials. In particular, many *in silico* respiratory studies are based on fluid dynamics simulation to generate accurate images of pulmonary functions, such as airway volume and resistance for individual patients. The technique already has been used in studying the respiratory structures of animals and — because the same functional parameters can be measured in humans — enables researchers to proceed more efficiently from pre-clinical to clinical trials. By accurately quantifying these relatively small changes in pulmonary functions, the approach can demonstrate respiratory drug effectiveness more quickly using fewer patients. This has the potential to

cut years from the development process and reduce costs by hundreds of millions of dollars.

The current gold standard for testing airway diseases is FEV1, the volume of air exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity. Another approach in widespread use for assessing patients with pulmonary disorders is the Saint George Respiratory Questionnaire (SGRQ), a set of questions aimed at comparative measurements of patient health.

These methods were developed primarily to measure long-term survival, but they lack the sensitivity to correlate with subtle differences in breathing that are more difficult to identify and quantify. Because of the uncertainty of these parameters and discrepancies between them, researchers must spend considerable time and expense gathering data on drug effectiveness and averaging results

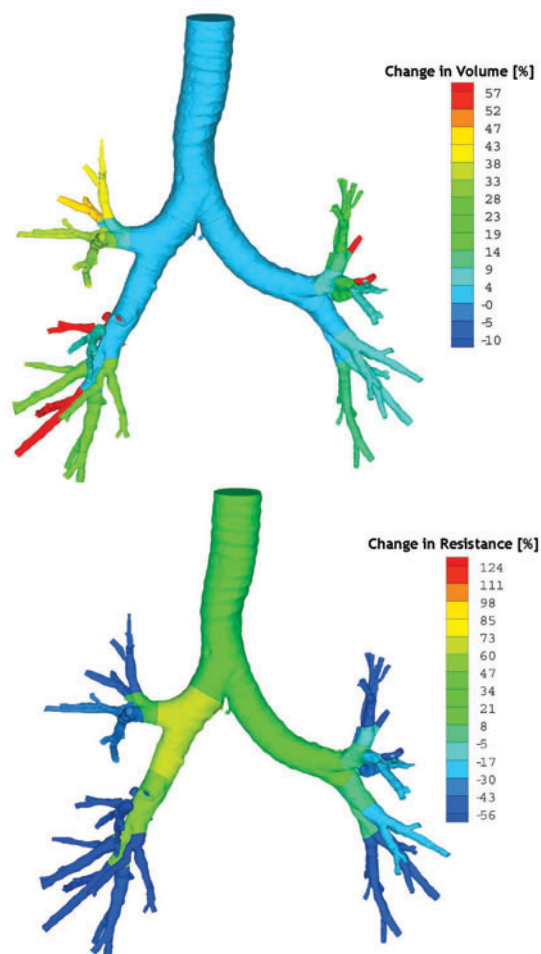


across large groups of participants over extended periods of time.

The time frame for respiratory drug development is staggering. Preclinical animal studies typically take two to four years, then additional time is needed to transition from animal studies to human clinical trials due to the lack of correlation and common denominators between the different species. Subsequent clinical trials last five to seven years and can involve thousands of patients. Regulatory agencies take up to three years to interpret and verify the clinical trial findings. The total time adds up to nine to 14 years before registration of the drug occurs and the medicine is available by prescription from healthcare professionals.

This leaves pharmaceutical companies with only a few years to recoup development costs before the 15-year patent limit expires. Lengthy development drives up the retail price of respiratory drugs, severely delaying their availability to patients. The process often discourages pharmaceutical companies from risking considerable amounts of resources for an uncertain ROI (return on investment).

By quantifying a new class of functional parameters linked more closely to pulmonary changes, computer modeling and simulation have the potential to significantly lower the time and cost of respiratory drug development. Resulting patient-specific functional-imaging data is an important component of this emerging field, called translational medicine. Researchers in this discipline continually search for parameters that can facilitate the transition of drugs from preclinical to clinical stages. Such methods already have been used to represent animal



Assessment of changes in airway volume and resistance through functional imaging using computational fluid dynamics^[2]

The Medical Value of in Silico Analyses

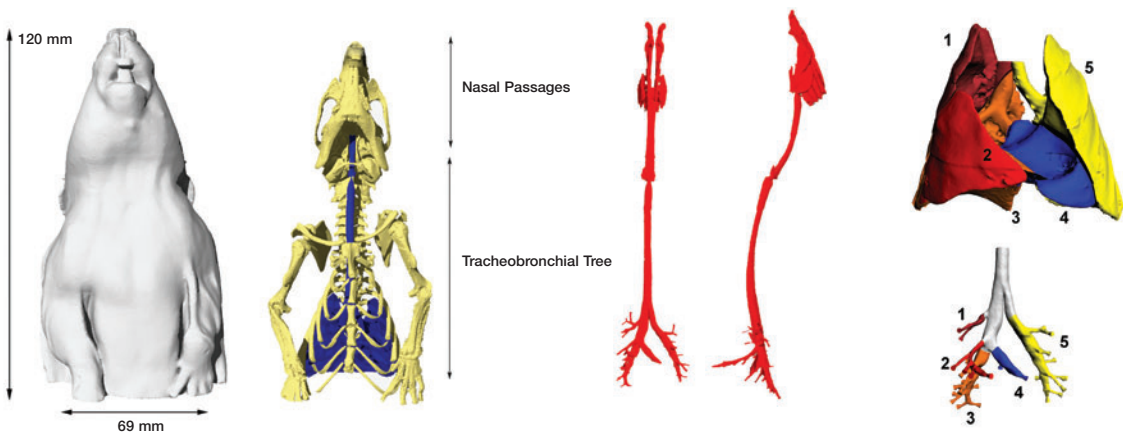
With the rapidly increasing computational power of standard PCs and the refinement of biomaterial models, clinicians are showing a growing interest in the routine use of simulation. Clinicians do not have the luxury of learning advanced user interfaces, however, so they need seamless interfaces between medical imaging and engineering simulation software. Furthermore, a fully integrated workflow must be developed for large-scale deployment of this technology in local hospitals.

Several successful attempts to make numerical modeling accessible and useful to the clinical world involve ANSYS tools. The @neuFUSE toolchain (www.aneurIST.org) allows physicians to access more information about the risk of cerebral aneurysm rupture, for example. During one recent @neurIST workshop, 90 percent of attending neurosurgeons confirmed the clear added value brought by this solution and indicated high interest in gaining access

to the technology for future work. Likewise, the Grid-Enabled Medical Simulation System (GEMSS) project aims to make biomedical vertical applications available from the web with encouraging successes in applications such as stent interfaces.

Ongoing projects such as the Virtual Physiological Human Osteoporosis Project (VPHOP), RT3S and ANGIOVISION multiply the opportunities to assist the medical world in lengthening life expectancy and increasing quality of life through more effective orthopedic, stent and endovascular treatments, respectively. The upcoming decade will undoubtedly see the development of computer-assisted surgery (CAS) and the rapid penetration of in silico technology throughout the medical world, including in facilities close to home.

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Segmentation of Sprague Dawley rat respiratory system^[4] illustrates modeling of the airway structures and corresponding lobar volumes derived from CT scans.

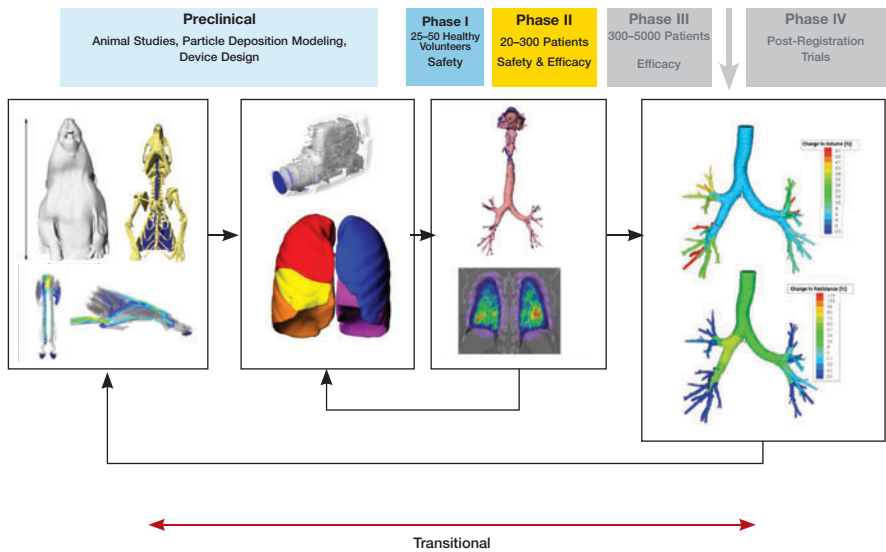
respiratory structures in studying inhalation profiles and deposition patterns for different respiratory devices. In these studies, the common parameters of airway volume and resistance determined through functional imaging provide for a more efficient transition from preclinical to clinical trials.

By changing the slope of the cost curve in a graph of development cost versus time, this translational approach could alter the cost slope from preclinical to clinical trials and significantly reduce expenses over the entire cycle. Furthermore, the approach could compress development time, moving registration forward much sooner and thus increasing the time for the pharmaceutical company to market products under patent protection. Indeed, patient-specific imaging and simulation coupled with

inhaler selection and modeling has the potential to shorten the development time from patent filing to registration by years and to save hundreds of millions of dollars if the approach is used throughout the entire process of bringing a single drug to market.

The impact of such savings could be stunning. When costs for the development of new compounds are reduced, the prices of these products could be lowered without affecting profit margins, thus allowing for continuous research and development of innovative new compounds in the pharmaceutical industry. Ultimately, the process could facilitate more sustainable healthcare systems.

Such savings are entirely possible in the foreseeable future, given the tremendous strides made in previous



Computer-based functional imaging facilitates the translational approach in respiratory drug development through the use of common parameters in moving from preclinical studies to clinical trials.

studies and ongoing work in computer-based modeling and simulation. Promising work already is pushing the envelope of functional imaging technology. Recent developments in the field of computational fluid dynamics and structural simulations have made it possible to simulate pulmonary airflow behavior in the pulmonary airways as well as to characterize surrounding tissue. The research is based on geometries extracted directly from high-resolution computed tomography (HRCT) scans.

Based on this work, computer-based technologies have the potential for researchers to perform modeling and simulations to derive functional parameters such as airway resistance as a biomarker on individual patients. A number of published trials — including FluidDA's studies — make use of these patient-specific HRCT-based models that were able to describe the distinct flow patterns in the respiratory system. Certain of these studies focused on the effect of inhalation medication and assessment of subsequent changes in airway volume and resistance through functional imaging using ANSYS FLUENT fluid dynamics software.^[2]

Correlation studies indicate good agreement with clinical parameters. Similar methods can be used to assess animal respiratory structures in preclinical research

and inhalation devices. Successes in this body of work demonstrate the value of functional imaging in both preclinical and clinical development stages as well as the tremendous potential of the approach in revolutionizing the development of new inhalation compounds for combating respiratory disease and improving the quality of life for patients worldwide. ■

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