Innovation Will Eliminate the Need for Inhalation Anesthesia

Steven L. Shafer, M.D.
Professor of Anesthesiology, Perioperative and Pain Medicine, Stanford University
Adjunct Associate Professor of Biopharmaceutical Sciences, UCSF
Editor-in-Chief, Anesthesia & Analgesia
Disclosures

- Signature Therapeutics (PF0713)
- Medicines Company (ABP-700)
- Johnson & Johnson
  - S-ketamine for psychiatric use
  - Sedasys
- Branequest
- Fresenius-Kabi
- FDA SGE
Disclosures

- AstraZeneca
- Novartis
- Takeda
- Grunenthal
- Concentric Analgesics
- Singchn
- Alexza
Innovation Will Eliminate the Need for Inhalation Anesthesia

Steven L. Shafer, M.D.
Professor of Anesthesiology, Perioperative and Pain Medicine, Stanford University
Adjunct Associate Professor of Biopharmaceutical Sciences, UCSF
Editor-in-Chief, Anesthesia & Analgesia
No, it won’t.
I concede the debate.
Intravenous “anesthetic” drugs

- Hypnotics
  - Propofol, midazolam, etomidate, dexmedetomidine, ketamine

- Analgesics
  - Fentanyl, remifentanil, hydromorphone
  - Ketorolac, acetaminophen, diclofenac

- Relaxants
  - Rocuronium, vecuronium, cisatracurium
INNOVATIONS!

- **Hypnotics**
  - Propofol, midazolam, etomidate, dexmedetomidine, ketamine

- **Analgesics**
  - Fentanyl, remifentanil, hydromorphone
  - Ketorolac, acetaminophen, diclofenac

- **Relaxants**
  - Rocuronium, vecuronium, cisatracurium
Remimazolam
Remimazolam

ABP-700

Ketamine analogs
Society for Technology in Anesthesia

2016 Annual Meeting

The Future of Anesthesiology and Innovation in Perioperative Care
What technology can replace inhaled anesthetics for ...
Children?
Cardiac Surgery?
The Future of Anesthesiology and Innovation in Perioperative Care
No innovation in intravenous anesthetic delivery has reached the United States for 30 years.
The Future of Anesthesiology and Innovation in Perioperative Care
Target Controlled Infusions
The Past of Anesthesiology and Innovation in Perioperative Care
Old-world puppet theater reflects just how antiquated it may seem in the face of current technology to be manually administering powerful anesthetic drugs to ill-defined endpoints. Against the backdrop evocative of the passage of time, our patient descends into sleep while a powerful figure, an overseer of her consciousness, inundates her with hypnotic elixir.
Target-controlled infusion (TCI) is a technique of infusing IV drugs to achieve a user-defined predicted ("target") drug concentration in a specific body compartment or tissue of interest. In this review, we describe the pharmacokinetic principles of TCI, the development of TCI systems, and technical and regulatory issues addressed in prototype development. We also describe the launch of the current clinically available systems. (Anesth Analg 2016;122:56–69)
Target- controlled infusions (TCIs) have been used in research and clinical practice for >2 decades. Nonapproved TCI software systems have been used during the conduct of almost 600 peer-reviewed published studies involving large numbers of patients. The first-generation pumps were first approved in 1996, and since then an estimated 25,000 units have been sold and used. Second-generation pumps were first approved in 2003. During 2004 to 2013, >36,000 units were sold. Currently, TCI systems are approved or available in at least 96 countries. TCI systems are used to administer propofol and opioids for IV sedation and general anesthesia for millions of patients every year. In countries where TCI systems are approved, nonapproved software is still commonly used in studies of the pharmacology of hypnotics and opioids, because research software offers greater flexibility than approved TCI systems. Research software is also readily integrated into data management modules. Although TCI is a part of established practice around the world, TCI devices have not received regulatory approval in the United States. In the United States, TCI administration of propofol and opioids for sedation and anesthesia is only possible using research software in IRB-approved research studies. (Anesth Analg 2016;122:70–8)
The Safety of Target-Controlled Infusions

Thomas W. Schnider, Prof. Dr. med.,*† Charles F. Minto, MBChB, PhD, FANZCA,‡
Michel M. R. F. Struys, MD, PhD, FRCA (Hon),§||
and Anthony R. Absalom, MBChB, FRCA, MD (UCT)§

Target-controlled infusion (TCI) technology has been available in most countries worldwide for clinical use in anesthesia for approximately 2 decades. This infusion mode uses pharmacokinetic models to calculate infusion rates necessary to reach and maintain the desired drug concentration. TCI is computationally more complex than traditional modes of drug administration. The primary difference between TCI and conventional infusions is that TCI decreases the infusion rate at regular intervals to account for the uptake of drug into saturable compartments. Although the calculated infusion rates are consistent with manually controlled infusion rates, there are concerns that TCI administration of IV anesthetics could introduce unique safety concerns. After approximately 2 decades of clinical use, it is appropriate to assess the safety of TCI. Our aim in this article was to describe safety-relevant issues related to TCI, which should have emerged after its use in millions of patients. We collected information from published medical literature, TCI manufacturers, and publicly available governmental Web sites to find evidence of safety issues with the clinical use of TCI. Although many case reports emphasize that IV anesthesia is technically more demanding than inhaled anesthesia, including human errors associated with setting up IV infusions, no data suggest that a TCI mode of drug delivery introduces unique safety issues other than selecting the wrong pharmacokinetic model. This is analogous to the risk of selecting the wrong drug with current infusion pumps. We found no evidence that TCI is not at least as safe as anesthetic administration using constant rate infusions. (Anesth Analg 2016;122:79–85)
Target-Controlled Infusions Could Improve the Safety and Efficacy of Emergency Department Propofol Sedation

Steven M. Green, MD,* and Baruch S. Krauss, MD, EdM†‡

Target-controlled infusion (TCI) technology is now well established worldwide, except in the United States where it has not been approved by the Food and Drug Administration. TCI provides clinicians the convenience of thinking in terms of target concentrations rather than bolus doses and infusion rates.1 Target-controlled drug delivery is based on ever-advancing pharmacokinetic models,2 enhancing accurate drug delivery, and decreasing variability relative to bolus injection dosing.1

in children. For the same reason, anesthesiologists choose to sedate with propofol, in our practice propofol is our principal deep sedative, with preseduction analgesia achieved with titrated opioids.7–10

Current monitoring modalities detect but do not predict adverse events during procedural sedation. Therefore, there is no objective means to gauge the ongoing risk of ventilatory compromise, making it difficult to know when the patient is at high risk for adverse events. It may be chal-
Target-Controlled Infusions: Paths to Approval

Paul E. Dryden, BS, MBA

Target-controlled infusion of IV anesthetic drugs is approved worldwide with the exception of the United States. The purpose of this special article is to review regulatory pathways that could lead to target-controlled infusion (TCI) clearance or approval in the United States. (Anesth Analg 2016;122:86–9)

Medical devices are defined by the U.S. Food and Drug Administration (FDA) in section 201(h) of the Federal Food, Drug, and Cosmetic Act. A device is:

- “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment,

WHAT ARE THE MAJOR REGULATORY PATHWAYS FOR MEDICAL DEVICES WITHIN THE UNITED STATES?

All regulatory pathways require demonstrating that a device is safe and effective for the intended use and that the potential benefits to patients justify the risks associated with any medical device. The 3 regulatory pathways for medical devices are as follows:

1. Premarket notification (510(k))—based on substantiated equivalence compared with existing legally marketed predicate devices, referred to as “predicates.”
2. Premarket Approval—data are generated, which demonstrate device safety and effectiveness
3. De novo—based on the low-to-moderate risk devices
Target-Controlled Infusions: Surfing USA Redux

Steven L. Shafer, MD,* and Talmage Egan, MD†

For 2 mellow guys, our 2003 editorial about target-controlled drug infusions (TCI) of anesthetic drugs in *Anesthesiology* was pretty harsh. The subtitle was barbed: *Surfing USA Not!* We made the snarky observation that “exactly 0 of the estimated 13 million propofol anesthetics administered worldwide with TCI since the introduction of the Diprifusor™ (AstraZeneca, Gothenburg, Sweden) in Europe, Asia, the South Pacific, South America, and Africa have been performed in North America.”! We placed the blame for the fact that TCI was only unavailable in the United States directly on the Food and Drug Administration (FDA), who spent 8 years reviewing a TCI application from Graseby Medical (Graseby Medical Ltd., Upper Pemberton [Fresenius Kabi, Lake Zurich, IL]), not on the same propofol used in the pump. With propofol now at generic price points, the business model has evaporated. That pump companies submitted a TCI application to the FDA since propofol is a generic suggests that perhaps they do not see an attractive business proposition. Of course part of the calculus is the attractiveness of the TCI business proposition compared to the estimated cost of meeting the regulatory requirements, so it is complicated.

In any case, we still do not have TCI in the United States. However, commercialization of TCI has continued elsewhere. Three articles in the current issue of *Anaesthesia*, solicited by the Editor-in-Chief (SLS)
Target-controlled Infusion: A Mature Technology

Anthony R. Absalom, MBChB, FRCA, MD,* John (Iain) B. Glen, BVMS, PhD, FRCA,† Gerrit J. C. Zwart, MD,* Thomas W. Schneider, MD, PhD,‡§ and Michel M. R. F. Struys, MD, PhD, FRCA (Hons)*‖

Target-controlled infusions (TCIs) have been used in research and clinical practice for >2 decades. Nonapproved TCI software systems have been used during the conduct of almost 600 peer-reviewed published studies involving large numbers of patients. The first-generation pumps were first approved in 1996, and since then an estimated 25,000 units have been sold and used. Second-generation pumps were first approved in 2003. During 2004 to 2013, >36,000 units were sold. Currently, TCI systems are approved or available in at least 96 countries. TCI systems are used to administer propofol and opioids for IV sedation and general anesthesia for millions of patients every year. In countries where TCI systems are approved, nonapproved software is still commonly used in studies of the pharmacology of hypnotics and opioids, because research software offers greater flexibility than approved TCI systems. Research software is also readily integrated into data management modules. Although TCI is a part of established practice around the world, TCI devices have not received regulatory approval in the United States. In the United States, TCI administration of propofol and opioids for sedation and anesthesia is only possible using research software in IRB-approved research studies. (Anesth Analg 2016;122:70-8)

T

target-controlled infusion (TCI) systems have been in use for >2 decades. The history of the development of TCI and the underlying concepts is discussed in an accompanying article.¹

Initially, only custom-made prototype systems were available, having been developed by different research groups who tended to use disparate names and acronyms to describe their systems. In 1996, a group of investigators proposed a standard nomenclature.² It included the use of the generic term “target-controlled infusion,” and the brain as a tissue device (original mode) or the effect site (e.g., the brain, based on the models of blood–brain equilibration) was introduced.

Since its introduction, TCI technology has transformed from a research tool in expert hands to a routine part of clinical anesthesia practice in many countries. However, the use of nonapproved software and prototypes did not stop with the introduction of commercial TCI systems. Several such programs also include data management modules that generate an electronic record of details indispensable for PK and pharmacodynamic (PD) studies. These also allow the practitioner to external
The World is Using TCI

- Over 500 peer-reviewed articles in Medline on TCI
- Most are now using second generation systems
  - Incorporate patient covariates
  - Target the effect site
  - About 35K second generation systems sold
- Conservative estimate of routine clinical use:
  - 20 million cases
Target-controlled infusion (TCI) technology has been available in most countries worldwide for clinical use in anesthesia for approximately 2 decades. This infusion mode uses pharmacokinetic models to calculate infusion rates necessary to reach and maintain the desired drug concentration. TCI is computationally more complex than traditional modes of drug administration. The primary difference between TCI and conventional infusions is that TCI decreases the infusion rate at regular intervals to account for the uptake of drug into saturable compartments. Although the calculated infusion rates are consistent with manually controlled infusion rates, there are concerns that TCI administration of IV anesthetics could introduce unique safety concerns. After approximately 2 decades of clinical use, it is appropriate to assess the safety of TCI. Our aim in this article was to describe safety-relevant issues related to TCI, which should have emerged after its use in millions of patients. We collected information from published medical literature, TCI manufacturers, and publicly available governmental Web sites to find evidence of safety issues with the clinical use of TCI. Although many case reports emphasize that IV anesthesia is technically more demanding than inhaled anesthesia, including human errors associated with setting up IV infusions, no data suggest that a TCI mode of drug delivery introduces unique safety issues other than selecting the wrong pharmacokinetic model. This is analogous to the risk of selecting the wrong drug with current infusion pumps. We found no evidence that TCI is not at least as safe as anesthetic administration using constant rate infusions. (Anesth Analg 2016;122:79–85)
The authors collected information from
The authors collected information from

- published medical literature,
The authors collected information from

- published medical literature,
- TCI manufacturers,
The authors collected information from

- published medical literature,
- TCI manufacturers,
- publicly available governmental web sites
The authors collected information from

- published medical literature,
- TCI manufacturers,
- publicly available governmental web sites

to find evidence of safety issues with the clinical use of TCI.
Number of adverse events related to pharmacokinetic control in TCI:
Number of adverse events related to pharmacokinetic control in TCI:

0
“Not a single report has identified an adverse incident that was related to the TCI algorithm for a PK-based infusion.”

- Conservative estimate: 20 million cases
- Rule of 3, upper 95% confidence estimate of risk is 1 in 7 million
Target-controlled Infusions for Intravenous Anesthetics

Surfing USA Not!
Target-controlled Infusions for Intravenous Anesthetics

Surfing USA Not!

Twenty years have elapsed since Helmut Schwilden first outlined the computer algorithm for anesthetic drugs. Although these developments began in Germany, American investigators added fundamental contributions. How ironic that America, the country that brought the world surfing,* continues to deny physicians access to the fundamental tools to surf the concentration response curves of intravenous anesthetic agents.

We have matured somewhat since 2003. We now have a better understanding of the statutory limitations that define exactly what the FDA can and cannot do. We recognize that no sponsor has attempted to bring TCI to the United States since 2003. The FDA obviously cannot approve devices for which an application has not been submitted.
For a given patient, a TCI device delivers a given infusion profile of drug within conventional limits of infusion accuracy.

Otherwise, it is just administering an approved drug, for an approved indication, at doses entirely consistent with the package insert.
Why is TCI important for innovation in anesthetic drug delivery technology?
TCI is imbedded in closed loop systems
Drug Administration

$V_2$
Rapidly Equilibrating Compartment

$V_1$
Central Compartment

$V_3$
Slowly Equilibrating Compartment

$k_{12}$
$k_{21}$

$k_{13}$
$k_{31}$

$k_{10}$
$k_{1e}$

$k_{e0}$

Drug Effect

Effect Site Concentration

50% Effect

$E_0$
$E_{max}$

$C_{50}$
Model Based Controller

Desired Effect
Model Based Controller

Desired Effect

Effect Site Concentration

Drug Effect

50% Effect

$E_0$

$E_{max}$

$n$

$C_{50}$
Model Based Controller

- Desired Effect
- Effect Site Concentration
Model Based Controller

Desired Effect → Effect Site Concentration

V₂ → k₁₂ → V₁ → k₁₃ → V₃
Rapidly Equilibrating Compartment

Central Compartment

Slowly Equilibrating Compartment

Drug Administration → Vₑ → k₁ₑ → kₑ₀

Effect Site Vₑ
Model Based Controller

Desired Effect → Effect Site Concentration → Infusion Rate
Model Based Controller

- Desired Effect
- Effect Site Concentration
- Infusion Rate
- Observed Effect
Model Based Controller

- Desired Effect
- Effect Site Concentration
- Infusion Rate

Observed Effect

Flow from Desired Effect to Effect Site Concentration to Infusion Rate.
Model Based Controller

- Desired Effect
- Observed Effect
- Effect Site Concentration
- Infusion Rate
- TCI
A Multicenter Evaluation of a Closed-Loop Anesthesia Delivery System: A Randomized Controlled Trial

Goverdhan D. Puri, MD, PhD,* Preethy J. Mathew, MD,* Indranil Biswas, MD,* Amitabh Dutta, MD,† Jayashree Sood, PGDHMH, FFARCS, MD, MBBS, FICA,† Satinder Gombar, MD,‡ Sanjeev Palta, MD,‡ Morup Tsering, MD,§ P L. Gautam, MD,¶ Aveek Jayant, MD, DM,* Inderjeet Arora, MSc,* Vishal Bajaj, MD,¶ T. S. Punia, MD,¶ and Gurjit Singh, MSc#

%Time within target: 81 vs 61, p < 0.0001
CLOSED-LOOP FEEDBACK CONTROL OF PROPOFOL ANAESTHESIA BY QUANTITATIVE EEG ANALYSIS IN HUMANS

H. SCHWILDEN, H. STOECKEL AND J. SCHUTTLER

If median EEG frequency was outside this range, the difference between the measured and predicted values served to adapt the model parameters. On the basis of the updated parameters, a new infusion scheme was calculated for achieving and maintaining a concentration inducing a median EEG frequency of 2.5 Hz.
Comparison of Some Control Strategies for Three-Compartment PK/PD Models

Chuanpu Hu, William S. Lovejoy, and Steven L. Shafer

This paper investigates several control strategies in the framework of a three-compartment PK model plus an effect site with a PD model. Using computer simulations under different assumptions, we show that a MAP (maximum a posteriori) Bayesian type of strategy is effective, nevertheless in high-risk situations a stochastic control strategy hedging against estimation errors provides better performance at computational cost.
Comparison of Some Control Strategies for Three-Compartment PK/PD Models

Chuanpu Hu, William S. Lovejoy, and Steven L. Shafer
Closed-loop controlled administration of propofol using bispectral analysis

E. Mortier, M. Struys, T. De Smet, L. Versichelen and G. Rolly
Estimation of Optimal Modeling Weights for a Bayesian-Based Closed-Loop System for Propofol Administration Using the Bispectral Index as a Controlled Variable: A Simulation Study

De Smet T, Struys MMRF, Greenwald S, Mortier EP, Shafer SL
Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts

Struys, MMRF, Sahinovic M., Lichtenbelt BJ, Vereecke HEM, Absalom AR
Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study

A Brain-Machine Interface for Control of Medically-Induced Coma

Shanechi MM, Chemali JJ, Liberman M, Solt K, Brown EN
Robust control of burst suppression for medical coma

Westover MB, Kim ES, Ching SN, Patrick L Purdon PL, Brown EN
Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade

Janda M, Simanski P, Bajorat J, Pohl B, Noeldge-Schomburg GFE, Hofmockel R
Safety and Efficacy of Drug-Induced Sleep Endoscopy Using a Probability Ramp Propofol Infusion System in Patients with Severe Obstructive Sleep Apnea

Joshua H. Atkins, MD, PhD,* Jeff E. Mandel, MD, MS,* and Giulia Rosanova, BA†
A Wrinkle In Time

FEATURED ARTICLE COLLECTION
Using Anesthesia to Mimic Sleep for Obstructive Sleep Apnea Patients: Challenges and Some Solutions
A Wrinkle In Time

FEATURED ARTICLE COLLECTION
Using Anesthesia to Mimic Sleep for Obstructive Sleep Apnea Patients: Challenges and Some Solutions
Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial

T. M. Hemmerling¹*, E. Arbeid², M. Wehbe¹, S. Cyr¹, R. Taddei² and C. Zaouter²

Fig 3 Flow chart showing the induction phase of the McSleepy group.
QUALITY AND PATIENT SAFETY

Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial

T. M. Hemmerling¹*, E. Arbeid², M. Wehbe¹, S. Cyr¹, R. Taddei² and C. Zaouter²
Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial

T. M. Hemmerling, E. Arbeid, M. Wehbe, S. Cyr, R. Taddei and C. Zaouter
Car Crashes Kill 40,000 in U.S. Every Year

Imagine a plane full of people crashing, killing everyone on board, every single day. That’s how many people die on America’s roads daily, says the Insurance Institute for Highway Safety.

“Motor vehicle crashes in the United States result in more than 40,000 deaths per year,” says the Institute in the journal Injury Prevention. “That is, on each of the 6,209 consecutive days included in this study, an equivalent of a plane load or more of people died on the roads.”

But not all days are alike. Weekends are worse than weekdays, summer and fall months have more deadly crashes than winter or spring months, and holidays top the list for crash deaths.

The Institute studied U.S. Department of Transportation data from 1986-2002. Information covered crashes on public roads resulting in a death within 30 days, including pedestrian deaths.

On average, more than 100 people per day died in car crashes in the U.S. The death toll for a single day can range from 45 to 252 people, say the researchers.
Health care in the United States is not as safe as it should be—and can be. At least 44,000 people, and perhaps as many as 98,000 people, die in hospitals each year as a result of medical errors that could have been prevented, according to estimates from two major studies. Even using the lower estimate, preventable medical errors in hospitals exceed attributable deaths to such feared threats as motor-vehicle wrecks, breast cancer, and AIDS.
Best Care at Lower Cost
The Path to Continuously Learning Health Care in America

Mark D. Smith, MD, MBA, Study Chair
The Vision

New Tools

• Computing Power
• Connectivity
• Improvements in organizational capabilities
• Collaboration between teams of clinicians and with patients
To Err is HUMAN

- Computers don’t yell, argue, have substance abuse problems, fall asleep, get angry, get hungry, get moody, get cold, flirt, bully, sulk, pee, get sick, get migraines, ignore alarms, forget why they are there.

- We have a responsibility to use computing technology wherever we can deploy it to reduce human error.
Barriers to Innovation in Anesthetic Drug Delivery
Primary candidates for innovation are generic

- Rocuronium
- Remifentanil
- Propofol
- Dexmedetomidine
If innovation in anesthesia drug delivery requires changes in the product label,

WE WILL NEVER SEE INNOVATION IN ANESTHETIC DRUG DELIVERY
What about SEDASYS?
$500,000,000
**Initiation of MAC Sedation:** For initiation of MAC sedation, either an infusion or a slow injection method may be utilized while closely monitoring cardiorespiratory function. With the infusion method, sedation may be initiated by infusing DIPRIVAN Injectable Emulsion at **100 to 150 µg/kg/min (6 to 9 mg/kg/h) for a period of 3 to 5 minutes** and titrating to the desired clinical effect while closely monitoring respiratory function. With the slow injection method for initiation, patients will require approximately 0.5 mg/kg administered over 3 to 5 minutes and titrated to clinical responses. When DIPRIVAN Injectable Emulsion is administered slowly over 3 to 5 minutes, most patients will be adequately sedated, and the peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects occurring at high plasma levels.

In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS .) The rate of **administration should be over 3-5 minutes** and the dosage of DIPRIVAN Injectable Emulsion should be reduced to **approximately 80%** of the usual adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION .)

**Maintenance of MAC Sedation:** For maintenance of sedation, a variable rate infusion method is preferable over an intermittent bolus dose method. With the variable rate infusion method, patients will generally require maintenance rates of **25 to 75 µg/kg/min** (1.5 to 4.5 mg/kg/h) **during the first 10 to 15 minutes** of sedation maintenance. Infusion rates should subsequently be **decreased** over time to **25 to 50 µg/kg/min** and adjusted to clinical responses. In titrating to clinical effect, allow approximately **2 minutes for onset** of peak drug effect.
Sedasys is NOT groundbreaking

• The $500,000,000 price tag can never be justified for an anesthetic drug delivery system.

• Inflexible adherence to the drug package insert will kill innovation.
  • Sedasys was lucky that rigid adherence to the propofol label actually worked.
Overcoming Barriers

- TCI devices give
  - approved drugs
  - by approved routes
  - for approved indications
  - at doses that conform to the package insert

- There should be minimal regulatory burden for TCI devices since the drug, route, indication, and doses are approved.
Redefine “dose”

- If the “dose” of drug administered by new technology is “substantially equivalent to the dose stated in the package insert”, then the device conforms to the label.

- *Just a clarification of the phrase “mutually conforming dose.”*

- Permits infusions to replace boluses

- Permits rapid changes and titrations that only computers can accomplish
Innovation Will Eliminate the Need for Inhalation Anesthesia

The statement is **false**, until there is a path to bringing innovation in anesthetic drug delivery to the United States.
Why will this time be different?