1 Introduction

The cost of developing a new drug is more than $800 million and typically takes well over a decade. The clinical trial failure rate in late stage development is unacceptably high at around 50% and the public has been surprised by the recent number of drugs previously regarded as safe, but which have been found to cause unacceptable toxicity once on the market. Of all the new chemical entities that enter clinical testing, only 21.5% achieve final clinical success and FDA marketing approval[1]. The number of new molecular entities approved by the FDA has been declining, down to 25 in 2002 from a high of 53 in 1996, mainly due to the decline in the number of new applications submitted to the FDA. Thus, improvements in biomedical science have not translated into a better success rate for investigational treatments.

The FDA has publicly stated its desire to participate in improving drug development productivity and quality in providing safe and effective medicines to American patients. It is recognized that while the cost of drug development continues to soar, productivity has continued to decrease in terms of a decreased number of new, meaningful drugs to patients. The clinical trial failure rate in late stage development is unacceptably high at around 50% and the public has been surprised by the recent number of drugs previously regarded as safe, but which have been found to cause unacceptable toxicity once on the market. Little has changed in the style of drug development over the past 30 years even though many promising innovations have occurred in biomarkers to measure drug effect or disease change, newer trial designs can be more informative earlier in the process, and a variety of information technology tools (database, simulation) allow scientists to contribute to key development decisions in a quantitative manner.

One of the major criticisms against drug development is its negligence to employ prior knowledge to drive drug development decisions such as trial design and analysis. The value of quantitative thinking in drug development and regulatory review is increasingly being appreciated. Modeling and simulation of data pertaining to pharmacokinetic, pharmacodynamic and disease progression is often referred to as the *pharmacometrics analyses.* Forty-two New Drug Applications (NDAs) which needed pharmacometrics reviews and submitted between 2000-2004 to the Cardio-renal, Oncology and Neuropharmacology drug products divisions were surveyed[2]. Similarly 32 NDAs which needed a pharmacometrics review and submitted to the FDA between 2005-2006 (all therapeutic areas) were also surveyed (manuscript in preparation). Opinions of the pharmacometrics, clinical pharmacology and medical teams were polled. Pharmacometric reviews with a critical role in the regulatory decision making were ranked as pivotal. Decision making here refers to the thought process specific to the question and not merely to whether a NDA was approved or not in general. Pharmacometric reviews which were worthwhile in confirming the

regulatory decision making were considered as supportive. About 90% of the 74 NDA reviews were either pivotal or supportive to the drug approval and labeling decisions. The impact of pharmacometrics reviews is consistent amongst the previous (2000-2004) and the current surveys (2005-2006). Thus far this is the largest survey to measure the value of quantitative clinical pharmacology efforts. Greater impact occurred when there was collaboration among the FDA pharmacometrics, clinical pharmacology, medical and statistical reviewers and the sponsor. Several of these case studies highlight the importance of applying pharmacometric techniques to either the design or analysis of late phase clinical trials. Extracting prior knowledge within the FDA on disease change or placebo effect was required to solve some of these case problems. Sponsors also valued this information that was not proprietary. This led to the idea that developing a mechanism to share disease, placebo and dropout models would be a valuable service for FDA to offer the scientific community to improve drug and regulatory development decisions.

Disease models for the purpose of this discussion are defined as the collection of sub-models that describe the distribution of exclusion/inclusion criteria (e.g.: baseline disease severity distribution and its relation with other risk factors); disease progression and its relationship to relevant biomarkers (e.g.: the contribution of changes in HbA1c to the risk of MI over time); drug effects (e.g.: concentration-HbA1c relationship) and drop-out model (e.g.: characteristics of patients who drop-out). The main objective of this initiative is to advance the utility and application of models to account for patient, disease, and drug effects on effectiveness and toxicity targeted to facilitate decision by product sponsors (e.g., go/no go, trial design), government (approval, labeling, trial design, value) and clinicians (drug selections, dosing).

In the current session, an overview of the impact of quantitative thinking on drug approval and labeling decisions will be presented which is followed by an overview of disease models. Summary of different sub-parts of the disease models for obesity and Parkinson's disease will be presented to allow discussion around the following questions. Other disease models have been employed or are under development. (e.g., type 2 diabetes, non-small cell lung cancer, HIV, transplant)

A summary of our disease modeling for obesity and Parkinson's disease are presented in the current document. Our efforts pertaining to Parkinson's disease model are more complete and that work should form the main basis for discussing the following questions.

1. Is the overall approach to quantifying various part of the disease models reasonable?
2. Is the approach to select data for modeling reasonable?
3. Is the approach to qualifying the models reasonable?
4. How should this information be publicly communicated?

2 Disease Models

The following section a brief description of the disease models for obesity and Parkinson's disease are provided. For each of the disease areas the data used and details of the patient population, placebo/disease progression and drop-out models are presented.

Obesity

Data

Demographic, body weight and drop-out data in about 600 obese patients over 2 years who received placebo along with diet and exercise control were employed to build the disease model for obesity.

Patient Population Model

Table 1 shows the mean and standard deviation of the logarithmic baseline bodyweights for Caucasian and African-American males and females. The data included 20% African-Americans of the total population, and 25% males. The QQ plots on log transformed bodyweight suggested that log-normal distribution is appropriate for simulating baseline bodyweights (not shown).

Table 1. Mean and Standard Deviation of Natural log-transformed Baseline Bodyweight.

	Caucasian		Black	
	Males	Females	Males	Females
Mean (kg) ± SD	4.80±0.17	4.60±0.18	4.88±0.20	4.67±0.18

Placebo Model

The percentage of bodyweight change from baseline over time is described by the equation below:

$$\%weightchange = -WTLoss_{max}(1 - exp(-k \bullet Time))$$

By this model, the % of bodyweight change from baseline can increase or decrease over the time to reach the maximal placebo effect, $WTLoss_{max}$. The constant k is the first-order rate constant of bodyweight change over time. The

between-patient variability for maximal placebo effect ($WTLoss_{max}$) and the residual variability were assumed to be normally distributed, whereas for rate of bodyweight changes from baseline (k) a log-normal distribution was assumed. Missing data were not imputed using last observation carry forward (LOCF) for estimation. The data was modeled by NONMEM V and FOCE method was used. The estimated parameters are presented in Table 2.

Table 2. Placebo model parameters to describe the % of bodyweight changes from baseline over time.

	Population Mean		Inter-subject variability	
	Estimate	Standard Error (%)	CV (%)	Standard Error (%)
WT loss rate (k, $month^{-1}$)	0.11	13.0	119%	14.3
Maximal weight loss from baseline ($WTLoss_{max}$, %)	2.06	19.9	392%	9.6
Residual Error (SD, kg)	1.4	6.7		

* correlation between random effects of k and $WTLoss_{max}$ was estimated to be 0.24

The model suggested the average maximal % of change from baseline in placebo group was about 2% and the time to reach to the maximal effect was about 25 weeks.

Drop-out Model

The dropout rate and the mean bodyweight change from baseline in the patients who dropped out and those who remained in the study at 3, 6, 9 and 12 months, are summarized in Table 3.

Table 3. Mean bodyweight changes in patients who dropped-out and those remained in the trial at various time points.

	< 12 weeks	12-24 weeks	24-36 weeks	36-52 weeks
% drop-out	24%	13%	9%	4%
Mean of % body weight change from baseline at the time of dropout in the subjects who dropped out	0.01	-0.55	-0.36	-0.38
Mean of % body weight change from baseline in subjects who remained in the study	-2.15	-2.99	-3.19	-2.77

As shown in Table 3, patients with less bodyweight changes from baseline are more likely to drop out from the study.

Both Cox-proportional hazards and parametric survival analyses, with an exponential hazard function, were conducted to explore the effect of percent bodyweight change from baseline on drop out. The results showed that the dropout pattern is significantly related to the % bodyweight loss, indicating that the greater percent weight loss, the less chance a subject would drop out from the study, consistent with Table 3. However, this survival analysis is only preliminary. The underlying assumption of this analysis is that the percent bodyweight change from baseline is associated with the probability of a patient to drop out from the study and the extent of the effect is the same across the study time. The final drop-out model parameters are presented in Table 4.

Table 4: Drop-out model parameters obtained using parametric survival analysis assuming an exponential distribution.

	Estimate	Standard Error	p value
Intercept	6.916	0.308	<0.0001
Effect of sex (male=1,female=2)	-0.3823	0.163	0.02
% of bodyweight change before dropout	-0.0621	0.0115	<0.0001

Parkinson's Disease

Parkinsonism is a clinical syndrome comprising of motor problems: bradykinesia (slowness and decreased amplitude of movement), tremor-at-rest, muscle rigidity, loss of postural reflexes, flexed posture, and the freezing phenomenon (where the feet are transiently "glued" to the ground)[3]. Not all six of these cardinal features need to be present, but at least two should be before diagnosis of Parkinsonism is made, with at least one of them being tremor-at-rest or bradykinesia. Parkinson's disease (PD) is the major cause of Parkinsonism. PD is a slowly progressive parkinsonian syndrome that begins insidiously, gradually worsens in severity and usually affects one side of the body before spreading to involve the other side. The management of PD can be divided into three categories (a) symptomatic treatment (b) protective/disease modifying treatment (c) surgical or restorative treatment.

Several drugs are approved by the FDA for symptomatic treatment (based on effects on Total UPDRS scores) such as L-Dopa, dopamine agonists (ropinirole, pramipexole), MAO-B inhibitors (Selegiline) etc. Novel clinical trial designs and statistical methods for data analysis are being pursued currently to clearly define a disease modifying drug[4]. In terms of novel clinical trial design, there is only one published study or rasagiline that has utilized delayed start design to study disease modifying benefits[5]. Questions have been raised on the effects of

missing data on the final outcome of a rasagiline clinical trial [6]. Model based repeated measures analysis could provide more clear evidence of disease modifying benefits[7-10].
We developed a quantitative model describing the patient characteristics, disease/placebo effects and drop-out patterns to explore various clinical trial designs and endpoints by computer simulation.

Data Sources

Demographic, longitudinal symptom scores (UPDRS) and times of drop-outs for each patient enrolled across six the clinical trials were employed for model building. Data from a total of 1400 patients collected over a duration of 0.5 to 3 years from double-blind, randomized and parallel or titration studies were available.

Patient Population Model

The influence of prognostic factors such as patient's age and time since diagnosis on the baseline UPDRS score was tested. Both age and time since diagnosis of disease were significant factors.

Disease Progression Model

Disease progression analysis for placebo was performed using linear mixed effects (PROC MIXED in SAS Ver 8.2). Briefly each patient's progression is defined by his/her own slope and intercept. Owing to the early placebo and symptomatic effects, we analyzed the data post 8 weeks. The model for change in total UPDRS score from baseline (cUPDRS) in treatment groups (Placebo, Drug) can be described as below:

$$\text{cUPDRS} = \beta_0 + \beta_1 \bullet \text{Week} + \beta_2 \bullet \text{Treatment} + \beta_3 \bullet \text{Week} \bullet \text{Treatment}$$

Where $\beta 0$, $\beta 1$, $\beta 2$, $\beta 3$ refer to intercept, slope in placebo group, symptomatic effect and slope differences between the treatment, placebo.

As can be seen in the equation above, if the treatment were to have disease modifying benefits, the difference in slope between the treatment groups would be statistically significant. The effects of various covariates (i.e., age, disease duration, age at disease onset, individual components of total UPDRS score) were also tested for their statistical significance on the slope. The final disease progression model parameter estimates are shown in Table 5.

Table 5. Parkinson's disease model parameters that were employed for clinical trial simulations. The inter-individual variability on all parameters was approximately 50%. The half-life to drug effect equilibration was derived from

preliminary analyses and from the fact that most studies showed maximal decrease in UPDRS by 4-8 weeks.

Placebo model parameter	Mean
Baseline UDPRS	25
Progression in placebo group (U/Wk)	0.16
Placebo effect (U)	-0.14
Symptomatic effect in treatment group (U)	-2
Half-life to drug effect equilibration, Wk	1
Residual Variability (U)	4

The relationship between model predicted vs observed mean total UPDRS score is shown in Figure 1. The model reasonably describes the data.

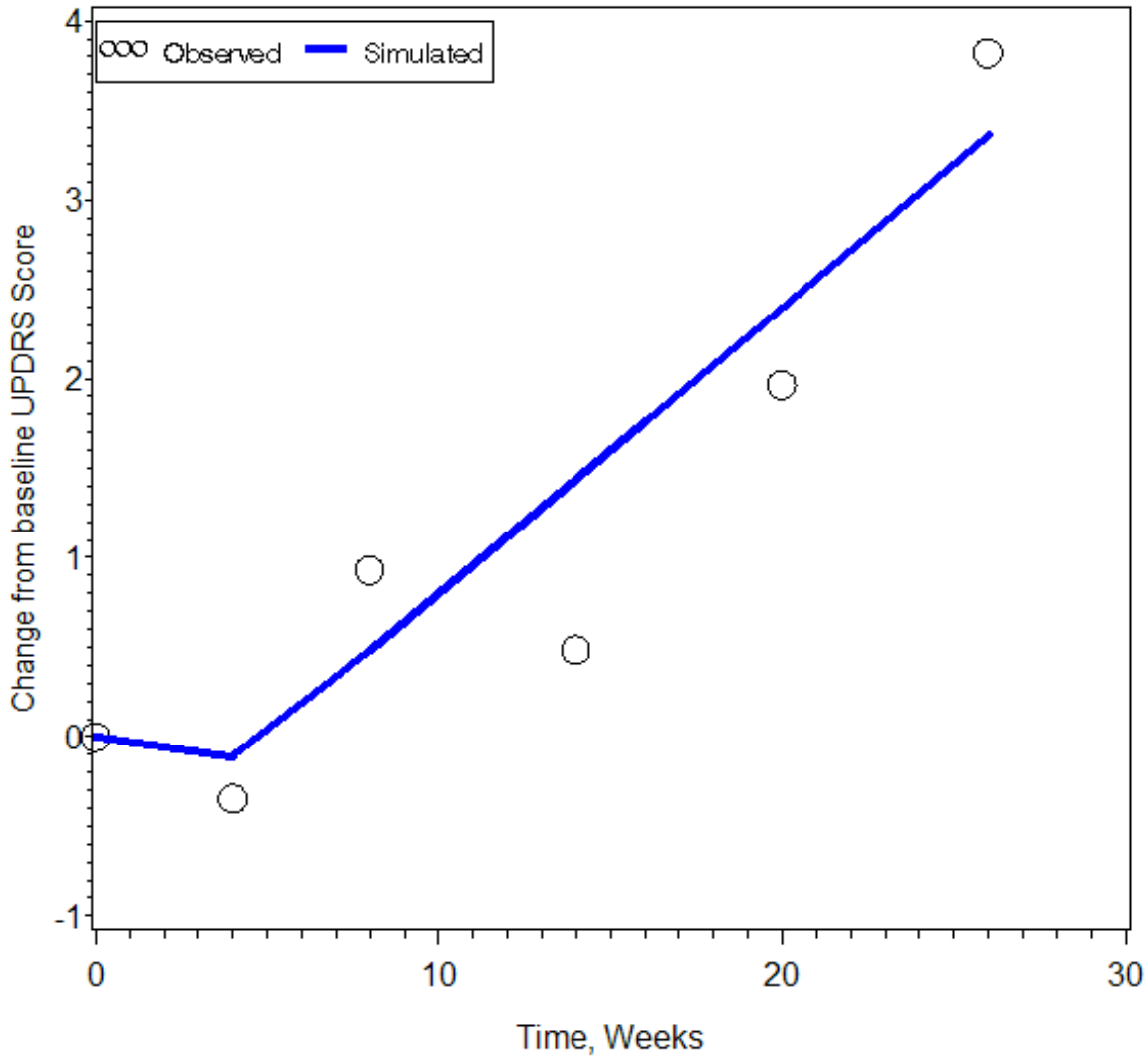

Figure 1. Observed disease progression, as reflected by the change in UPDRS

score, matches that of the model predicted well.

Drop-out model

Studies that evaluated the effectiveness of various treatments in idiopathic Parkinson's patients were reviewed. The various studies published in literature evaluated the effectiveness of treatments such as L-Dopa, Creatine, Co-Enzyme10, Rasagiline, Minocycline along with placebo[11-14]. In all the published trials, the predominant reason for drop-out is due to worsening of symptoms which ranged from 15% to 50% depending on the trial duration and drug. In other words, most of the treatment discontinuations were due to lack of effectiveness. We explored the relationship between time-to-rescue (T) and duration adjusted change in UPDRS score using accelerated failure time models (PROC LIFEREG; exponential, weibull, gamma, logistic, log-logistic distribution for T) in SAS (Ver 8.2). Figure 2 shows that faster the rate of progression the greater the likelihood of discontinuation is.

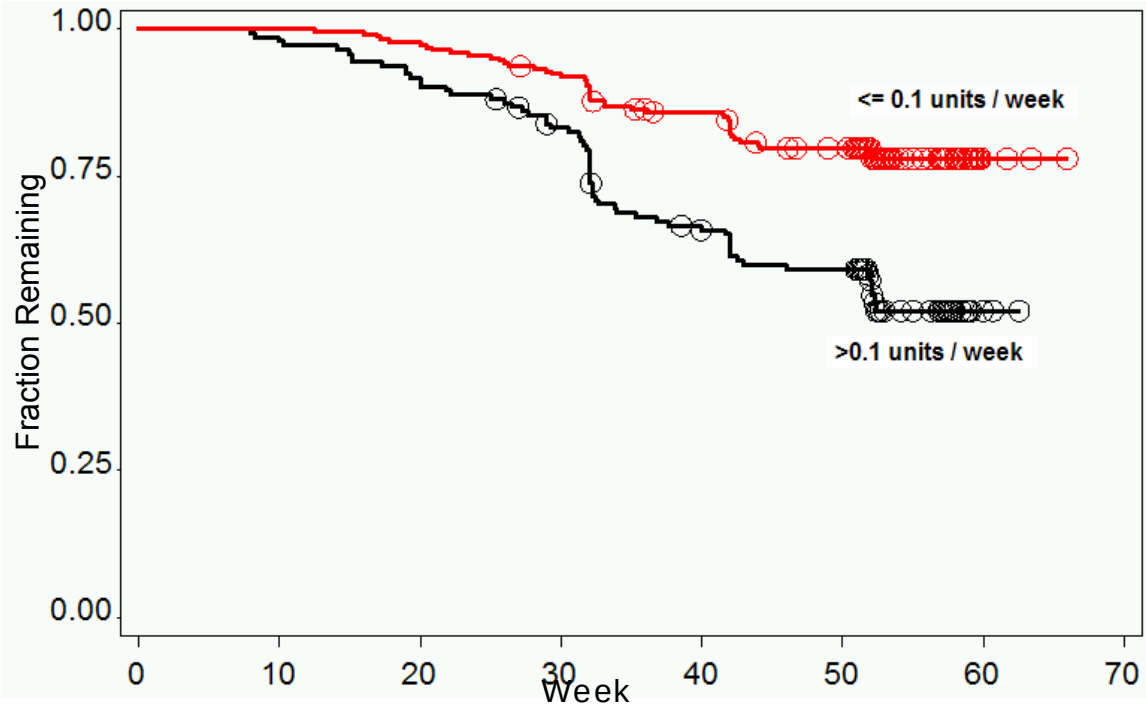

Figure 2. The proportion of patients remaining in the trial whose rate of change in UPDRS scores is less than 0.1 units/wk versus greater than 0.1 units/wk.

Model Qualification

To check if the input model for simulations is reasonable, predictive check was performed to ensure that the model simulated data are consistent with the

observed for:

1. Distribution of UPDRS scores at baseline
2. Mean time course of ΔUPDRS scores
3. Distribution of ΔUPDRS scores at Week 8, 26 and 52 weeks.
4. Hazard model to predict the probability of drop-out under various trial designs and trial duration.

Clinical Trial Simulations

The model developed for Parkinson's disease model (patient population, disease progression and drop-out models) was used to simulate data according to a delayed start design to explore the influence of drop-out data patterns (drop-out is independent vs. dependent of symptoms/toxicity) on the false-positive rate. We used both empirical as well as hazard based models for simulating missing data. All the simulations presented here assume that the drug effect is purely symptomatic and not disease modifying. The key objective of the simulations was to assess the false-positive (Type-1) error rate under various drop-out scenarios. Simulations to determine the appropriate duration of the trial (pivotal versus proof-of-concept) and sample size are underway and are not discussed in the current report.

Trial Design

According to the delayed start design, patients are randomized to either drug or placebo initially and after say 26 weeks placebo arm is switched to the drug, in a blinded manner. In our simulations, we assumed that the drug elicits only symptomatic effect i.e., no disease modifying effect. The design of the simulated trial is as shown below in Figure 3. The simulation conditions are shown in Table 6.

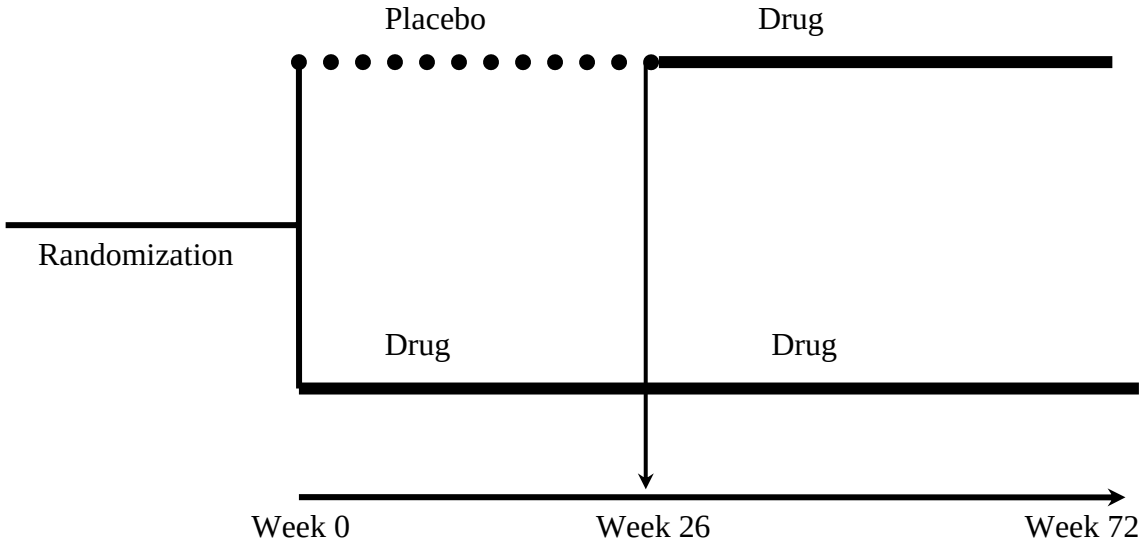

Figure 3. Schematic representation of the delayed start design. The initial 26

week period is called the 'placebo phase' and the subsequent period is called the 'active phase'.

Table 6. Simulation conditions used for the clinical trial simulations.

Sample Size	500
Number of Arms	2
Allocation	1:1
Trial Duration	72 weeks
Placebo Phase	0-26 weeks
Active Phase	26-72 weeks
UPDRS Measurements	0, 4, 8, 16, 20, 26, 32, 42, 52, 58, 72 weeks
Cumulative drop-out rate	30-50% (across placebo, active phases)
Drug effect	Only symptomatic

Statistical Analysis

The influence of various drop-out patterns were explored via computer simulations. Missing data were imputed using different techniques. For patient who drops out in the active phase, no imputations are used and the available data is used for analysis.

Analyses were conducted using

1. MMRM (Mixed Model Repeated Measures) approach for
   (a) ITT datasets (Intention-to-Treat datasets with no drop-outs and datasets with imputed values for missing information)
   (b) Non-ITT datasets (Datasets with only patients who completed the placebo controlled phase and have at least one post 26 weeks data).
2. ANOVA with imputation using LOCF approach
   (a) ITT with change from baseline at last observation (72 weeks)

In the LOCF analyses, change from baseline to the last observation was the dependent variable and treatment was the only independent (fixed) variable in the analysis of variance. Standard errors were obtained using mean square error as the estimate of residual variance. For the MMRM analyses, changes from baseline at all post-baseline times were the dependent variables. Independent variables included treatment, time and the treatment-by-time interaction. Denominator degrees of freedom were estimated using Satterthwaite's approximation [11: p 38]. Parameters were estimated using Restricted Maximum Likelihood with the Newton-Raphson algorithm. Each data set was analyzed with an UN correlation structure.

Several scenarios of drop-outs are being explored to understand their impact on Type-I error. Sample results will be presented at the Advisory Committee meeting.

References

1. DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, *The price of innovation: new estimates of drug development costs.* J Health Econ, 2003. **22**(2): p. 151-85.
2. Bhattaram, V.A., et al., *Impact of pharmacometrics on drug approval and labeling decisions: a survey of 42 new drug applications.* Aaps J, 2005. **7**(3): p. E503-12.
3. Olanow, C.W., *The scientific basis for the current treatment of Parkinson's disease.* Annu Rev Med, 2004. **55**: p. 41-60.
4. Clarke, C.E., *A "cure" for Parkinson's disease: can neuroprotection be proven with current trial designs?* Mov Disord, 2004. **19**(5): p. 491-8.
5. *A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease.* Arch Neurol, 2004. **61**(4): p. 561-6.
6. Shults, C.W., *Reexamination of the TEMPO Study.* Arch Neurol, 2005. **62**(8): p. 1320; author reply 1321.
7. Holford, N.H., et al., *Disease Progression and Pharmacodynamics in Parkinson Disease - Evidence for Functional Protection with Levodopa and Other Treatments.* J Pharmacokinet Pharmacodyn, 2006.
8. Chan, P.L. and N.H. Holford, *Drug treatment effects on disease progression.* Annu Rev Pharmacol Toxicol, 2001. **41**: p. 625-59.
9. Chan, P.L., J.G. Nutt, and N.H. Holford, *Modeling the short- and long-duration responses to exogenous levodopa and to endogenous levodopa production in Parkinson's disease.* J Pharmacokinet Pharmacodyn, 2004. **31**(3): p. 243-68.
10. Hauser, R.A. and N.H. Holford, *Quantitative description of loss of clinical benefit following withdrawal of levodopa-carbidopa and bromocriptine in early Parkinson's disease.* Mov Disord, 2002. **17**(5): p. 961-8.
11. *A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease.* Neurology, 2006. **66**(5): p. 664-71.
12. Fahn, S., et al., *Levodopa and the progression of Parkinson's disease.* N Engl J Med, 2004. **351**(24): p. 2498-508.
13. Shults, C.W., et al., *Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline.* Arch Neurol, 2002. **59**(10): p. 1541-50.
14. *A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study.* Arch Neurol, 2002. **59**(12): p. 1937-43.