Commands and Estimates for D. Carpenter, M. Chernew, D. G. Smith, and A. M. Fendrick, "Approval Times For New Drugs: Does The Source Of Funding For FDA Staff Matter?" *Health Affairs* (Web Exclusive) December 17, 2003, pp. W3-618-624.

[This note by Daniel P. Carpenter]

This notes lists some statistical estimates on which the analysis and discussion in the Health Affairs article was based.

All models were estimated in **STATA 8.0**. As a check, I am currently developing several estimators for this problem (and related ones) in **R**. These include models in which NDA submissions are endogenous to regulatory action, and models in which there are competing risks. Check back in a few months and I'll try to post those runs on the website by then.

Methodological Points: Robustness to Alternative Distributional Assumptions and Inclusion of Firm- and Disease- Indicator Variables

I begin with "full-sample" models which include (1) fixed effects for the firm submitting the NDA and (2) shared frailties (essentially a form of "random effects" in duration models) for the primary indication of the NDA.[1] This essentially controls for all disease-level and firm-level factors associated with approval times. I present these under eight different distributional assumptions.

- Weibull, gamma frailty
- Weibull, inverse Gaussian frailty
- Lognormal, gamma frailty
- Lognormal, inverse Gaussian frailty
- Gamma, gamma frailty
- Log-logistic, gamma frailty
- Gompertz, gamma frailty
- Cox model with firm fixed-effects only

Confounding Influences. It is worth repeating what we acknowledge explicitly in the article: that our analysis is observational, not experimental. Put differently, the effect of staff cannot be experimentally differentiated from other changes occurring at the same time. While no model can fully account for

[1] I generate fixed effects for firms and shared frailties (akin to random effects) for primary indications because this is the easiest way to facilitate estimation of the maximum likelihood models here that allows for convergence without non-concavity in the iterations of the likelihood maximization.

these effects, all of our models do include a “time trend,” in the form of the year of submission of the NME, which at least rules out those mechanisms that increased/decreased linearly with time (we can also include quadratic and cubic functions of time, neither of which change the results here appreciably). In addition, in other models (not reported here but which we can send you if necessary) we have controlled for changes in presidential administration, congressional committee oversight, and other political variables that may capture some of the politically influenced changes in FDA procedure that were occurring during the period in which our sample was generated.

I then report estimates from a number of models in which a number of observed covariates are added to estimation. These include both epidemiological and firm-level covariates.

Outliers/Influential Observations. Finally I do one check on influential observations in one of the simplest models, namely excluding the top percentile of observations (which in a duration model context are subject to being outliers) and re-estimating the likelihood equation. The last two pages of the notes show that this sample exclusion makes little difference to the results. Obviously other tests could be run here, but for a first glance this shows that influential positive outliers are not an issue.

Competing Risks. I have not presented competing risks models here but I can pass along estimations that show that a competing risks framework does not change the substantive findings.

Format of Presentation. In what follows I will present a number of model runs by printing the relevant output from STATA8. I have in most cases suppressed the printing of log-likelihood values at successive iterations of maximum likelihood convergence, as well as coefficient values for firm-level fixed effects and primary-indication-level random effects (combined, there are nearly 250 of these in the models with the largest samples).

One final note on presentation. I have marked marginal effects estimates for the CDER staff variable (STAFCDER) in aqua blue. Notes about the interpretation of coefficients and effects/elasticities appear in yellow.

Weibull model, Gamma Frailty, Complete Battery of Fixed Effects for Firms and Shared Frailties for Primary Indications, and control for Time Trend.

NOTICE THAT THE COEFFICIENTS ARE IN HAZARD FORM, SO POSITIVE COEFFICIENT MEANS INCREASE IN APPROVAL PROBABILITY AND REDUCTION IN APPROVAL TIME.

```
. streg stafcder subyear fmx*, dist(weibull) frailty(gamma) shared(discode)
note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity

Weibull regression --
         log-relative hazard form               Number of obs      =       843
         Gamma shared frailty                   Number of groups   =       180
Group variable: discode

No. of subjects =          843                  Obs per group: min =         1
No. of failures =          523                                 avg =  4.683333
Time at risk    =  36292.47129                                 max =        85

                                                LR chi2(56)        =    423.94
Log likelihood  =   -841.47418                  Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |   1.002479   .0005501     4.51   0.000     1.001402    1.003558
     subyear |   1.020743   .0234056     0.90   0.371      .975884    1.067663
-------------+----------------------------------------------------------------
       /ln_p |   .4515741   .0302051    14.95   0.000     .3923732    .5107751
     /ln_the |  -.8854326     .22576    -3.92   0.000    -1.327914   -.4429512
-------------+----------------------------------------------------------------
           p |   1.570783   .0474457                      1.48049    1.666583
         1/p |   .6366252   .0192294                     .6000303     .675452
       theta |   .4125357    .093134                     .2650295    .6421385
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =    71.56 Prob>=chibar2 = 0.000
```

NOTICE THAT MARGINAL EFFECTS AND ELASTICITIES FOR WEIBULL MODEL ARE REPORTED IN TERMS OF PREDICTED MEDIAN APPROVAL TIME, SO A NEGATIVE COEFFICIENT MEANS A REDUCTION IN REVIEW TIME.

```
. mfx compute, dydx

Marginal effects after weibullhet
      y  = predicted median _t (predict)
         =  26.165997
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0543998      .01161   -4.69   0.000  -.077149 -.031651   1299.47
 subyear |   .1976721      .43943    0.45   0.653  -.663593  1.05894   1988.95
orderent |   .3253007      .22441    1.45   0.147  -.114529   .76513   8.83312
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after weibullhet
      y  = predicted median _t (predict)
         =  26.165997
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -2.701623      .51826   -5.21   0.000   -3.7174 -1.68585   1299.47
 subyear |   15.02563      33.529    0.45   0.654  -50.6892  80.7404   1988.95
orderent |    .109815      .07024    1.56   0.118  -.027847  .247477   8.83312
------------------------------------------------------------------------------
```

Weibull model, Inverse Gaussian Frailty, Complete Battery of Fixed Effects for Firms and Shared Frailties for Primary Indications, and Control for Time Trend.

NOTICE THAT THE COEFFICIENTS ARE IN HAZARD FORM, SO POSITIVE COEFFICIENT MEANS INCREASE IN APPROVAL PROBABILITY AND REDUCTION IN APPROVAL TIME.

```
. streg stafcder subyear fmx*, dist(weibull) frailty(invg) shared(discode)

note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity

Weibull regression --
         log-relative hazard form               Number of obs      =       843
         Inverse-Gaussian shared frailty        Number of groups   =       180
Group variable: discode

No. of subjects =          843                  Obs per group: min =         1
No. of failures =          523                                 avg =  4.683333
Time at risk    =  36292.47129                                 max =        85

                                                LR chi2(56)        =    435.60
Log likelihood  =   -841.98304                  Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |   1.002464   .0005545     4.45   0.000     1.001378    1.003552
     subyear |   1.022313   .0235693     0.96   0.338     .9771458    1.069567
-------------+----------------------------------------------------------------
       /ln_p |    .453745   .0302342    15.01   0.000      .394487    .5130029
     /ln_the |  -.4148135   .3140935    -1.32   0.187    -1.030426    .2007985
-------------+----------------------------------------------------------------
           p |   1.574196   .0475946                      1.483623    1.670299
         1/p |   .6352447   .0192061                      .5986951    .6740257
       theta |   .6604634   .2074473                      .3568551    1.222378
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =    70.54 Prob>=chibar2 = 0.000
```

NOTICE THAT MARGINAL EFFECTS AND ELASTICITIES FOR WEIBULL MODEL ARE REPORTED IN TERMS OF PREDICTED MEDIAN APPROVAL TIME, SO A NEGATIVE COEFFICIENT MEANS A REDUCTION IN REVIEW TIME.

```
. mfx compute, dydx

Marginal effects after weibullhet
      y  = predicted median _t (predict)
         =  25.056163
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0595963      .01145   -5.21   0.000  -.082036 -.037157   1296.46
 subyear |   .4540731      .41845    1.09   0.278  -.366078  1.27422   1988.93
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after weibullhet
      y  = predicted median _t (predict)
         =  25.056163
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -3.083643      .52139   -5.91   0.000  -4.10554 -2.06174   1296.46
 subyear |   36.04379      33.107    1.09   0.276  -28.8444  100.932   1988.93
------------------------------------------------------------------------------
```

Lognormal Model, Gamma Frailty, Complete Battery of Fixed Effects for Firms and Shared Frailties for Primary Indication, with control for time trend

NOTICE THAT COEFFICIENTS, MARGINAL EFFECTS AND ELASTICITIES FOR LOGNORMAL MODEL ARE REPORTED IN TERMS OF PREDICTED MEDIAN APPROVAL TIME, SO A NEGATIVE COEFFICIENT MEANS A REDUCTION IN REVIEW TIME.

```
. streg stafcder subyear fmx*, dist(logn) frailty(gamma) shared(discode)
note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity

Log-normal regression --
         accelerated failure-time form          Number of obs      =       843
         Gamma shared frailty                   Number of groups   =       180
Group variable: discode

No. of subjects =          843                 Obs per group: min =         1
No. of failures =          523                                avg =  4.683333
Time at risk    =  36292.47129                                max =        85

                                               LR chi2(56)        =    263.48
Log likelihood  =   -832.55965                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0013065   .0003594    -3.64   0.000    -.0020109   -.0006021
     subyear |  -.0109988   .0150533    -0.73   0.465    -.0405028    .0185051
       _cons |   27.21312   29.51312     0.92   0.356    -30.63154    85.05778
-------------+----------------------------------------------------------------
     /ln_sig |  -.3177416   .0447072    -7.11   0.000    -.4053662   -.2301171
     /ln_the |  -1.061313    .222591    -4.77   0.000    -1.497584   -.6250432
-------------+----------------------------------------------------------------
       sigma |   .7277908   .0325375                      .6667326    .7944406
       theta |   .3460011   .0770167                        .22367    .5352383
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =    82.56 Prob>=chibar2 = 0.000

. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  22.181383
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0241754       .00833   -2.90   0.004  -.040493 -.007858   1296.46
 subyear |   -.375134       .3427   -1.09   0.274  -1.04682  .296553   1988.93
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after lnormalhet
      y  = predicted median _t (predict)
         =  22.181383
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -1.413011       .47245   -2.99   0.003  -2.33899 -.487027   1296.46
 subyear |  -33.63698       30.654   -1.10   0.273  -93.7186  26.4446   1988.93
------------------------------------------------------------------------------
```

LogNormal Model, Inverse Gaussian frailty, full battery of fixed effects for firms and Shared Frailties for diseases, with control for time trend.

NOTICE THAT COEFFICIENTS, MARGINAL EFFECTS AND ELASTICITIES FOR LOGNORMAL MODEL ARE REPORTED IN TERMS OF PREDICTED MEDIAN APPROVAL TIME, SO A NEGATIVE COEFFICIENT MEANS A REDUCTION IN REVIEW TIME.

```
. streg stafcder subyear fmx*, dist(logn) frailty(invg) shared(discode)
note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity

Log-normal regression --
        accelerated failure-time form          Number of obs      =       843
        Inverse-Gaussian shared frailty        Number of groups   =       180
Group variable: discode

No. of subjects =          843                 Obs per group: min =         1
No. of failures =          523                                avg =  4.683333
Time at risk    =  36292.47129                                max =        85

                                               LR chi2(56)        =    265.81
Log likelihood  =   -833.69242                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0013295   .0003609    -3.68   0.000     -.002037   -.0006221
     subyear |    -.01015   .0151241    -0.67   0.502    -.0397927    .0194927
       _cons |   25.56375   29.65355     0.86   0.389    -32.55614    83.68365
-------------+----------------------------------------------------------------
     /ln_sig |   -.319232     .04715    -6.77   0.000    -.4116443   -.2268196
     /ln_the |  -.7299569   .2840916    -2.57   0.010    -1.286766   -.1731476
-------------+----------------------------------------------------------------
       sigma |    .726707   .0342643                      .6625599    .7970646
       theta |   .4819298   .1369122                      .2761624    .8410135
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =    80.29 Prob>=chibar2 = 0.000

. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  21.931525
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |   -.025024      .00833   -3.00   0.003  -.041358  -.00869   1296.46
 subyear |  -.3357476      .34125   -0.98   0.325  -1.00459  .333092   1988.93
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after lnormalhet
      y  = predicted median _t (predict)
         =  21.931525
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -1.479271      .47629   -3.11   0.002  -2.41279  -.54575   1296.46
 subyear |  -30.44832      30.839   -0.99   0.323  -90.8915  29.9948   1988.93
------------------------------------------------------------------------------
```

Gompertz Model, Gamma Frailty, Complete Battery of Fixed Effects for Firms and Random Effects for Primary Indication, with control for time trend

NOTICE THAT THE COEFFICIENTS ARE IN HAZARD FORM, SO POSITIVE COEFFICIENT MEANS INCREASE IN APPROVAL PROBABILITY AND REDUCTION IN APPROVAL TIME.

```
. streg stafcder subyear fmx*, dist(gomp) frailty(gamma) shared(discode)

note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity


Gompertz regression --
         log relative-hazard form               Number of obs      =       843
         Gamma shared frailty                   Number of groups   =       180
Group variable: discode

No. of subjects =          843                 Obs per group: min =         1
No. of failures =          523                                avg =  4.683333
Time at risk    =  36292.47129                                max =        85

                                               LR chi2(56)        =    268.72
Log likelihood  =   -901.48772                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |   1.001511   .0004972     3.04   0.002     1.000537    1.002486
     subyear |   1.012941   .0209024     0.62   0.533     .9727904    1.054749
-------------+----------------------------------------------------------------
       gamma |  -.0012275   .0014345    -0.86   0.392    -.0040389     .001584
     /ln_the |  -2.055647   .3704618    -5.55   0.000    -2.781739   -1.329555
-------------+----------------------------------------------------------------
       theta |     .12801   .0474228                      .0619307    .2645949
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =    18.27 Prob>=chibar2 = 0.000
```

NOTICE THAT MARGINAL EFFECTS AND ELASTICITIES FOR GOMPERTZ MODEL ARE REPORTED IN TERMS OF PREDICTED MEDIAN APPROVAL TIME, SO A NEGATIVE COEFFICIENT MEANS A REDUCTION IN REVIEW TIME.

```
. mfx compute, dydx

Marginal effects after gompertzhet
      y  = predicted median _t (predict)
         =  24.236698
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0485965      .01348   -3.60   0.000   -.07502 -.022173   1296.46
 subyear |   .2385155      .52045    0.46   0.647  -.781554  1.25859   1988.93
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after gompertzhet
      y  = predicted median _t (predict)
         =  24.236698
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -2.599508      .66368   -3.92   0.000   -3.9003 -1.29871   1296.46
 subyear |   19.57323      42.657    0.46   0.646  -64.0338   103.18   1988.93
------------------------------------------------------------------------------
```

Gamma model, Gamma frailty, with control for time trend. (Gamma model does not support shared frailties in STATA8, so frailty is not grouped here.)

NOTICE THAT COEFFICIENTS, MARGINAL EFFECTS AND ELASTICITIES FOR LOGNORMAL MODEL ARE REPORTED IN TERMS OF PREDICTED MEDIAN APPROVAL TIME, SO A NEGATIVE COEFFICIENT MEANS A REDUCTION IN REVIEW TIME.

```
. streg stafcder subyear, dist(gamma) frailty(gamma)

Gamma regression -- accelerated failure-time form
                 Gamma frailty

No. of subjects =          843                     Number of obs   =       843
No. of failures =          523
Time at risk    =  36292.47129
                                                   LR chi2(3)      =    165.00
Log likelihood  =   -940.22469                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0010883   .0003272    -3.33   0.001    -.0017295   -.0004471
     subyear |  -.0266162   .0136876    -1.94   0.052    -.0534435    .0002111
       _cons |    57.4792   26.83101     2.14   0.032     4.891391     110.067
-------------+----------------------------------------------------------------
     /ln_sig |  -.7833145   .0886469    -8.84   0.000    -.9570591   -.6095698
      /kappa |   .5874128   .1080451     5.44   0.000     .3756482    .7991774
     /ln_the |   .8615113   .1492063     5.77   0.000     .5690724     1.15395
-------------+----------------------------------------------------------------
       sigma |   .4568891   .0405018                      .3840206    .5435846
       theta |   2.366735   .3531317                      1.766627    3.170693
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =    73.01 Prob>=chibar2 = 0.000

. mfx compute, dydx

Marginal effects after gammahet
      y  = predicted median _t (predict)
         =  31.538965
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.      z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0343231       .0105   -3.27   0.001    -.0549 -.013746   1296.46
 subyear |  -.8394486      .43222   -1.94   0.052  -1.68658  .007679   1988.93
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after gammahet
      y  = predicted median _t (predict)
         =  31.538965
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.      z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -1.410907      .42414   -3.33   0.001  -2.24221 -.579607   1296.46
 subyear |   -52.9378      27.224   -1.94   0.052  -106.295  .419777   1988.93
------------------------------------------------------------------------------
```

Log-Logistic Model, Gamma Frailty, with Full Battery of Fixed and Random Effects for Firms and Diseases, with Control for Time Trend

NOTICE THAT COEFFICIENTS, MARGINAL EFFECTS AND ELASTICITIES FOR LOGLOGISTIC MODEL ARE REPORTED IN TERMS OF PREDICTED MEDIAN APPROVAL TIME, SO A NEGATIVE COEFFICIENT MEANS A REDUCTION IN REVIEW TIME.

```
. streg stafcder subyear fmx*, dist(loglog) frailty(gamma) shared(discode)

note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity

Log-logistic regression --
        accelerated failure-time form          Number of obs      =       843
        Gamma shared frailty                   Number of groups   =       180
Group variable: discode

No. of subjects =          843                 Obs per group: min =         1
No. of failures =          523                                avg =  4.683333
Time at risk    =  36292.47129                                max =        85

                                               LR chi2(56)        =    251.28
Log likelihood  =   -816.12435                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |   -.001028   .0003329    -3.09   0.002    -.0016805   -.0003754
     subyear |  -.0156374   .0140761    -1.11   0.267    -.0432261    .0119514
       _cons |   35.85387   27.60132     1.30   0.194    -18.24372    89.95146
-------------+----------------------------------------------------------------
     /ln_gam |  -1.024648   .0569088   -18.01   0.000    -1.136187   -.9131087
     /ln_the |  -.7705357   .1954608    -3.94   0.000    -1.153632   -.3874396
-------------+----------------------------------------------------------------
       gamma |   .3589228   .0204259                      .3210408    .4012748
       theta |   .4627651   .0904524                      .3154889    .6787926
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =   114.60 Prob>=chibar2 = 0.000

. mfx compute, dydx

Marginal effects after llogistichet
      y  = predicted median _t (predict)
         =  20.063503
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0160747      .00644   -2.49   0.013  -.028704 -.003445   1296.46
 subyear |   -.507045      .27307   -1.86   0.063  -1.04224  .028155   1988.93
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after llogistichet
      y  = predicted median _t (predict)
         =  20.063503
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -1.038711      .41144   -2.52   0.012  -1.84511 -.232307   1296.46
 subyear |  -50.26422      26.882   -1.87   0.062  -102.953   2.4244   1988.93
------------------------------------------------------------------------------
```

Cox proportional hazards estimates, STAFCDER with full battery of firm fixed effects, time trend and order of market entry

NOTICE THAT COEFFICIENTS, MARGINAL EFFECTS AND ELASTICITIES ARE ALL PRESENTED IN HAZARD FORM, SO POSITIVE COEFFICIENT MEANS INCREASE IN APPROVAL PROBABILITY AND REDUCTION IN APPROVAL TIME.

Cox regression -- Breslow method for ties

No. of subjects =	843	Number of obs =	843
No. of failures =	523		
Time at risk =	36292.47129		
		LR chi2(56) =	459.42
Log likelihood =	-2925.5154	Prob > chi2 =	0.0000

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
stafcder	1.002054	.000475	4.33	0.000	1.001123	1.002986
subyear	1.023069	.0199427	1.17	0.242	.9847192	1.062912

FMX* Suppressed

. mfx compute, dydx

Marginal effects after cox
y = relative hazard (predict)
= 24.079434

variable	dy/dx	Std. Err.	z	P>|z|	[	95% C.I.	]	X
stafcder	.059088	.01866	3.17	0.002	.022522	.095654		1296.46

. mfx compute, eyex

Elasticities after cox
y = relative hazard (predict)
= 24.079434

variable	ey/ex	Std. Err.	z	P>|z|	[	95% C.I.	]	X
stafcder	3.181358	.24023	13.24	0.000	2.71051	3.6522		1296.46

THE COX MODEL IN STATA DOES NOT ALLOW FOR FRAILTIES/HETEROGENEITY

Lognormal results with controls for FDA Drug Priority Ratings (firm fixed effects, shared frailties by primary indication, etc)

```
. streg stafcder subyear  rat1p rat1a rat1b rat1c rat1aa fmx*, dist(logn) frail
> ty(invg) shared(discode)

Log-normal regression --
         accelerated failure-time form          Number of obs      =       701
         Inverse-Gaussian shared frailty        Number of groups   =       179
Group variable: discode

No. of subjects =          701                  Obs per group: min =         1
No. of failures =          521                                 avg =  3.916201
Time at risk    =  20041.97261                                 max =        59

                                                LR chi2(61)        =    371.48
Log likelihood  =    -582.0334                  Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0012245   .0002854    -4.29   0.000    -.0017838   -.0006651
     subyear |  -.0550233   .0118149    -4.66   0.000    -.0781802   -.0318665
       rat1p |  -.6396107   .0806674    -7.93   0.000    -.7977158   -.4815056
       rat1a |   -1.43886   .1498952    -9.60   0.000     -1.73265   -1.145071
       rat1b |  -1.024453   .1346323    -7.61   0.000    -1.288328   -.7605787
       rat1c |    -.75293   .1265364    -5.95   0.000    -1.000937   -.5049232
      rat1aa |  -.4506145   .3057475    -1.47   0.141    -1.049869    .1486397
       _cons |   115.0242   23.25714     4.95   0.000     69.44105    160.6074
-------------+----------------------------------------------------------------
     /ln_sig |  -.4798497   .0367459   -13.06   0.000    -.5518703    -.407829
     /ln_the |  -3.444204   1.996009    -1.73   0.084    -7.356309    .4679017
-------------+----------------------------------------------------------------
       sigma |   .6188764   .0227412                      .5758717    .6650926
       theta |   .0319302   .0637329                      .0006386    1.596641
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     0.20 Prob>=chibar2 = 0.327


. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  23.840255
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.      z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0258471      .00691   -3.74   0.000  -.039396 -.012299   1324.53
 subyear |  -1.538905      .29374   -5.24   0.000  -2.11462  -.96319   1989.34
   rat1p*|  -13.55721      1.3955   -9.71   0.000  -16.2923 -10.8221   .178317
   rat1a*|   -19.6209     1.34837  -14.55   0.000  -22.2637 -16.9781   .051355
   rat1b*|  -18.37371      1.6838  -10.91   0.000  -21.6739 -15.0735   .128388
   rat1c*|  -16.44649     2.20485   -7.46   0.000  -20.7679 -12.1251   .275321
  rat1aa*|  -9.130688      4.2228   -2.16   0.031  -17.4072 -.854161   .015692
------------------------------------------------------------------------------
```

LogNormal Model with PDUFA dummy variable (0 until 1992, 1 thereafter) and FDA Drug Priority Ratings. Full Battery of Firm Fixed Effects, Shared Frailties by Primary Indication, and Time Trend Control

```
. streg stafcder subyear pdufadum rat1p rat1a rat1b rat1c rat1aa fmx*, dist(log
> n) frailty(invg) shared(discode)

note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity

Log-normal regression --
         accelerated failure-time form          Number of obs      =       701
         Inverse-Gaussian shared frailty        Number of groups   =       179
Group variable: discode

No. of subjects =          701                 Obs per group: min =         1
No. of failures =          521                                avg =  3.916201
Time at risk    =  20041.97261                                max =        59

                                               LR chi2(62)        =    372.84
Log likelihood  =   -581.35323                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0009819   .0003532    -2.78   0.005    -.0016742   -.0002896
     subyear |  -.0544363   .0118071    -4.61   0.000    -.0775779   -.0312947
    pdufadum |  -.1528813   .1310265    -1.17   0.243    -.4096885    .1039259
       rat1p |  -.6434245   .0806409    -7.98   0.000    -.8014778   -.4853711
       rat1a |  -1.435447   .1496885    -9.59   0.000    -1.728831   -1.142063
       rat1b |  -1.021378   .1338839    -7.63   0.000    -1.283786   -.7589707
       rat1c |  -.7471027   .1255952    -5.95   0.000    -.9932649   -.5009406
      rat1aa |  -.4602798   .3063838    -1.50   0.133    -1.060781    .1402214
       _cons |   113.5953   23.25169     4.89   0.000     68.02281    159.1678
-------------+----------------------------------------------------------------
     /ln_sig |  -.4813204   .0368744   -13.05   0.000    -.5535928    -.409048
     /ln_the |  -3.401976   1.933771    -1.76   0.079    -7.192098    .3881465
-------------+----------------------------------------------------------------
       sigma |   .6179669   .0227871                      .5748806    .6642823
       theta |   .0333074   .0644089                      .0007525    1.474246
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     0.21 Prob>=chibar2 = 0.322
```

LogNormal Model with FirmSales x STAFCDER interaction, plus fixed effects and shared frailties.

IN THE FOLLOWING
salereal_defl1000 = SALES OF SUBMITTING FIRM IN SUBMISSION YEAR OF NME, DEFLATED AND DIVIDED BY MILLIONS OF U.S. 2000 DOLLARS
staff8fsales_def1000 = STAFCDER * salereal_defl1000

```
. streg stafcder   salereal_defl1000 staff8fsales_def1000 fmx*, dist(logn) frai
> lty(invg) shared(discode)

note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxMallinckrodt dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity


Log-normal regression --
         accelerated failure-time form          Number of obs      =       447
         Inverse-Gaussian shared frailty        Number of groups   =       149
Group variable: discode

No. of subjects =          447                  Obs per group: min =         1
No. of failures =          363                                 avg =         3
Time at risk    =  10784.41645                                 max =        37

                                                LR chi2(56)        =    161.24
Log likelihood  =    -401.0583                  Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |   -.001575   .0002249    -7.00   0.000    -.0020157   -.0011342
salerea~1000 |  -.0452584   .0267673    -1.69   0.091    -.0977213    .0072046
staff8f~1000 |   .0000311   .0000189     1.65   0.100    -5.92e-06    .0000682
       _cons |   5.569758   .3462112    16.09   0.000     4.891196    6.248319
-------------+----------------------------------------------------------------
     /ln_sig |  -.5103173   .0482474   -10.58   0.000    -.6048805   -.4157541
     /ln_the |  -1.902325   .5795843    -3.28   0.001     -3.03829   -.7663611
-------------+----------------------------------------------------------------
       sigma |   .6003051   .0289632                      .5461397    .6598425
       theta |   .1492212   .0864863                      .0479168     .464701
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     5.86 Prob>=chibar2 = 0.008
```

LogNormal Model with Epidemiological and Political Covariates, Inverse Gaussian Frailties (Shared by Primary Indication), Fixed Firm Effects, plus time trend and other controls

```
. streg stafcder subyear prevgenx lethal deathrt1 hosp01 hospdisc hhosleng acut
> ediz femdiz01 mandiz01 peddiz01 orphdum natreg wpnoavg3 orderent fmx*, dist(l
> ogn) frailty(invg) shared(discode)


note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxGenzyme dropped due to collinearity
note: fmxMylan dropped due to collinearity
note: fmxNovoNordisk dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity
note: fmxSankyo dropped due to collinearity
note: fmxTEVA dropped due to collinearity
note: fmxUCB dropped due to collinearity
note: fmxZambon dropped due to collinearity

Log-normal regression --
         accelerated failure-time form          Number of obs      =       450
         Inverse-Gaussian shared frailty        Number of groups   =        87
Group variable: discode

No. of subjects =          450                  Obs per group: min =         1
No. of failures =          296                                 avg =  5.172414
Time at risk    =  20829.23837                                 max =        78

                                                LR chi2(63)        =    214.08
Log likelihood  =   -465.50959                  Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0033316   .0005986    -5.57   0.000    -.0045049   -.0021583
     subyear |   .0701404   .0272355     2.58   0.010     .0167599    .1235209
    prevgenx |    .001934   .0006239     3.10   0.002      .000711    .0031569
      lethal |  -.0385211   .1817948    -0.21   0.832    -.3948324    .3177902
    deathrt1 |  -.3779325   .1819253    -2.08   0.038    -.7344995   -.0213655
      hosp01 |  -.0262252   .2224424    -0.12   0.906    -.4622043    .4097539
    hospdisc |   8.79e-07   4.82e-07     1.82   0.068    -6.56e-08    1.82e-06
    hhosleng |  -.0268771   .0170082    -1.58   0.114    -.0602127    .0064584
    acutediz |  -.2144682   .1689756    -1.27   0.204    -.5456542    .1167178
    femdiz01 |   -.129141   .2708761    -0.48   0.634    -.6600484    .4017665
    mandiz01 |  -.3190436   .3739797    -0.85   0.394     -1.05203    .4139432
    peddiz01 |   .6582589   .3919559     1.68   0.093    -.1099605    1.426478
     orphdum |  -.2385158   .1527015    -1.56   0.118    -.5378053    .0607737
      natreg |   .0048876   .0023794     2.05   0.040     .0002241    .0095512
    wpnoavg3 |  -.0008318   .0006582    -1.26   0.206    -.0021219    .0004582
    orderent |   .0093892   .0065397     1.44   0.151    -.0034284    .0222067
       _cons |  -131.4016   53.44383    -2.46   0.014    -236.1496   -26.65358
-------------+----------------------------------------------------------------
     /ln_sig |  -.2326355   .0671761    -3.46   0.001    -.3642982   -.1009728
     /ln_the |  -1.411016    .731406    -1.93   0.054    -2.844546    .0225132
-------------+----------------------------------------------------------------
       sigma |   .7924424   .0532332                      .694684    .9039576
       theta |   .2438953   .1783865                     .0581607    1.022769
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     5.75 Prob>=chibar2 = 0.008

. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  24.679092
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
```

stafcder	-.0677186	.01904	-3.56	0.000	-.10503	-.030407	1305.74
subyear	1.100494	.73515	1.50	0.134	-.340376	2.54136	1989.63
prevgenx	.0283913	.01914	1.48	0.138	-.009126	.065909	114.074
lethal*	-1.233564	5.51105	-0.22	0.823	-12.035	9.56789	.631111
deathrt1	-4.072539	5.75146	-0.71	0.479	-15.3452	7.20012	.094283
hosp01*	-.949024	6.7817	-0.14	0.889	-14.2409	12.3429	.8
hospdisc	.0000247	.00001	1.99	0.047	3.5e-07	.000049	133483
hhosleng	-.4917482	.48186	-1.02	0.307	-1.43618	.452688	5.37016
acutediz*	.388031	7.44399	0.05	0.958	-14.2019	14.978	.373333
femdiz01*	-2.971792	6.83036	-0.44	0.664	-16.3591	10.4155	.046667
mandiz01*	-3.787329	8.37603	-0.45	0.651	-20.204	12.6294	.026667
peddiz01*	23.80344	24.06	0.99	0.323	-23.3537	70.9606	.037778
orphdum*	-3.961529	3.67747	-1.08	0.281	-11.1692	3.24619	.12
dcancer*	11.2522	12.447	0.90	0.366	-13.1425	35.6469	.128889
dcardio*	12.12807	10.188	1.19	0.234	-7.84014	32.0963	.306667
dneuro*	11.99576	25.114	0.48	0.633	-37.2268	61.2183	.013333
dmental*	11.65877	14.531	0.80	0.422	-16.8212	40.1387	.077778
durology*	7.537394	13.356	0.56	0.573	-18.6392	33.714	.037778
dmuscske*	14.95973	17.805	0.84	0.401	-19.9379	49.8574	.035556
natreg	.0576663	.08021	0.72	0.472	-.09954	.214872	16.6711
wpnoavg3	-.020303	.0204	-1.00	0.320	-.060279	.019673	67.4272
orderent	.0320158	.20087	0.16	0.873	-.361686	.425718	10.5489

(*) dy/dx is for discrete change of dummy variable from 0 to 1

```
. streg stafcder subyear prevgenx lethal deathrt1 hosp01 hospdisc hhosleng acut
> ediz femdiz01 mandiz01 peddiz01 orphdum natreg wpnoavg3 orderent fsubmits fmx
> *, dist(logn) frailty(invg) shared(discode)

note: fmxAkzoNobel dropped due to collinearity
…
note: fmxZambon dropped due to collinearity

Log-normal regression --
         accelerated failure-time form          Number of obs      =       348
         Inverse-Gaussian shared frailty        Number of groups   =        86
Group variable: discode

No. of subjects =          348                  Obs per group: min =         1
No. of failures =          290                                 avg =  4.046512
Time at risk    =  9981.238352                                 max =        47

                                                LR chi2(64)        =    169.69
Log likelihood  =   -348.02838                  Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0023909   .0005069    -4.72   0.000    -.0033843   -.0013975
     subyear |   .0432303   .0239753     1.80   0.071    -.0037605    .0902211
    prevgenx |   .0015101   .0005795     2.61   0.009     .0003744    .0026458
      lethal |   .0002638   .1649605     0.00   0.999    -.3230528    .3235804
    deathrt1 |  -.1205568   .1485724    -0.81   0.417    -.4117533    .1706398
      hosp01 |   .0553999   .2097829     0.26   0.792     -.355767    .4665667
    hospdisc |   7.99e-07   4.70e-07     1.70   0.090    -1.23e-07    1.72e-06
    hhosleng |  -.0429822   .0162014    -2.65   0.008    -.0747363    -.011228
    acutediz |   -.151759   .1474433    -1.03   0.303    -.4407426    .1372245
    femdiz01 |  -.1524103   .2379233    -0.64   0.522    -.6187314    .3139108
    mandiz01 |  -.1633682   .3195515    -0.51   0.609    -.7896777    .4629412
    peddiz01 |   .3963856   .3591297     1.10   0.270    -.3074957    1.100267
     orphdum |   .0591442   .1284041     0.46   0.645    -.1925232    .3108117
      natreg |   .0049175   .0020634     2.38   0.017     .0008733    .0089617
    wpnoavg3 |  -.0011352   .0006171    -1.84   0.066    -.0023446    .0000742
    orderent |   .0176731   .0056944     3.10   0.002     .0065122     .028834
    fsubmits |  -.0181817   .0147951    -1.23   0.219    -.0471796    .0108163
       _cons |  -79.71792   47.10353    -1.69   0.091    -172.0391    12.60331
-------------+----------------------------------------------------------------
     /ln_sig |  -.4238354    .062762    -6.75   0.000    -.5468467   -.3008241
     /ln_the |  -1.154004   .6811368    -1.69   0.090    -2.489008    .1809994
-------------+----------------------------------------------------------------
       sigma |   .6545316   .0410797                      .578772     .740208
       theta |   .3153715   .2148111                     .0829923    1.198415
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     5.99 Prob>=chibar2 = 0.007

. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  21.211912
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0439477       .0114   -3.85   0.000  -.066295   -.0216   1359.65

. mfx compute, eyex

Elasticities after lnormalhet
      y  = predicted median _t (predict)
         =  21.211912
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -2.816978      .70731   -3.98   0.000  -4.20327 -1.43068   1359.65
------------------------------------------------------------------------------
```

LogNormal Model with Epidemiological and Political Covariates, Inverse Gaussian Frailties (Shared by Submitting Firm), plus time trend and other controls

```
. streg stafcder subyear prevgenx lethal deathrt1 hosp01 hospdisc hhosleng acut
> ediz femdiz01 mandiz01 peddiz01 orphdum natreg wpnoavg3 orderent, dist(logn)
> frailty(invg) shared(firmcode)


Log-normal regression --
         accelerated failure-time form          Number of obs      =       448
         Inverse-Gaussian shared frailty        Number of groups   =       116
Group variable: firmcode

No. of subjects =          450                  Obs per group: min =         1
No. of failures =          296                                 avg =  3.862069
Time at risk    =  20829.23837                                 max =       100

                                                LR chi2(16)        =    128.32
Log likelihood  =   -417.65839                  Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0021069   .0005127    -4.11   0.000    -.0031117   -.0011021
     subyear |   .0291715   .0233203     1.25   0.211    -.0165355    .0748785
    prevgenx |   .0014344   .0004199     3.42   0.001     .0006115    .0022573
      lethal |   -.160955   .1197563    -1.34   0.179     -.395673     .073763
    deathrt1 |  -.1167153   .1236353    -0.94   0.345     -.359036    .1256054
      hosp01 |    .099901   .1556945     0.64   0.521    -.2052545    .4050566
    hospdisc |   8.82e-07   3.41e-07     2.58   0.010     2.13e-07    1.55e-06
    hhosleng |  -.0343216   .0125586    -2.73   0.006    -.0589359   -.0097073
    acutediz |  -.3325538   .1145099    -2.90   0.004    -.5569891   -.1081186
    femdiz01 |  -.2417569   .1942864    -1.24   0.213    -.6225512    .1390374
    mandiz01 |   .0329728   .2455123     0.13   0.893    -.4482224    .5141679
    peddiz01 |   .1279047   .2841728     0.45   0.653    -.4290638    .6848732
     orphdum |   .0482062   .1291739     0.37   0.709      -.20497    .3013823
      natreg |   .0038731   .0015964     2.43   0.015     .0007441    .0070021
    wpnoavg3 |  -.0008072   .0004091    -1.97   0.048     -.001609   -5.43e-06
    orderent |   .0087556   .0046095     1.90   0.058    -.0002789    .0177901
       _cons |  -52.21651   45.75975    -1.14   0.254     -141.904    37.47096
-------------+----------------------------------------------------------------
     /ln_sig |  -.3833364   .0598852    -6.40   0.000    -.5007093   -.2659636
     /ln_the |   .0712865   .3253251     0.22   0.827     -.566339    .7089121
-------------+----------------------------------------------------------------
       sigma |   .6815836   .0408168                      .6061006    .7664671
       theta |   1.073889    .349363                      .5675996    2.03178
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =   240.89 Prob>=chibar2 = 0.000

. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  22.704002
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |   -.047835      .01264   -3.78   0.000   -.07261  -.02306   1304.25
 subyear |     .66231      .53565    1.24   0.216  -.387541  1.71216    1989.6
prevgenx |   .0325671      .01004    3.24   0.001   .012891  .052243    114.58
  lethal*|  -3.735299     2.85789   -1.31   0.191 -9.33667  1.86607   .629464
deathrt1 |  -2.649905     2.84686   -0.93   0.352 -8.22965  2.92984   .094581
  hosp01*|   2.202297     3.35892    0.66   0.512 -4.38107  8.78566   .799107
hospdisc |     .00002      .00001    2.57   0.010   4.8e-06  .000035    133765
hhosleng |   -.779238      .29572   -2.64   0.008 -1.35884 -.199635   5.24279
acutediz*|  -7.276298     2.51085   -2.90   0.004 -12.1975 -2.35512      .375
femdiz01*|   -4.93132     3.58382   -1.38   0.169 -11.9555  2.09285   .046875
mandiz01*|   .7604203     5.74826    0.13   0.895  -10.506  12.0268   .026786
```

```
peddiz01*|   3.084603     7.28883    0.42   0.672  -11.2012  17.3704   .033482
 orphdum*|   1.115025     3.03679    0.37   0.713  -4.83698  7.06703   .116071
  natreg |   .0879347      .03687    2.38   0.017   .015666  .160203   16.7455
wpnoavg3 |  -.0183273      .00934   -1.96   0.050  -.036638 -.000017   67.7176
orderent |   .1987871      .10462    1.90   0.057  -.006263  .403838   10.5804
------------------------------------------------------------------------------
(*) dy/dx is for discrete change of dummy variable from 0 to 1

. mfx compute, eyex

Elasticities after lnormalhet
      y  = predicted median _t (predict)
         =  22.704002
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.      z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -2.747918      .66864   -4.11   0.000  -4.05843 -1.43741   1304.25
 subyear |   58.03952      46.398    1.25   0.211   -32.899  148.978    1989.6
prevgenx |   .1643555      .04811    3.42   0.001   .070068  .258643    114.58
  lethal |  -.1013154      .07538   -1.34   0.179  -.249062  .046431   .629464
deathrt1 |   -.011039      .01169   -0.94   0.345  -.033958   .01188   .094581
  hosp01 |   .0798316      .12442    0.64   0.521   -.16402  .323684   .799107
hospdisc |   .1180027      .04566    2.58   0.010   .028519  .207487    133765
hhosleng |   -.179941      .06584   -2.73   0.006  -.308989 -.050893   5.24279
acutediz |  -.1247077      .04294   -2.90   0.004  -.208871 -.040544      .375
femdiz01 |  -.0113324      .00911   -1.24   0.213  -.029182  .006517   .046875
mandiz01 |   .0008832      .00658    0.13   0.893  -.012006  .013772   .026786
peddiz01 |   .0042825      .00951    0.45   0.653  -.014366  .022931   .033482
 orphdum |   .0055954      .01499    0.37   0.709  -.023791  .034982   .116071
  natreg |    .064857      .02673    2.43   0.015   .012461  .117254   16.7455
wpnoavg3 |  -.0546636       .0277   -1.97   0.048  -.108959 -.000368   67.7176
orderent |   .0926373      .04877    1.90   0.058   -.00295  .188225   10.5804
------------------------------------------------------------------------------
```

LogNormal Model with Firm Covariates (Sales, Lobbying and Previous Submissions), with Firm Fixed Effects, and Inverse Gaussian Frailties (Shared by Primary Indication).

```
. streg stafcder orphdum orderent fsubmits lnlobtot lnrsales_deflated fmx*, dis
> t(logn) frailty(invg) shared(discode)

        failure _d:  aprovdum
  analysis time _t:  acttime
note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxMallinckrodt dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity


Log-normal regression --
        accelerated failure-time form          Number of obs      =       414
        Inverse-Gaussian shared frailty        Number of groups   =       144
Group variable: discode

No. of subjects =          414                 Obs per group: min =         1
No. of failures =          347                               avg =     2.875
Time at risk    =  10124.61371                               max =        37

                                               LR chi2(59)        =    158.07
Log likelihood  =    -372.1706                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0013053   .0002221    -5.88   0.000    -.0017405     -.00087
     orphdum |  -.1188736   .1103174    -1.08   0.281    -.3350918     .0973445
    orderent |   .0165905   .0051607     3.21   0.001     .0064757     .0267053
    fsubmits |  -.0140588   .0135953    -1.03   0.301    -.0407051     .0125874
    lnlobtot |   -.001778   .0227944    -0.08   0.938    -.0464543     .0428983
lnrsales_d~d |  -.0375268   .0222667    -1.69   0.092    -.0811687     .0061151
       fmx3M |  -.4277318   .3398152    -1.26   0.208    -1.093757     .2382938
   fmxAbbott |  -.1289077   .3739324    -0.34   0.730    -.8618017     .6039863
    fmxAlcon |  -.5829792   .2862014    -2.04   0.042    -1.143924    -.0220348
 fmxAllergan |   .0318754   .4544415     0.07   0.944    -.8588135     .9225643
fmxAmHomeP~s |   1.552303   .5378037     2.89   0.004      .498227     2.606379
    fmxAmgen |   2.903448   1749.819     0.00   0.999     -3426.68     3432.487
fmxAstaMed~a |   -1.49668   .6434025    -2.33   0.020    -2.757726     -.235634
    fmxAstra |   -.454332   .4544779    -1.00   0.317    -1.345092     .4364284
  fmxAventis |   .1424753     .36104     0.39   0.693    -.5651501     .8501007
    fmxBayer |  -.0473627   .2539426    -0.19   0.852    -.5450811     .4503557
fmxBoehrin~r |  -.6862872   .3843934    -1.79   0.074    -1.439684     .0671099
      fmxBMS |  -.1393937    .369101    -0.38   0.706    -.8628183     .5840309
fmxCibaGeigy |  -.3246168   .2903523    -1.12   0.264    -.8936969     .2444634
   fmxDuPont |  -.0999926   .6680505    -0.15   0.881    -1.409348     1.209362
 fmxEliLilly |  -.0617294   .2659396    -0.23   0.816    -.5829613     .4595026
 fmxFujisawa |  -.6209017   .3685358    -1.68   0.092    -1.343219     .1014151
fmxGenentech |    1.85666   3234.911     0.00   1.000    -6338.452     6342.165
  fmxGenzyme |  -.4880675   .4911998    -0.99   0.320    -1.450801     .4746664
    fmxGlaxo |  -.4726448   .2727791    -1.73   0.083    -1.007282     .0619924
fmxGlaxoWe~e |  -.5026022   .3815104    -1.32   0.188    -1.250349     .2451443
  fmxHoechst |   .1055179   .3743154     0.28   0.778    -.6281269     .8391627
fmxJohnson~n |   .1395185   .3745093     0.37   0.709    -.5945061     .8735431
    fmxMerck |  -.3992984   .4224803    -0.95   0.345    -1.227344     .4287478
   fmxSearle |  -1.067182   .7051697    -1.51   0.130    -2.449289     .3149252
    fmxMylan |  -.8314287   .6776736    -1.23   0.220    -2.159645     .4967873
 fmxNovartis |   .1255809   .4714178     0.27   0.790     -.798381     1.049543
fmxNovoNor~k |  -.8940566   .6315505    -1.42   0.157    -2.131873     .3437596
      fmxOno |    2.94804   1030.786     0.00   0.998    -2017.356     2023.252
  fmxOrganon |  -.1929693   .2857955    -0.68   0.500    -.7531182     .3671796
   fmxOtsuka |   .1519188   .5790661     0.26   0.793    -.9830299     1.286868
   fmxPfizer |   .2028198   .4031922     0.50   0.615    -.5874224      .993062
fmxPharmac~n |  -.1057513   .3714392    -0.28   0.776    -.8337588     .6222562
fmxProctor~e |   .5599248   .4390529     1.28   0.202    -.3006031     1.420453
    fmxRhone |  -.2691112   .4212503    -0.64   0.523    -1.094747     .5565242
```

```
    fmxRoche |  -.0807772   .3763687    -0.21   0.830    -.8184462    .6568919
   fmxSandoz |  -.1506878   .2695957    -0.56   0.576    -.6790858    .3777101
   fmxSankyo |  -.9262604   .5387103    -1.72   0.086    -1.982113    .1295925
   fmxSanofi |  -.6567411   .3061857    -2.14   0.032    -1.256854   -.0566282
 fmxSchering |   -.089814   .6324131    -0.14   0.887    -1.329321    1.149693
fmxScherin~h |   .5722593     .40838     1.40   0.161    -.2281509    1.372669
  fmxSearle2 |  -.3188834   .6351753    -0.50   0.616    -1.563804    .9260374
      fmxSKB |  -.2989702   .3715357    -0.80   0.421    -1.027167    .4292264
   fmxSolvay |  -.0350326    .454372    -0.08   0.939    -.9255853    .8555201
   fmxSyntex |  -.2258194   .2621957    -0.86   0.389    -.7397135    .2880747
   fmxTakeda |  -.3472028   .4489156    -0.77   0.439    -1.227061    .5326555
     fmxTEVA |  -.0643297   .6873657    -0.09   0.925    -1.411542    1.282882
      fmxUCB |  -.4800962   .6646247    -0.72   0.470    -1.782737    .8225443
   fmxUpjohn |  -.3401047   .4567508    -0.74   0.457     -1.23532    .5551104
fmxWarnerL~t |  -.1237763   .3837992    -0.32   0.747    -.8760088    .6284562
fmxBurroughs |  -.5552468   .2662064    -2.09   0.037    -1.077002   -.0334919
fmxWyethAy~t |   .3305463   .2625933     1.26   0.208    -.1841271    .8452196
   fmxZambon |   .3453084   .6316715     0.55   0.585     -.892745    1.583362
   fmxZeneca |   -.272564   .4189986    -0.65   0.515    -1.093786    .5486582
       _cons |   5.208467    .358377    14.53   0.000     4.506061    5.910873
-------------+----------------------------------------------------------------
     /ln_sig |  -.5350573   .0491628   -10.88   0.000    -.6314146      -.4387
     /ln_the |  -1.280164   .4668613    -2.74   0.006    -2.195196   -.3651329
-------------+----------------------------------------------------------------
       sigma |   .5856357   .0287915                      .531839    .6448742
       theta |   .2779917   .1297835                     .1113368    .6941044
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     9.88 Prob>=chibar2 = 0.001
```

Check on Influence of Outliers. Exclude obs > 99th Percentile of Sample, Re-Estimate LogNormal Model

```
. tabstat acttime, s(mean sd p1 p10 p90 p99)

    variable |      mean        sd        p1       p10       p90       p99
-------------+--------------------------------------------------------------
     acttime |  42.64988  50.61818  1.216438  6.016438  108.0329  216.1315
------------------------------------------------------------------------------

. streg stafcder subyear if(acttime < 216), dist(logn) frailty(invg) shared(dis
> code)

         failure _d:  aprovdum
   analysis time _t:  acttime

Fitting comparison lnormal model:


Log-normal regression --
         accelerated failure-time form         Number of obs      =       834
         Inverse-Gaussian shared frailty       Number of groups   =       180
Group variable: discode

No. of subjects =          834                 Obs per group: min =         1
No. of failures =          523                                avg =  4.633333
Time at risk    =  34240.43839                                max =        84

                                               LR chi2(2)         =     93.87
Log likelihood  =   -905.47186                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |  -.0011877   .0003643    -3.26   0.001    -.0019018   -.0004737
     subyear |  -.0120322   .0154153    -0.78   0.435    -.0422456    .0181812
       _cons |   28.56371   30.22757     0.94   0.345    -30.68124    87.80866
-------------+----------------------------------------------------------------
     /ln_sig |  -.2751687   .0480175    -5.73   0.000    -.3692812   -.1810561
     /ln_the |  -.4179571   .2553905    -1.64   0.102    -.9185132     .082599
-------------+----------------------------------------------------------------
       sigma |    .759444   .0364666                      .691231    .8343885
       theta |   .6583905   .1681467                      .399112    1.086106
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =   143.99 Prob>=chibar2 = 0.000

. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  21.933916
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -.0260516      .00829   -3.14   0.002  -.042298 -.009805   1299.53
 subyear |   -.263913      .33871   -0.78   0.436  -.927771  .399945   1989.01
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after lnormalhet
      y  = predicted median _t (predict)
         =  21.933916
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -1.543499      .47343   -3.26   0.001   -2.4714 -.615598   1299.53
 subyear |  -23.93218      30.661   -0.78   0.435  -84.0271  36.1627   1989.01
------------------------------------------------------------------------------
```

Baseline LogNormal Model for Comparison to Previous Page

```
. streg stafcder subyear, dist(logn) frailty(invg) shared(discode)

        failure _d:  aprovdum
  analysis time _t:  acttime


Log-normal regression --
        accelerated failure-time form          Number of obs      =       843
        Inverse-Gaussian shared frailty        Number of groups   =       180
Group variable: discode

No. of subjects =          843                 Obs per group: min =         1
No. of failures =          523                                avg =  4.683333
Time at risk    =  36292.47129                                max =        85

                                               LR chi2(2)         =     95.41
Log likelihood  =   -918.89635                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    stafcder |   -.001141   .0003674    -3.11   0.002    -.0018611    -.000421
     subyear |  -.0153089   .0155053    -0.99   0.323    -.0456987    .0150809
       _cons |   35.01552   30.40358     1.15   0.249    -24.57441    94.60544
-------------+----------------------------------------------------------------
     /ln_sig |  -.2726315   .0487074    -5.60   0.000    -.3680961   -.1771668
     /ln_the |  -.3477697   .2523383    -1.38   0.168    -.8423436    .1468042
-------------+----------------------------------------------------------------
       sigma |   .7613733   .0370845                      .6920507    .8376401
       theta |   .7062615   .1782168                         .4307    1.158127
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =   155.51 Prob>=chibar2 = 0.000

. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  21.931525
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.      z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |    -.025024      .00833   -3.00   0.003  -.041358  -.00869   1296.46
 subyear |  -.3357476      .34125   -0.98   0.325  -1.00459  .333092   1988.93
------------------------------------------------------------------------------

. mfx compute, eyex

Elasticities after lnormalhet
      y  = predicted median _t (predict)
         =  21.931525
------------------------------------------------------------------------------
variable |      ey/ex    Std. Err.      z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
stafcder |  -1.479271      .47629   -3.11   0.002  -2.41279  -.54575   1296.46
 subyear |  -30.44832      30.839   -0.99   0.323  -90.8915  29.9948   1988.93
------------------------------------------------------------------------------
```