Final Report

Evaluation of MAUDE Reporting Rates, Sales Estimates and Comparative Bench Testing Related to Vena Cava Filters

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December 15th, 2004

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Executive Summary

Introduction

This analysis considered selected types of adverse events related to the use of vena cava filters (VCF) as reported in the MAUDE database maintained by the FDA for medical device reporting. These reported events were compared to estimated sales data to establish apparent reporting rates for each category of adverse event. The risk for each reporting rate was compared between the Bard Recovery VCF and the other products individually and as aggregated by using relative risk calculations with confidence intervals and significance testing.

Once a reporting rate for VCF migration was established, it was compared to bench testing performed by Bard Peripheral Vascular (BPV) Division, and correlations calculated between observed reporting rates and observed migration resistance performance.

In considering any of these conclusions, it is important to consider the multiple sources of potential error and bias in the underlying data. It is my opinion, and that of most of the expert literature, that quantitative assessment of reporting rates to the FDA's spontaneous reporting systems (MAUDE for devices and AERS for drugs) cannot be used to prove assertions about actual incidence rates for any events. Rather, substantial increases in reporting rates are useful as signals indicating the need for further evaluation of potential risks. Please refer to Appendix A, "Problems with quantitative interpretation of MAUDE and sales data" for a full treatment of these complex issues.

An additional caveat is that this analysis did not include a formal assessment of benefit, a critical element of meaningful risk-benefit appraisals of medical product clinical performance. If the Recovery VCF provides unique benefit to a class of patients, then the suggestion of a small absolute increase in risk of death related to its use needs to be considered in light of its potential benefit, even if that benefit cannot be quantified at this time.

Findings

A summary of the report findings follows. The major analysis centered around the relative risk (RR) of reporting rates between the Recovery VCF and aggregates of the other commercialized VCF, reported as a RR with a statistical significance. Other filters were also compared, and bench testing was reported and compared to MAUDE reporting rates for filter movement.

- Recovery compared with permanent VCFs: The relative risk (RR) for the Recovery VCF report rate compared with all other VCFs was significantly higher for the following categories of reports:
  - Reports of death (RR = 4.6, p = 0.000)
  - Reports of all adverse events (RR = 1.9, p = 0.000)
  - Reports of filter fracture (RR = 5.3, p = 0.000)
  - Reports of caval perforation (RR = 4.1, p = 0.001)
  - Reports of filter movement (RR = 4.4, p = 0.000)
  - Reports of filter embolization (RR = 3.2, p = 0.002)
  - Reports of filter embolization deaths (RR = 12.8, p = 0.000)

- Recovery compared with retrievable VCFs: The RR for the Recovery VCF report rate compared with all retrievable VCFs (Tulip and Optease) was significantly higher for the following categories of reports:
  - Reports of all adverse events (RR = 1.6, p = 0.022)
  - Reports of filter fracture (RR = 13.6, p = 0.006)
  - Reports of filter movement (RR = 2.6, p = 0.012)
  - Reports of filter embolization deaths (RR = 5.7, p = 0.053)

- Other significant comparisons:
  - The TrapEase VCF was associated with a significantly higher RR than other VCFs for reports of caval thrombosis, as follows:
    - TrapEase vs. all other VCFs (RR = 32.2, p = 0.000)
    - TrapEase vs. other permanent VCFs (RR = 106.0, p = 0.000)
    - TrapEase vs. retrievable VCFs (RR = 7.7, p = 0.000)
  - The VenaTech VCF was associated with a significantly higher RR than other VCFs for reports of filter embolization, as follows:
    - VenaTech vs. all other VCFs (RR = 3.9, p = 0.000)
    - VenaTech vs. other permanent VCFs (RR = 4.6, p = 0.000)
    - VenaTech vs. retrievable VCFs (RR = 1.9, p = 0.074)

- Bench testing for migration resistance: The Recovery VCF had the lowest mean migration resistance in a simulated inferior vena cava test apparatus, with a mean value of 50 mm Hg, closely followed by the Tulip VCF at 55 mm Hg.

- Correlation of MAUDE reporting rates for filter movement with bench testing for migration resistance: There is a significant inverse linear relationship between these two measures of VCF performance, suggesting:
  - That bench testing may be predictive for clinical performance
  - That the two independent datasets (MAUDE report rates and bench testing results) contain significant relevant signals regarding VCF performance related to VCF migration.

- No consideration of benefit: None of this analysis considers relative VCF benefits, and thus can only indirectly support a risk – benefit assessment related to overall product performance.

Conclusion: This data and analysis provides two significant signals (MAUDE rates and bench test data) that further investigation of the Recovery VCF filter performance in relation to migration and fracture is urgently warranted. Given the multiple known flaws in the data available, this analysis is insufficient to demonstrate conclusively that any of the VCFs analyzed presents an excess risk. Valid product performance assessment must also consider product benefit.

CAVEAT

Reporting rates must not be equated with true event rates, and in fact may differ from formal incidence rates by orders of magnitude for a variety of complex reasons. In addition, the biases and confounding factors that produce such distortions may be quite different between VCFs, and an unknown proportion of the observed differences reported below could arise from these defects in the data. In addition to considerable flaws regarding reporting data, the use of sales data as a proxy for device exposure, while a widely practiced expedient, has many potential shortcomings.

Therefore, this analysis cannot by its nature offer conclusive evidence of comparative risk, but at best can only suggest hypotheses that need further, independent investigation. Appendix A details the complex issues involved, and is an integral part of this report.

1.0 Methods:

1.1 MAUDE reports:

The Manufacturer and User Facility Device Experience Database (MAUDE[1]) was searched by Bard Peripheral Vascular (BPV) personnel and an initial list of relevant reports relating to VCFs was compiled for the time period starting January, 2000, and concluding in September, 2004. The author reviewed the listing and performed repetitive additional searches of the MAUDE database using product code ("DTK"), manufacturer name (including spelling variants), product name (including spelling variants) and key adverse event categories, using both text and category search facilities provided by the FDA.[2] The BPV database categorization was sampled by reviewing approximately 300 of the 600 reports including all reports for analyzed categories, and discrepancies discussed with BPV personnel and further reports reviewed until consensus was reached. The attribution of category, fatal outcome and potential report duplication were ultimately determined for this analysis by the author. When uncertainty remained despite reasonable effort, the attributions were made in a way that did not favor the Recovery VCF; these instances were quite infrequent. These reports and their categories were stored in an Excel spreadsheet[3] which aggregated report types across all filters. This database and analysis does not include any Recovery or other VCF events reported after September 2004.

[1] http://www.fda.gov/cdrh/maude.html
[2] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm
[3] Please refer to Appendix C.

1.2 Sales data:

Sales data was received from BPV based on IMS estimates for the period of interest, projected forward for part of 2004 to match the corresponding period of MAUDE review.[4] Actual sales figures for the Recovery VCF were used, as the IMS estimates were known to be erroneous.[5]

1.3 Risk calculations:

Reporting rates for each VCF and groupings of VCFs in each category of events were compared to create relative risks (RR). For each relative risk, confidence intervals (CI) and a significance test were performed. The grouping of retrievable VCFs included Optease and Tulip given their current indications, both recently receiving FDA concurrence.[6] In addition, a sample proportional reporting ratio (PRR) as used in pharmacovigilance was calculated.

1.4 Bench test data:

Comparative migration resistance testing for several VCFs including the Recovery VCF was received from BPV as raw data. Average values for the pressure gradient across the device associated with migration in a simulated inferior vena cava (IVC) model were determined for several test fixture diameters (25, 28, 30 and 32 mm)[7] and averaged across this clinically relevant range. These pressures were compared with the reported rates of filter movement, and a univariate regression analysis and significance test was performed.

[4] BPV staff reviewed other sales estimates and concluded that IMS mean sales figures for total sales of VCFs were generally at the high end of all estimates, with other estimated sales rates being 10 – 20% (sales based) or 30 – 35% (procedure based) lower than the mean estimates of IMS. This suggests that the IMS estimates for some or all of the other filters may be somewhat high.

[5] According to BPV personnel, the Recovery VCF was registered late with IMS; in addition new product sales tend to be substantially underestimated during the first year of commercialization.

[6] This is another source of bias, as Tulip's indication is only for the last year despite >4 years of sales data. However, Tulip has been used off label as a retrievable VCF for some time in the U.S., based on the European precedent, and there is no way to separate out this factor in the current dataset.

[7] The variability of IVC diameters and the inaccuracies of cavography and ultrasound in measuring the IVC are well documented in the literature. It is likely that in many clinical situations the IVC has periods of substantial enlargement, such as during cough, Valsalva, fluid overload, straining at stool, when the filter is occluded with large volumes of clot, or during CPR. Given these many uncertainties related to actual IVC dimensions associated with migration, it seems reasonable to use an average of testing diameters bracketing the indicated upper limits of measured IVC diameters.

2.0 MAUDE reporting rates:

2.1 Overview

The report categories of interest analyzed below are listed and defined in Table One:

Table One: Categories of MAUDE Reports

Category of report	Definition for categorizing MAUDE reports
Death	Any VCF report in which the patient was reported as deceased, without attempt to assess causality
Total adverse events	Any VCF report except those without patient impact of any kind, such as mislabeling
Filter fracture	Any VCF report describing a device found in two or more separate pieces
Caval perforation	Any VCF report stating or implying penetration, perforation or disruption of the IVC wall, with or without consequences
Filter movement[8]	Any VCF report in which the VCF was reported as having moved from the initial implant site
Filter embolization[9]	A subset of filter movement reports in which the VCF moved to a new anatomic region
Filter embolization death	A subset of filter embolization reports which were also death reports

Table Two lists the estimated sales data and counts for each report type.

Table Two: Sales and Report Counts

VCF	1Q00 - 3Q04 Sales*	Nonduplicate report counts from the MAUDE database for: Deaths	Total AEs	Fractures	Caval perforation	Movement	Emboliz'ns	Emboliz'n deaths
Recovery	19,537	7	42	6	7	16	9	5
SNF	66,968	0	42	2	6	2	1	0
Vena Tech	42,125	3	41	1	0	22	21	2
Greenfield	178,785	12	256	8	9	39	30	1
Bird's Nest	6,457	1	24	5	8	2	1	0
TrapEASE	155,493	19	138	10	16	19	12	6
Tulip	35,788	4	49	0	7	13	8	2
OptEASE	8,500	2	10	1	0	1	0	0
Totals	513,653	48	602	33	53	114	82	16

* Recovery sales are actual, all others IMS estimates projected thru 3Q04

[8] This is often called 'migration', but the term is variably used by authors and so the neutral term 'movement' is substituted in this report. As a practical matter, this included all VCF movements in which the filter remained in the IVC, even if above the renal vessels.

[9] As a practical matter, these almost always involved movements into the thorax, including the superior vena cava, the chambers and valves of the heart and the pulmonary artery.

When these counts are divided by the sales data and multiplied by 100,000, the normalized MAUDE reporting rates per 100,000 units sold results, as shown in Table Three:

Table Three: Calculated MAUDE Reporting Rates per 10^5 unit sales

	Calculated MAUDE reporting rates for:						
VCF	Deaths	Total AEs	Fractures	Caval perforation	Movement	Emboliz'ns	Emboliz'n deaths
Recovery	36	215	31	36	82	46	26
SNF	0	63	3	9	3	1	0
Vena Tech	7	97	2	0	52	50	5
Greenfield	7	143	4	5	22	17	1
Bird's Nest	15	372	77	124	31	15	0
TrapEASE	12	89	6	10	12	8	4
Tulip	11	137	0	20	36	22	6
OptEASE	24	118	12	0	12	0	0

In reviewing these reporting rates, we see that the largest reporting for adverse events overall is for the Bird's Nest filter at 372 reports / 10^5 sales, followed by the Recovery filter with 215 reports / 10^5 sales. Death is reported at the highest rate for the Recovery filter at 36 reports / 10^5 sales, followed by Optease at 24 reports / 10^5 sales. Fractures and caval perforation are reported at the highest rate for the Bird's Nest Filter at 77 and 124 reports / 10^5 sales respectively. The highest rate of filter movement reports is seen with the Recovery filter at 82 reports / 10^5 sales, followed by the Vena Tech VCF at 52 reports / 10^5 sales. Filter embolization, in which the VCF moves to a new anatomic region, often in the heart or pulmonary artery, is reported at the highest rate by Vena Tech at 50 reports / 10^5 sales, followed by Recovery at 46 reports / 10^5 sales. Finally, reports of filter embolization associated with death were reported at the highest rate for the Recovery filter at 26 reports / 10^5 sales.

It may be inferred from this dataset that different VCFs are reported to have different patterns of events, and also that the Recovery filter has relatively high reporting rates of total death, filter movement, filter embolization and filter embolization death reporting. For further depiction of other VCF extremes, see Tables Eleven and Twelve below.

Each of these reporting rates can be used to calculate relative risks of individual VCFs and aggregated categories of VCFs compared with the Recovery device. The following tables display this calculation, including comparisons of Recovery to each individual competitor VCF, to all other VCFs, to all other VCFs indicated for permanent placement, and to all other VCFs indicated for retrievable placement.

It is important to remember that these rates are reporting rates, and not in any way true incidence rates or even accurate predictors of incidence rates. The associated statistical calculations are technically accurate but cannot correct the underlying poor data validity or necessarily imply clinical significance.

2.2 Reports of death

Table Four: Reports of death

Filter		Sales	Death reports	Death reports per 10^5 sales	Recovery RR	p value	Lower 95% CI	Upper 95% CI
	Recovery	19,537	7	36				
Permanent	SNF	66,968	0	0	∞	0.000	∞	∞
Permanent	Vena Tech	42,125	3	7	5.0	0.024	1.3	19.5
Permanent	Greenfield	178,785	12	7	5.3	0.000	2.1	13.6
Permanent	Bird's Nest	6,457	1	15	2.3	0.690	0.3	18.8
Permanent	TrapEASE	155,493	19	12	2.9	0.025	1.2	7.0
Retrievable	Tulip	35,788	4	11	3.2	0.099	0.9	11.0
Retrievable	OptEASE	8,500	2	24	1.5	0.868	0.3	7.3
Totals	Non Recovery	494,116	41	8	4.3	0.000	1.9	9.6
Totals	Permanent	449,828	35	8	4.6	0.000	2.0	10.4
Totals	Retrievable	44,288	6	14	2.6	0.129	0.9	7.9

This table shows that Recovery is 4.3 times more like to have a MAUDE report associated with patient death than all other VCFs combined, 4.6 times more likely than for permanent VCFs and 2.6 times more likely than retrievable VCFs. Neither the overall comparison of Recovery to other retrievable VCFs nor Tulip or Optease individually was significant. However, the overall trend is that Recovery had a higher rate of reporting associated with patient death than any other VCF individually or as aggregated.

2.3 Reports of Adverse Events

Table Five: Reports of Adverse Events

Filter		Sales	Total AE reports	AE reports per 10^5 sales	Recovery RR	p value	Lower 95% CI	Upper 95% CI
	Recovery	19,537	42	215				
Permanent	SNF	66,968	42	63	3.4	0.000	2.2	5.3
Permanent	Vena Tech	42,125	41	97	2.2	0.000	1.4	3.4
Permanent	Greenfield	178,785	256	143	1.5	0.018	1.1	2.1
Permanent	Bird's Nest	6,457	24	372	0.6	0.043	0.3	1.0
Permanent	TrapEASE	155,493	138	89	2.4	0.000	1.7	3.4
Retrieve	Tulip	35,788	49	137	1.6	0.040	1.0	2.4
Retrieve	OptEASE	8,500	10	118	1.8	0.112	0.9	3.6
Totals	Non Recovery	494,116	560	113	1.9	0.000	1.4	2.6
Totals	Permanent	449,828	501	111	1.9	0.000	1.4	2.6
Totals	Retrievable	44,288	59	133	1.6	0.022	1.1	2.4

This table shows that Recovery has a rate of adverse event reporting that is almost twice as high as other VCFs combined, and 1.6 times as high as other retrievable VCFs. These overall comparisons are statistically significant as is the comparison with the Tulip VCF, but not Optease.

2.4 Reports of Filter Fracture

Table Six: Reports of Filter Fracture

Filter		Sales	Filter fracture reports	Fracture reports per 10^5 sales	Recovery RR	p values	Lower 95% CI	Upper 95% CI
	Recovery	19,537	6	31				
Permanent	SNF	66,968	2	3	10.3	0.002	2.1	51.0
Permanent	Vena Tech	42,125	1	2	12.9	0.008	1.6	107.5
Permanent	Greenfield	178,785	8	4	6.9	0.000	2.4	19.8
Permanent	Bird's Nest	6,457	5	77	0.4	0.217	0.1	1.3
Permanent	TrapEASE	155,493	10	6	4.8	0.003	1.7	13.1
Retrievable	Tulip	35,788	0	0	∞	0.004	∞	∞
Retrievable	OptEASE	8,500	1	12	2.6	0.609	0.3	21.7
Totals	Non Recovery	494,116	27	5	5.6	0.000	2.3	13.6
Totals	Permanent	449,828	26	6	5.3	0.000	2.2	12.9
Totals	Retrievable	44,288	1	2	13.6	0.006	1.6	113.0

This table shows that Recovery has a rate of reporting of filter fracture that is 5.6 times higher than all other VCFs, and 13.6 times as high as other retrievable VCFs. Only the Bird's Nest Filter had an equivalent reporting rate (RR = 0.4, NS).

0.0412 = 0.000412
= 4.1/10,000

0.0894 = 0.000894
= 8.9/10,000

0.1126 = 0.001126
= 11.3/10,000

2.5 Reports of Caval Perforation

Table Seven: Reports of Caval Perforation

Filter		Sales	Caval perf'n reports	Caval perf'n reports per 10^5 sales	Recovery RR	p values	Lower 95% CI	Upper 95% CI
	Recovery	19,537	7	36				
Permanent	SNF	66,968	6	9	4.0	0.018	1.3	11.9
Permanent	Vena Tech	42,125	0	0	∞	0.001	∞	∞
Permanent	Greenfield	178,785	9	5	7.1	0.000	2.7	19.1
Permanent	Bird's Nest	6,457	8	124	0.3	0.024	0.1	0.8
Permanent	TrapEASE	155,493	16	10	3.5	0.009	1.4	8.5
Retrievc	Tulip	35,788	7	20	1.8	0.384	0.6	5.2
Retrievc	OptEASE	8,500	0	0	∞	0.182	∞	∞
Totals	Non Recovery	494,116	46	9	3.8	0.001	1.7	8.5
Totals	Permanent	449,828	39	9	4.1	0.001	1.8	9.2
Totals	Retrievable	44,288	7	16	2.3	0.199	0.8	6.5

This table shows that Recovery has a rate of reporting of caval perforation that is 3.8 times higher than all other VCFs. It has a significantly smaller reporting rate for this event than the Bird's Nest Filter (RR = 0.3, p = 0.024). The Recovery VCF has a 2.3 times higher rate than other retrievable VCFs, but this is not a statistically significant difference.

2.6 Reports of Filter Movement

Table Eight: Reports of Filter Movement

Filter		Sales	Filter mov't reports	Filter mov't reports per 10^5 sales	Recovery RR	p value	Lower 95% CI	Upper 95% CI
	Recovery	19,537	16	82				
Permanent	SNF	66,968	2	3	27.4	0.000	6.3	119.3
Permanent	Vena Tech	42,125	22	52	1.6	0.228	0.8	3.0
Permanent	Greenfield	178,785	39	22	3.8	0.000	2.1	6.7
Permanent	Bird's Nest	6,457	2	31	2.6	0.282	0.6	11.5
Permanent	TrapEASE	155,493	19	12	6.7	0.000	3.4	13.0
Retrieva	Tulip	35,788	13	36	2.3	0.041	1.1	4.7
Retrieva	OptEASE	8,500	1	12	7.0	0.054	0.9	52.5
Totals	Non Recovery	494,116	98	20	4.1	0.000	2.4	7.0
Totals	Permanent	449,828	84	19	4.4	0.000	2.6	7.5
Totals	Retrievable	44,288	14	32	2.6	0.012	1.3	5.3

This tables shows that Recovery had a 4 times higher reporting rate for filter movement compared with all other VCFs, as well as a 2.6 times higher rate when compared to other retrievable VCFs.

2.7 Reports of Filter Embolization

Table Nine: Reports of Filter Embolization

Filter		Sales	Filter embol'n reports	Filter embol'n reports per 10^5 sales	Recovery RR	p values	Lower 95% CI	Upper 95% CI
	Recovery	19,537	9	46				
Permanent	SNF	66,968	1	1	30.9	0.000	3.9	243.6
Permanent	Vena Tech	42,125	21	50	0.9	0.998	0.4	2.0
Permanent	Greenfield	178,785	30	17	2.7	0.012	1.3	5.8
Permanent	Bird's Nest	6,457	1	15	3.0	0.471	0.4	23.5
Permanent	TrapEASE	155,493	12	8	6.0	0.000	2.5	14.2
Retrievd	Tulip	35,788	8	22	2.1	0.205	0.8	5.3
Retrievd	OptEASE	8,500	0	0	∞	0.106	∞	∞
Totals	Non Recovery	494,116	73	15	3.1	0.002	1.6	6.2
Totals	Permanent	449,828	65	14	3.2	0.002	1.6	6.4
Totals	Retrievable	44,288	8	18	2.6	0.083	1.0	6.6

This tables shows that Recovery had a 3 times higher reporting rate for filter embolization compared with all other VCFs, as well as a 2.6 times higher rate when compared to other retrievable VCFs although the latter difference was not quite significant statistically.

2.8 Reports of Filter Embolization Deaths

Table Ten: Reports of Filter Embolization Deaths

Filter		Sales	FE death reports	FE death reports per 10^5 sales	Recovery RR	p value	Lower 95% CI	Upper 95% CI
	Recovery	19,537	5	26				
Permanent	SNF	66,968	0	0	∞	0.000	∞	∞
Permanent	Vena Tech	42,125	2	5	5.4	0.064	1.0	27.8
Permanent	Greenfield	178,785	1	1	45.8	0.000	5.3	391.8
Permanent	Bird's Nest	6,457	0	0	∞	0.442	∞	∞
Permanent	TrapEASE	155,493	6	4	6.6	0.002	2.0	21.7
Retrievable	Tulip	35,788	2	6	4.6	0.109	0.9	23.6
Retrievable	OptEASE	8,500	0	0	∞	0.323	∞	∞
Totals	Non Recovery	494,116	11	2	11.5	0.000	4.0	33.1
Totals	Permanent	449,828	9	2	12.8	0.000	4.3	38.2
Totals	Retrievable	44,288	2	5	5.7	0.053	1.1	29.2

This tables shows that Recovery had an 11.5 times higher reporting rate for filter embolization deaths compared with all other VCFs. This ratio was 5.7 for other retrievable VCFs, a difference that was borderline statistically significant.

2.9 Assessment of Other VCFs

It is important to note that the preceding analyses "single out" the Recovery VCF; that was the nature of the assignment. However, it is instructive to look at other VCFs and adverse event report types, such as caval thrombosis or filter embolization, and note that the same sort of disproportionate reporting rates exist for other widely used VCFs.

Table Eleven: Caval thrombosis and the TrapEase VCF

Filter		Sales	Caval thromb. reports	Caval thromb. reports per 10^5 sales	TrapEase RR	p value	Lower 95% CI	Upper 95% CI
	TrapEASE	155,493	56	36				
Permanent	SNF	66,968	0	0	∞	0.000	∞	∞
Permanent	Vena Tech	42,125	0	0	∞	0.000	∞	∞
Permanent	Greenfield	178,785	1	1	64.4	0.000	8.9	465.3
Permanent	Bird's Nest	6,457	0	0	∞	0.236	∞	∞
Retrieve	Recovery	19,537	0	0	∞	0.015	∞	∞
Retrieve	Tulip	35,788	1	3	12.9	0.002	1.8	93.1
Retrieve	OptEASE	8,500	2	24	1.5	0.764	0.4	6.3
Totals	Non TrapEase	358,160	4	1	32.2	0.000	11.7	88.9
Totals	Other Permanent	294,335	1	0.3	106.0	0.000	14.7	766.1
Totals	Retrievable	63,825	3	5	7.7	0.000	2.4	24.5

In evaluating the TrapEase VCF, we see a 32 fold increased risk of caval thrombosis reports compared to all other VCFs, 106 times higher for other permanent VCFs and almost 8 times higher than the retrievable VCFs.

Table Twelve: Filter embolization and the VenaTech VCF

Filter		Sales	Filter embol'n reports	Filter embol'n reports per 10^5 sales	Vena Tech RR	p value	Lower 95% CI	Upper 95% CI
	Vena Tech	42,125	21	50				
Permanent	SNF	66,968	1	1	33.4	0.000	4.5	248.3
	Greenfield	178,785	30	17	3.0	0.000	1.7	5.2
	Bird's Nest	6,457	1	15	3.2	0.371	0.4	23.9
	TrapEASE	155,493	12	8	6.5	0.000	3.2	13.1
Retrieve	Tulip	35,788	8	22	2.2	0.072	1.0	5.0
	Recovery	19,537	9	46	1.1	0.998	0.5	2.4
	OptEASE	8,500	0	0	∞	0.077	∞	∞
Totals	Non Vena Tech	471,528	61	13	3.9	0.000	2.3	6.3
	Other Permanent	407,703	44	11	4.6	0.000	2.7	7.8
	Retrievable	63,825	17	27	1.9	0.074	1.0	3.5

In evaluation the VenaTech VCF for filter embolization reports, we find 3.9 times the reporting rate for VenaTech when compared to all other VCFs, 4.6 times the reporting rate for other permanent VCFs, and 1.9 times the reporting rate (marginal significance) compared with retrievable VCFs.

These two examples show the hazard in focusing on one type of VCF in such analyses, by demonstrating higher reporting rates for a variety of other widely used VCFs.

2.11 Summary regarding MAUDE report analysis:

- In this dataset, Recovery demonstrates a consistent, statistically significant and potentially clinically important higher rate of reporting of adverse events in many analyzed categories.
- Given the pattern of the reported events, the higher rate of death reports seems related to filter movement and filter embolization associated with death.
- These conclusions must be substantially tempered in light of the poor quality and validity of the data available, and the fact that it analyzes reporting behavior as much as it does adverse events.
- Other successful VCFs are also found to have significantly higher reporting rates than other VCFs for serious complications such as caval thrombosis (TrapEase) and filter embolization (VenaTech), as well as higher proportional reporting rates for death (OptEase) and filter movement and embolization (Vena Tech).
- VCF benefits have not been considered, given the absence of any quantitative information, but must be considered in the evaluation of device performance even if not quantifiable.
- The observed differential reporting rates are large enough and consistent enough to constitute a signal for further evaluation, preferably of all devices in this class.

3.0 Analysis of Bench Testing for Migration Resistance

3.1 Overview

Bard Peripheral Vascular personnel devised and implemented a testing device for assessing VCF migration resistance in the lab. This consisted of a closed loop circulation of 37°C saline solution through a silastic tube with variable diameters between 15 and 32mm, lined with sausage casing to simulate the endothelium. A test VCF was deployed in the silastic tube between two pressure transducers, and artificial emboli were then introduced serially until the VCF moved a specified amount. The test output was the pressure gradient at which the test article moved.

3.2 Test data

This test was used to compare many of the commercially available VCFs, and the following mean gradients were observed for the diameters the author felt to be relevant for this failure mode. In the following results table, each of four test diameters is reported, with the mean pressure gradient (MR25 = 25 mm diameter, etc.)

Table Fourteen: Mean Migration Resistance Test Data, in Rank Order

	BPV testing results					MAUDE data
	Resistance, mm Hg					Move[1] reports
Migration:	MR25	MR28	MR30	MR32	Mean	# per 10^5 sales
Recovery	74	51	40	35	50	82
Tulip	87	43	56	36	55	36
Vena-Tech	108	76	75	59	80	52
SNF	117	89	93	79	94	3
Greenfield*	131	90	90	76	97	22
Trapease	139	123	96	74	108	12
Optease	146	137	103	86	118	12
Averages	114	87	79	63		

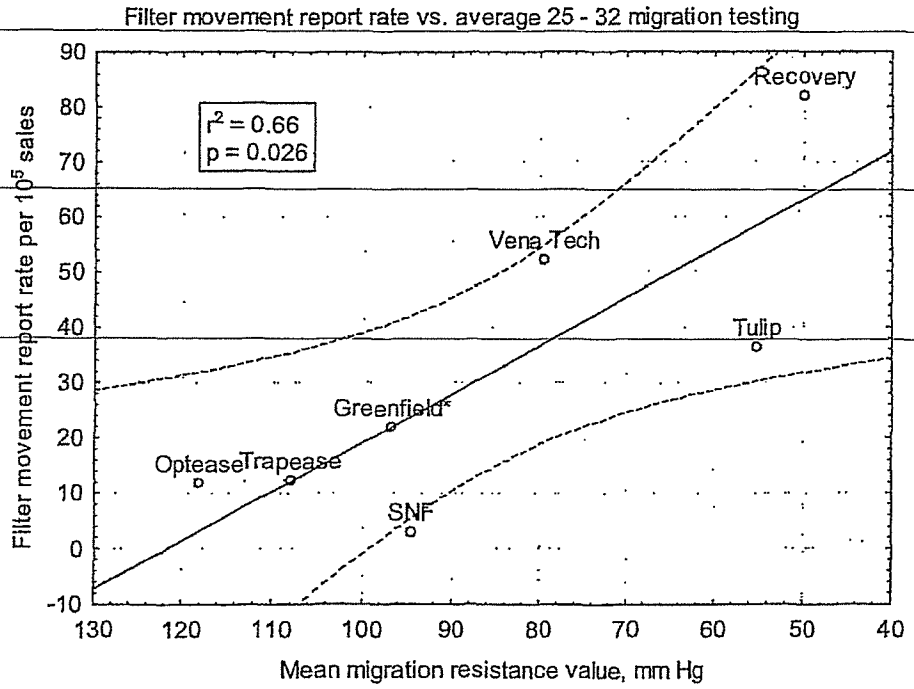
This demonstrates several initial facts:

- Migration resistance declines as the test fixture increases in diameter (bottom row averages, left to right)
- Mean migration resistance performance is substantially different between VCFs (column entitled Mean)
- The Tulip testing may have an anomaly with the MR28 testing fixture, as it is the only filter to have a dramatic deviation from declines in performance with each increase in diameter.

Inspection of the mean migration resistance values indicates that the Recovery (= 50 mm Hg) and Tulip (=55 mm Hg) VCFs have the lowest test performance in resisting migration, and have the first (= 82 / 10^5 unit sales) and third (= 36 / 10^5 unit sales) highest filter movement report rates respectively in the MAUDE analysis.

3.3 Correlation with MAUDE reporting rates:

The final observation related to this testing data is the possible inverse relationship between mean migration resistance and reported filter movement events. Indeed, if this bench test is a valid predictor of actual clinical performance in resisting filter movement, it should be inversely correlated with measures of clinical outcomes. Table Fourteen above also shows the MAUDE reporting rates for filter movement, and when these values are correlated with the mean migration resistance pressure values, the following linear relationship emerges:



This univariate regression suggests that there may be a predictive value for this particular testing procedure in assessing clinical VCF migration performance.

3.4 Summary regarding bench testing of migration resistance:

- In this analysis, the bench test data of simulated migration resistance revealed that the Recovery filter has the least ability to resist migration of all tested VCFs at larger simulated IVC diameters.
- This second, independent bench test demonstration of reduced migration resistance is of concern, given the similar signal present in the analysis of the MAUDE reporting rates.
- The mean migration resistance test results averaged over fixture diameters between 25 and 32 mm correlate well with MAUDE reporting rates for filter movement, suggesting the predictive value of the bench test for this failure mode.
- This correlation between two independent evaluations makes it less likely that both the MAUDE and bench testing analyses are failing to detect clinically meaningful information.

~~[Note: for overall summary and conclusion please see the Executive Summary.]~~

2.10 Proportional Reporting Rates

FDA pharmacovigilance procedures include a "numerator" only comparison method, which does not factor in exposure to a medical product, but only assesses the proportion that a certain category of report comprises out of all reports for that product. This proportional reporting rate (PRR) is then used as a signal generator when screening reports. For this analysis, a form of PRR appears in the following table:

Table Thirteen: Proportional Reporting Rates

	Proportional reporting rates for:					
VCF	Deaths	Fractures	Caval perforation	Movement	Emboliz'ns	Emboliz'n deaths
Recovery	17%	14%	17%	38%	21%	12%
SNF	0%	5%	14%	5%	2%	0%
Vena Tech	7%	2%	0%	54%	51%	5%
Greenfield	5%	3%	4%	15%	12%	0%
Bird's Nest	4%	21%	33%	8%	4%	0%
TrapEASE	14%	7%	12%	14%	9%	4%
Tulip	8%	0%	14%	27%	16%	4%
OptEASE	20%	10%	0%	10%	0%	0%
All others	7%	5%	8%	18%	13%	2%
Permanent	7%	5%	8%	17%	13%	2%
Retrievable	10%	2%	12%	24%	14%	3%

Here we see a variety of VCFs that have the highest proportional reporting rates for the event types of interest, with Optease having a 20% rate for deaths, Birds' Nest a 21% rate for fractures and a 33% rate for caval perforation, VenaTech having a 54% rate for filter movement and a 51% rate for filter embolization, and Recovery having a 12% rate for filter embolization death. Only in this last event category of filter embolization deaths is Recovery the most extreme in this analysis, again indicating the variability in VCF performance in such reporting rate assessments.