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May 4, 2007

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

Re: Docket No. 2007P-0044
Comments on "Public Citizen's petition to the FDA to ban third generation oral contraceptives containing desogestrel due to increased risk of venous thrombosis (HRG Publication #1799)," February 6, 2007

Dear Madam/Sir:

On behalf of Organon USA Inc., 56 Livingston Avenue, Roseland, New Jersey 07068, we submit the following comments in opposition to Public Citizen's Petition (Document # CP1 of Docket 2007P-0044) and its Supplement to the Petition (Document # AMD1) pursuant to the provisions of 21 C.F.R. § 10.30(d) (2007).

1.0 Introduction

Public Citizen submitted its Petition pursuant to 21 U.S.C. § 355(e)(3) (2007) (withdrawal of approval based on lack of substantial evidence of effect). Petitioner provides no "new information . . . that there is a lack of substantial evidence that [3rd generation oral contraceptives ("OCs")] will have the effect [they] purport[] or [are] represented to have under the conditions of use prescribed, recommended, or suggested in the labeling" *See id.* Therefore, the FDA should deny the Petition in its entirety. *See* 21 C.F.R. § 10.30(e)(2)(ii).

Because Petitioner brings charges unrelated to issues of efficacy pursuant to 21 U.S.C. § 355(e)(3), Organon focuses its comments on the issues as presented in the Petition. In particular, this Response addresses Petitioner's unsubstantiated allegations that: (a) 3rd generation OCs increase the risk of venous thrombosis compared to 2nd generation OCs; (b) this purported higher risk of venous thrombosis is biologically plausible; and (c) 3rd generation OCs show no clinical benefit compared to 2nd generation OCs. This Response also addresses Public Citizen's apparent misperception about the significant consequences of the 1995 pill scare in parts of Europe. Petitioner has failed to present "clinical or other experience, tests, or other scientific data show[ing] that [3rd generation OCs containing desogestrel are] unsafe for use under the conditions of use upon the basis of which the application was approved." *See* § 355(e)(1). Nor has Petitioner presented "new evidence of clinical experience" or "tests by new methods" that, when "evaluated together with the evidence available" to the FDA when the applications were

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approved, shows that 3rd generation OCs containing desogestrel are not safe for use under the conditions of use upon the basis of which the applications were approved. *See* § 355(e)(2). In sum, Petitioner fails to present any evidence that would support a withdrawal of 3rd generation OCs containing desogestrel, and, therefore, the Petition should be denied in its entirety.

2.0 Epidemiologic studies on venous thrombosis show no differential effect between 3rd and 2nd generation OCs.

In epidemiology, consistent, strong, statistically significant results, with appropriate control of bias and confounding, are a prerequisite to finding a valid association. The Petition selectively cites certain studies and two meta-analyses in support of the proposition that 3rd generation OCs pose significantly greater risk of venous thrombosis than do 2nd generation OCs. When the studies cited in the Petition, as well as the additional studies and data omitted by Petitioner, properly are considered collectively, there is no consistent, statistically significant difference between 3rd generation OCs and 2nd generation OCs and the risk of venous thrombosis. Some studies (with insufficient control of confounding, especially by duration of use) reported a higher relative risk or odds ratio of venous thrombosis in users of 3rd generation OCs compared to users of 2nd generation OCs, while others (controlling for confounding, especially by duration of use) reported estimates similar or lower in users of 3rd generation OCs.

2.1 Confounding is a major problem affecting the validity of OC epidemiologic studies.

One likely explanation for the inconsistencies in the epidemiologic studies on venous thrombosis is the difference in the degree of control for confounding factors. Observational studies (including case-control and cohort designs) by their very nature are susceptible to systematic error or bias (*Spitzer 1999*). The studies on OCs, especially those reported in the mid-1990's, are vulnerable to several such biases including age, duration of OC use, prescribing bias, healthy user effect, control selection bias, and referral bias.

Age and duration of OC use are directly or indirectly related to several essential factors affecting the risk estimates of venous thromboembolism ("VTE") (*Spitzer 1999*). For example, the association between VTE and OC use appears to be strongest in the first year of use and declines thereafter (*e.g., Poulter 1996, Lidegaard 1997, Suissa 1997*). But younger women are more likely to have used OCs for a shorter period of time and to use newer OCs on the market. The direct relationship of age and duration of use with both the exposure of interest and the disease outcome is a classic example of a confounder.

Additionally, at the time of the earlier epidemiologic studies, 3rd generation OCs were the most commonly used OCs for women newly starting oral contraception, whereas 2nd generation OC users were more commonly long-term existing users. A significant percentage of those users of

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OCs, more susceptible of side effects, would likely be eliminated over time from the 2nd generation OC long-term user pool (for example, by prudent physicians and by events in those users at risk of thrombosis who subsequently discontinue OC use), thus creating a healthy user bias (e.g., Spitzer 1999, Lewis 1996). See Fig. 1.

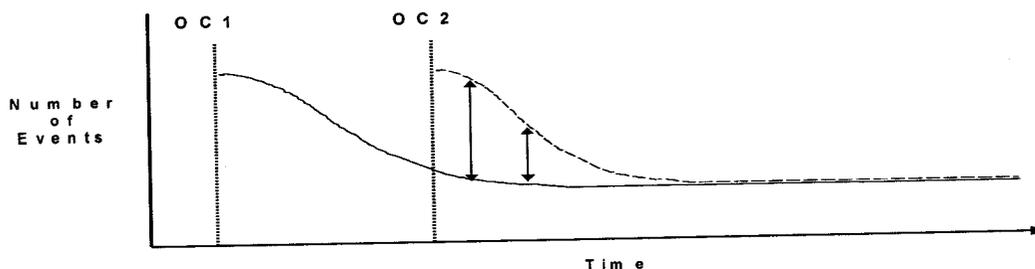


Fig. 1: The effect of attrition of susceptibles (healthy user bias) over time inducing artificial differences in risk between two populations of pill users. The number of events is a function of timing of introduction (Lewis 1999a).

Similarly, doctors may prescribe newer OCs with a perceived improved safety profile to users with cardiovascular disease risk factors—prescriber bias (Spitzer 1999). For example, it is well established that 3rd generation OCs are selectively more often prescribed than 2nd generation OCs to women with identifiable risk factors for cardiovascular disease, including venous thrombosis (e.g., Van Lunsen 1996, Jamin 1996). This prescribing bias tends to increase the apparent risk associated with the 3rd generation OCs when compared with 2nd generation OCs. The effects of prescribing bias have been clearly demonstrated (e.g., Lis 1993, Poulter 1996, Heinemann 1996, Farmer 1996a, Van Lunsen 1996, Jamin 1996, Lewis 1996, Farmer 1997, Lidegaard 1997, Dunn 1998, Farley 1995b, Jick 1995).

It is well established by now that the epidemiologic studies on OCs and VTE published in 1995 inadequately address these biases, especially confounding by duration of use. In contrast, the later studies, some of which were conducted in new data sets (Farmer 1997, Lidegaard 1998, Farmer 1998, Todd 1999, Lidegaard 2002, Heinemann 2002), and others of which were conducted in the data sets of some of the original studies (Suissa 1997, Lewis 1999b, Farmer 2000b, Suissa 2000), employ better adjustments for these biases. These better-controlled studies show no difference between 3rd generation OCs and 2nd generation OCs and their association with VTE.

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2.2 Epidemiologic studies assessing VTE risk: no difference between 3rd and 2nd generation OCs

Any fair review of the epidemiologic evidence supports the conclusion that no difference in VTE risk exists between 3rd and 2nd generation OCs. We describe those studies assessing the potential association between VTE and 2nd and 3rd generation OCs here. Where multiple analyses have been conducted in the same data source, they are presented together. In the tables, those odds ratios (“OR”) and relative risks (“RR”) that were selected in the Petition are marked with *, and product designations are: D=desogestrel, D30= 30 mcg EE/150 mcg desogestrel, D20=20 mcg EE/150 mcg desogestrel, G=gestodene, L=levonorgestrel, 3rd=desogestrel and gestodene, 2nd=levonorgestrel with or without norgestimate.

2.2.1 The WHO case-control study

The WHO case-control study was conducted in 17 countries around the world (and published in two papers (*Farley 1995a* and *Farley 1995b*). In only one country (U.K.) were there sufficient cases and controls exposed to 3rd generation OCs to allow a calculation of an odds ratio between the two generations of OCs. The appropriate data analyses from that country, presented in Table 1 below, show inconsistent results depending upon the nature of the control group. Even as to the one data set, the authors’ failure to adjust for confounding by duration of use limits the validity of this study.

Table 1: The WHO case-control study

published	period	design	cases/controls 3 rd and 2 nd	adjustment for duration of use	comparison	OR (95% CI)
Farley 1995b	89-93	case- control	88/124 (hospital controls)	no	D vs. L G vs. L D/G vs. L	2.3 (1.1-4.9) 2.0 (0.8-4.7) 2.2 (1.1-4.2)
			79/70 (GP based controls)	no	D vs. L G vs. L D/G vs. L	1.8 (0.7-4.8) 0.9 (0.3-2.8) 1.4 (0.6-3.1)
Farley 1995a (cited as WHO 1995 in the Petition)	89-93	case- control	155/214 (Europe)	No	3 rd vs. 2 nd	not reported
			121/144 (developing)		3 rd vs. 2 nd	not reported

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The Public Citizen petition misleadingly presents an odds ratio (not shown in Table 1 above) from *Farley 1995b* taken from an analysis comparing desogestrel with levonorgestrel in *all* centers, thus including study sites that contributed between 0 and 3 cases or controls. Petitioner's second presented odds ratio (not shown in Table 1 above) has been "calculated" by Petitioner rather than the authors of the study, a calculation which wrongly does not allow adjustment for confounding factors. (We observe that, though the Petition suggests otherwise, *WHO 1995* was not a distinct study but was instead Farley's publication (*1995a*) of additional data and analysis.)

2.2.2 The Transnational case-control study

Despite otherwise virtually identical methods and design to the WHO study, the Transnational case-control study had one major difference: it had as an objective at the outset an OC-type specific analysis. Of course, pre-specified aims are important in the conduct of epidemiologic studies because they can affect the statistics, analyses, and other study parameters. The first analysis of the data from the Transnational study was not adjusted for duration of use (*Spitzer 1996*). Subsequent analyses of the original data set with adjustment for confounding by duration of use (*Suissa 1997*, *Lewis 1999b*, *Suissa 2000*) showed no difference in risk between 2nd and 3rd generation OC users. See Table 2. Remarkably, Public Citizen failed to include the newer analyses in its presentation.

Table 2: Transnational case-control study

<i>published</i>	<i>period</i>	<i>design</i>	<i>cases/controls 3rd and 2nd</i>	<i>adjustment for duration of use</i>	<i>comparison</i>	<i>OR (95% CI)</i>
Spitzer 1996	93-95	case- control	259/651	no	D vs. 2 nd G vs. 2 nd 3 rd vs. 2 nd	1.5 (1.1-2.2)* 1.5 (1.0-2.2) 1.5 (1.1-2.1)
Suissa 1997	93-95	case- control	65/171	yes (spline model)	3 rd vs. 2 nd	1.0 (nr)
Suissa 2000	93-95	case- control	128/650 160/739	yes (repeat users switchers)	3 rd vs. 2 nd 3 rd vs. 2 nd	0.6 (0.3-1.2) 1.3 (0.7-2.4)
Lewis 1999b	93-95	case- control	287/683	yes (Cox regression)	3 rd vs. 2 nd	0.8 (0.5-1.3)

* risk estimate(s) selected in table 1 of the Public Citizen petition

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2.2.3 Danish case-control study

Potential control-selection bias affects the validity of the Danish case-control study cited by Petitioner; the authors used, for the first two years, the same control group that had been age-matched to stroke cases from another study. Consequently, 2nd generation OC users are likely overrepresented in the older control group, inflating the odds ratios of VTE for 3rd compared to 2nd generation OCs. Regardless, the results show no statistically significant differences between 3rd and 2nd generation OCs. The misleading recalculation of crude risk estimates in the Petition (not shown in Table 3) misrepresents the study results.

Table 3: Danish case-control study

published	period	design	cases/controls 3 rd and 2 nd	adjustment for duration of use	comparison	OR (95% CI)
Lidegaard 1998	94-95	case- control	151/178	yes	3 rd vs. 2 nd	1.4 (0.8-2.5)*
Lidegaard 2002	94-98	case- control	419/917 437/1035	yes	D vs. L G vs. L 3 rd vs. 2 nd	1.6 (1.0-2.4)* 1.0 (0.7-1.4) 1.3 (1.0-1.8)

* risk estimate(s) selected in table 1 of the Public Citizen petition

2.3.4 Dutch case-control studies

In the Dutch case-control studies cited by Petitioner, neither a post-hoc analysis in an existing set of patients recruited for research on thrombophilia (*Bloemenkamp 1995*), nor a second analysis in patients referred for suspicion of deep vein thrombosis (DVT) (*Bloemenkamp 1999*) observed a significant difference in DVT risk between OC generations. Also, neither of the studies adjusted for duration of use. Petitioner presents the key odds ratios of these studies correctly; that is, no statistically significant difference between 3rd generation and 2nd generation OCs.

Table 4: Dutch case-control studies

published	period	design	cases/controls 3 rd and 2 nd	adjustment for duration of use	comparison	OR (95% CI)
Bloemenkamp 1995	88-92	case- control	64/44	no	D vs. L	2.2 (0.9- 5.4)*
Bloemenkamp 1999	82-95	case- control	59/76	no	3 rd vs. L	1.9 (0.8- 4.5)*

* risk estimate(s) selected in table 1 of the Public Citizen petition

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2.3.5 German case-control study

In the German case-control study cited by Petitioner, the authors present risk estimates from the overall group and the hospital group separately to demonstrate the effect of selection bias. See Table 5. The authors ultimately recommended that it is best to avoid a hospital setting in a study investigating potential associations between OCs and VTE (*Heinemann 2002*). Petitioner exclusively presents the (non-statistically significant) results from the hospital-based group, thus misrepresenting the conclusions of the investigators: a study in a hospital-based setting has questionable reliability. Petitioner also omits the overall odds ratio of 0.9.

Table 5: German case-control study

published	period	design	cases/controls 3 rd and 2 nd	adjustment for duration of use	comparison	OR (95% CI)
Heinemann 2002	94-99	case- control	159/901 overall group	no	3 rd vs. 2 nd	0.9 (0.6-1.4)
			108/125 hospital group	no	3 rd vs. 2 nd	1.7 (0.9-3.8)*

* risk estimate(s) selected in table 1 of the Public Citizen petition

2.3.6 Database studies in the General Practice Research Database (GPRD)

Both Jick (1995, 2000) and Farmer (2000b) have used the General Practice Research Database (GPRD) computerized patient record database to assess the risk of VTE in users of different pill generations.¹ Petitioner quotes both cohort and case-control data from *Jick 1995* and *2000*, but quotes only one result from the case-control data from *Farmer 2000b*. Database studies do not allow sufficiently for adjustment for differences in duration of use because data from the period before subjects entered into the database are not available (left-censoring). Since age is a proxy for duration of use, close age matching (e.g., by exact year of birth) in these database studies can reduce the confounding effect of duration of use. In both the MediPlus and GPRD analyses by Farmer, exact age matching indeed showed a reduction of the odds ratios. Though Jick 2000 did not produce reduced odds ratios using exact age matching, the unexplained exclusion of study sites and discrepancies in case numbers in the overlapping period with Jick's 1995 study raises questions about the validity of the results.

¹ Both investigators have also used the GPRD to assess whether the switch from 3rd generation OCs to 2nd generation OCs after the October 1995 pill scare caused a reduction in VTE incidence in U.K. (see *Jick 2000, Farmer 2000a*). Neither found a statistically significant reduction in VTE after the 1995 pill scare, suggesting that the massive switch from 3rd to 2nd generation OCs in the U.K. did not result in a public health benefit. This confirms that the risk of VTE was not associated with the type of OC but rather with the background risk of VTE in women of reproductive age. It should be noted, however, that Jick interpreted his non-significant data as showing a reduction in VTE incidence after 1995.

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Table 6: Studies in the General Practice Research Database

published	period	design	cases/controls 3 rd and 2 nd	adjustment for duration of use	comparison	OR (95% CI)
Jick 1995	91-94	cohort	75	no	D vs. L G vs. L	1.9 (1.1-3.2)* 1.8 (1.0-3.2)
		case-control	75/300	yes (2-5 years age band matching)	D vs. L G vs. L	2.2 (1.1-4.4)* 2.1 (1.0-4.4)
Farmer 2000b	92-97	cohort	210	no	D30 vs. L G vs. L	1.3 (0.9-1.8) 1.3 (0.9-1.9)
		case-control	201/722	yes (year of birth matching)	D20 vs. L D30 vs. L G vs. L D20 vs. L	1.4 (0.8-2.4) 1.0 (0.6-1.6)* 1.3 (0.8-2.1) 0.8 (0.4-1.6)
Jick 2000	93-99	cohort	106	no	3 rd vs. L	1.9 (1.3-2.8)*
		case-control	106/569	yes (year of birth matching)	3 rd vs. L	2.3 (1.3-3.9)*

*: risk estimate(s) selected in table 1 of the Public Citizen petition

2.3.7 Database studies in the MediPlus databases

MediPlus database studies from the U.K. and Germany consistently find no significant difference between 3rd generation OCs and 2nd generation OCs with regard to VTE. Petitioner inexplicably did not cite the largest of the three MediPlus studies (*Todd 1999*), but did cite both the cohort and the case-control analysis from the initial MediPlus U.K. study (*Farmer 1997*). These latter data show that matching in wider (5-yr.) age bands inflates the risk estimate and that the more precise “year of birth matching” in the case-control group is a better control of the confounding effects of age as a proxy for duration of use.

Table 7: Studies in the MediPlus databases

published	period	design	cases/controls 3 rd and 2 nd	adjustment for duration of use	comparison	OR (95% CI)
Farmer 1997	91-95	cohort	83	yes (5 year age band)	D vs. L G vs. L	1.8 (0.9-3.5)* 1.3 (0.7-2.5)
		case-control	85/313	yes (year of birth matching)	D vs. L G vs. L	0.8 (0.4-1.9)* 0.9 (0.4-1.8)
Farmer 1998	92-95	case-control	42/168	yes (year of birth matching)	3 rd vs. 2 nd	0.8 (0.4-1.6)*
Todd 1999	92-97	case-control	99/366	yes (year of birth matching)	D30 vs. L	1.1 (0.5-2.6)
					D20 vs. L	1.1 (0.4-3.4)
					G vs. L	1.1 (0.5-2.4)

* risk estimate(s) selected in table 1 of the Public Citizen petition

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2.3.8 Studies with limited ability to control for confounding

The Petition refers to three additional studies on VTE in OC users, two presented in table 1 of the Petition (*Herings 1999a, Anderson 1998*) and another referred to in the text of the Petition (*Parkin 2000*). There are additional similar studies and analyses (*Farmer 1996b, Herings 1999b, Jick 2006*), not cited in the Petition, as well. Examples of limitations that affect the reliability of these studies are provided below.

The total number of cases and controls in these studies was small; accordingly, the 95% confidence intervals were extremely broad in some studies. In studies with such small sample sizes and imprecise associations, even minor biases can influence the results substantially. In fact, small sample size forced some investigators to unmatched their matched analysis (thus reducing control of bias in the study) and caused very unstable and unreliable results. See *Parkin 2000*. Also, the subanalysis of a study in a linked database system (*Herings 1999a*), cited in the Petition, only included six cases using 2nd generation OCs. This study had very limited confounder control and produced unstable results. The Petition does not cite the larger overall analysis that was published separately (*Herings 1999b*) and produced a lower risk estimate. (The larger analysis suffered from limitations similar to those of the subgroup analysis.) The investigators themselves classified the *Anderson 1998* study as too small; the unreliability of the analysis is evidenced by the large confidence intervals (0.4 – 260). Also, the study in the Meditel database was too small to allow robust risk estimation with sufficient confounder control (*Farmer 1996b*).

An additional analysis in an insurance claims database became available recently (*Jick 2006*) and reported an odds ratio of 1.7 (1.2-2.4) for VTE in users of desogestrel-containing OCs compared to levonorgestrel-containing OCs. Studies in such databases carry limitations. For example, there are insufficient clinical data for adjustment of confounding factors, and the exposure data cannot be reliably linked to the occurrence of the events. Similarly, studies based upon pharmacy records and hospital admissions/discharge records, such as *Herings 1999a, 1999b, Farmer 1996b*, and *Anderson 1998*, are subject to misclassification and confounding which limits the validity of their results.

Due to their small size, the instability of the risk estimates, the lack of confounder control, other biases, and the reservations expressed by the studies' authors, none of these smaller studies materially add to the totality of the evidence or provide support for Public Citizen's petition.

Table 8: Studies with limited ability for confounder control

published	period	design	cases/controls 3 rd and 2 nd	adjustment for duration of use	comparison	OR (95% CI)
Herings 1999a	88-92	case series	33 (first time)	no	3 rd vs. 2 nd	4.2 (1.7-10.2)*
Herings 1999b	88-92	case series	78 (overall)	yes (regression)	3 rd vs. 2 nd	2.3 (1.5-3.7)
Farmer 1996b	90-91	cohort	31	no	3 rd vs. L	1.3 (1.2-1.8)#
Andersen 1998	85-?	case- control	40/28	no	3 rd vs. other	9.7 (0.4- 259.6)*

* risk estimate(s) selected in table 1 of the Public Citizen petition

published confidence interval is incorrect; true confidence interval is not significant

2.3.9 Meta-analysis is not a reliable methodology.

Properly conducted, meta-analysis is a method of combining the results of randomized clinical trials (RCTs) in order to arrive at a summary estimate. The meta-analysis of RCTs is known to be difficult and fraught with pitfalls. The main problems include heterogeneity of populations, study circumstances, and exposures. Meta-analysis of observational studies is a much more difficult exercise, and no general consensus on its reliability has been reached in the scientific community.

The epidemiologic studies evaluating the risk of VTE in users of different types of OCs form a data set that is inappropriate for meta-analysis. Some studies with no-to-minimal correction for confounding observe a two-fold difference in risk of VTE between users of 3rd and 2nd generation OCs (OR~2), whereas other studies with better control for these confounders observe similar risks of VTE in the two groups (OR~1). Meta-analysis in this instance hides the essential reason for the differing results: methodologically different designs. Thus, it yields unreliable results.

The meta-analyses relied upon by Public Citizen (*Kemmeren 2001* and *Hennessy 2001*) suffer from the pitfall described above as well as the investigator bias that obtains from the selective use of studies (in this instance, the exclusion of some studies showing no differential effect of OC generations on VTE). These meta-analyses provide less information than the two sets of individual studies themselves.

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2.4 Conclusion: Epidemiologic data fail to demonstrate that 3rd generation OCs affect venous thrombosis differently from 2nd generation OCs.

Petitioner's interpretation of the growing body of epidemiologic studies is not tenable because:

- a. the odds ratios calculated by Petitioner should be disregarded—they are crude estimates and cannot be adjusted for any of the confounding variables in those studies;
- b. Petitioner excluded at least 5 publications of studies/analyses, many of which have better confounding control, and none of which show a difference in risk of VTE between 3rd and 2nd generation OCs (*Farmer 1996b, Suissa 1997, Todd 1999, Lewis 1999b and Suissa 2000*);
- c. Petitioner selectively quotes higher odds ratios rather than the key odds ratios based on the most robust analyses in the studies; and
- d. the overall impression is one of inconsistent results and, thus, no valid evidence of an increased comparative risk.

Petitioner also refers to a 1995 FDA statement based upon the flawed earlier epidemiologic studies: "New studies indicate about a two-fold increase in the risk of venous blood clots associated with products containing desogestrel." But the current FDA-approved product information of desogestrel-containing OCs reflects the newer studies that show no difference between 3rd and 2nd generation OCs:

"Several epidemiologic studies indicate that 3rd generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain 2nd generation oral contraceptives. In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this two-fold increase in risk."

In conclusion, there remains substantial evidence from adequate and well-controlled investigations to conclude that 3rd generation OCs containing desogestrel are safe and effective and will have the effects represented under the condition of use prescribed, recommended, or suggested in the labeling of these drugs. See § 355(e)(1)-(3).

3.0 Scientific research has not demonstrated a biologically-plausible explanation for the purported differential effects of OC generations on venous thrombosis.

Although it is premature in causation assessment to invoke mechanisms (biological plausibility) in the absence of a documented association with appropriate control of bias and confounding (or in this instance, a documented difference between 3rd and 2nd generation OCs), Public Citizen

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claims that different effects of 3rd generation OCs compared to 2nd generation OCs, on activated protein C resistance and protein S plasma levels, “provide a biological explanation to the increased risk of venous thrombosis with” 3rd generation OCs. Public Citizen’s speculation is reminiscent of earlier authors’ focus on sex hormone binding globulin (SHBG) (*Odlind 2002, Van Vliet 2005*) as a predictor of VTE. Although 3rd generation OCs increase SHBG more than 2nd generation OCs, SHBG has not been clinically linked to a risk of VTE, but instead to a reduced incidence of androgenic skin disorders such as acne. Others have focused on Factor VII which has been shown not to be predictive for venous thrombosis (*Koster 1994*).

3.1 Acquired reductions of protein S are not reliable predictors of venous thrombosis.

Several authors suggested that a reduction of free protein S in users of 3rd generation OCs could be responsible for an effect on the risk of VTE (*Villa 1996, Mackie 2001*). A genetic deficiency of total protein S has been suggested as a risk marker for VTE in family studies (*Bertina 1999*); however, acquired reduced serum levels of free protein S are not associated with VTE, as demonstrated in population-based studies including women (*Koster 1995, Faioni 1997, Liberti 1999*). Therefore, Petitioner’s hypothesis relating to acquired reduction of protein S levels in OC users cannot be accepted as a biological explanation for associations, if any, between OCs and venous thrombosis.

3.2 Activated protein C resistance

Some investigators have speculated that the use of OCs leads to acquired activated protein C (APC) resistance, which some authors link to venous thrombosis (*Rosing 1997b*). There are two basic ways to measure APC resistance: the APTT-based assay and the ETP-based assay.

3.2.1 OCs do not differentially affect APC resistance as measured by the APTT-based assay.

The conventional APC sensitivity assay, validated and standardized by Dahlback and Bertina (*Dahlback 1993, De Ronde 1994*), is based on the activated partial thromboplastin time (APTT). Various case-control and cross-sectional studies (*e.g., Dahlback 1993, De Ronde 1994*) have shown that a poor response to APC in this assay is correlated with an increased risk of VTE. A number of studies, however, have shown that 2nd and 3rd generation OCs either do not affect, or minimally affect, APC resistance as measured by this assay (*e.g., Schramm 1997, Rosing 1997, Tans 2000, Curvers 1999, Out 2003*).

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3.2.2 The ETP-based assay for APC resistance is not a reliable predictor of venous thrombosis.

The Rosing assay for APC resistance is based on the endogenous thrombin potential (ETP) (Rosing 1997). 3rd generation OC users show more resistance to APC than 2nd generation OC users when measured by the ETP-based assay; however, several studies have shown that APC resistance, as measured by this assay, is not associated with venous thrombosis (e.g., Heinemann 1998, Grand'Maison 2000, Zotz 2000, Hoibraaten 2001). The authors of one study (Tans 2003) claim that the ETP-based assay is predictive for the risk of VTE, but the observation was made only when patients with a Factor V Leiden mutation were included. This is irrelevant in a discussion about purported acquired resistance to APC in OC users.

3.3 Conclusion: No biological plausibility

Though Petitioner speculates otherwise, changes in protein S and APC resistance are not plausible biological explanations for the results in the OC-venous thrombosis epidemiologic studies. Other hemostatic variables also have not been shown in reliable scientific studies to be biologically-plausible mechanisms for any purported differential effects of OCs on venous thrombosis.

Public Citizen has not provided any new evidence on biological plausibility, and it certainly provides no evidence for a ban of 3rd generation OCs containing desogestrel. There continues to be substantial evidence for the safety, efficacy, and effects of these drugs as represented in their current labeling. See 21 U.S.C. § 355(e)(1)-(3).

4.0 3rd generation OCs provide clinical benefits over 2nd generation OCs.

Petitioner claims that 3rd generation OCs do not have a clinical benefit over 2nd generation OCs and that 2nd generation OCs "are equally effective and do not cause an increased risk of blood clots." However, epidemiologic studies show a clear clinical benefit: 3rd generation OCs are less associated with acute myocardial infarction (AMI) than 2nd generation OCs, and users of 3rd generation OCs have no increased risk of AMI compared to those not exposed to OCs.

For example, two studies (Lidegaard 1996, Lewis 1997) confirm the risk of AMI is lower in users of 3rd generation OCs than in users of 2nd generation OCs, the difference reaching statistical significance in the largest study (Lewis 1997). Two other studies (Poulter 1997, Jick 1996) were too small to arrive at sufficiently robust risk estimates or reach statistical significance in the comparison between OC types, and, therefore, should be regarded as supportive rather than conclusive analyses.

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The MICA mortality study (*Dunn 2001*), which was not affected by recall bias, is consistent with other studies showing a decreased risk for 3rd generation OCs compared to 2nd generation OCs. The results of the earlier MICA morbidity study (*Dunn 1999*) were likely affected by recall bias following the media attention in the U.K. in October 1995 and the subsequent massive changes in OC prescribing. Other investigators also have observed a decreased risk of AMI in users of 3rd generation OCs compared to users of 2nd generation OCs (*Tanis 2001*). It is remarkable that the latter study was omitted from the Petition; one of the signatories was a co-author of this publication.

Meta-analyses of the studies investigating 3rd and 2nd generation OCs and risk of AMI (*Spitzer 2002, Khader 2003, Baillargeon 2005*) support the clinical benefit of 3rd generation OCs seen in the individual studies. Table 9 is adapted from the publication by Spitzer.

Table 9: Epidemiologic studies assessing the risk of AMI in users of 2nd and 3rd generation OCs

Study	No of subjects	Adjusted OR (95% CI)		
		3 rd vs. non-use	2 nd vs. non-use	3 rd vs. 2 nd
GPRD <i>Jick 1996</i>	55	NR	NR	0.65 (0.05-4.97) †
Danish study <i>Lidegaard 1996</i>	1133	0.96 (0.4-2.29)†	1.90 (0.7-4.90)	0.51 (0.15-1.72) †
WHO study <i>Poulter 1997</i>	678	0.97 (0.14-6.96)	1.64 (0.49-5.54)	0.59 (0.09-3.75) †
Transnational <i>Lewis 1997</i>	817	0.85 (0.30-2.39)	2.99 (1.51-5.91)	0.24 (0.07-0.78)
MICA morbidity <i>Dunn 1999</i>	2176	1.96 (0.87-4.39)	1.10 (0.52-2.30)	1.78 (0.66-4.83)
MICA mortality <i>Dunn 2001</i>	432	0.83 (0.25-2.81)	2.88 (1.22-6.77)	0.29 (0.07-0.78) †
Leiden <i>Tanis 2001</i>	1173	1.3 (0.7-2.5)	2.5 (1.5-4.1)	0.52 (0.23-1.18) †

†: estimated by Spitzer

This clinical benefit on arterial disease is further exemplified by the Dunn mortality data. Based upon Dunn's risk estimates, 14 to 20 extra fatalities would be expected per 1,000,000 women-years of exposure to 2nd generation OCs. This figure is substantially higher than the estimated excess of 4 fatalities of VTE per 1,000,000 women-years of exposure to 3rd generation OCs even if in fact the 3rd generation OCs were associated with a higher risk of VTE (*Kemmeren 2001*), which they are not.

Finally, we observe that Public Citizen excluded from its review of data on clinical benefits all studies sponsored by pharmaceutical companies. These studies, however, show clear benefits of 3rd over 2nd generation OCs.

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In brief, Public Citizen presents no new information that would detract from the substantial evidence supporting a clinical benefit of 3rd generation OCs containing desogestrel.

5.0 Lessons learned: ban of 3rd generation OCs would adversely impact public health.

Public Citizen irresponsibly claims the “pill scare” in the mid-1990’s did not increase conception and abortion rates. To the contrary, after the U.K. Committee on Safety of Medicines’ (CSM) warning in October 1995, 12% of women on 3rd generation OCs discontinued use of all OCs (*Hope 1996*), and conception rates and abortion rates increased (*Wood 1998*). The British Office of National Statistics reported increased abortion rates and attributed these increases to the adverse publicity surrounding CSM’s announcement (*ONS Monitor 1997*).

Public Citizen cites a study in the GPRD (*Jick 1998*); again, Jick’s conclusions differ from others investigating the same issue. *See Table 10.*

Table 10: Increases in abortion figures in 1996 versus 1995 in countries where authorities restricted or advised against the use of 3rd generation OCs, or in those where the media paid extra attention to the debate on pill safety

Country	Change in abortion rate	Additional abortions (n)
England and Wales	+14%	5500
Norway		
all ages	+5%	700
< 25 years	+36%	
Germany	+34%	33,000*
Sweden	+4%	600
Netherlands	+7.5%	1500

*: an as yet unknown part of the increase is attributed to changed legislation regarding abortion reporting in Germany

In summary, Petitioner ignores governmental statistics and other published data on the adverse consequences of the pill scare in 1995 and provides no new studies showing a lack of evidence for the need for 3rd generation OCs containing desogestrel.

6.0 Summary: Substantial evidence continues to support the safety, effectiveness, and need of 3rd generation OCs.

6.1 Epidemiologic studies overall fail to demonstrate that 3rd generation OCs increase the risk of venous thrombosis more than 2nd generation OCs.

Overall, the epidemiologic studies fail to demonstrate any difference in the risk of venous thrombosis between 3rd generation and 2nd generation OCs and therefore provide no support for

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Public Citizen's contention that 3rd generation OCs double the risk of venous thrombosis compared to 2nd generation OCs.

Public Citizen presents no new epidemiologic studies (or interpretations of previous epidemiologic studies) that would call into question the substantial evidence supporting the safety, effectiveness, and need for 3rd generation OCs. Instead, Public Citizen lists selective studies and two meta-analyses in a table that contains misquoted risk estimates, a double inclusion of a study, recalculations of crude risk estimates, and unadjusted risk estimates where adjusted risk estimates were available. In addition, Public Citizen did not present risk estimates from additional studies which had lower risk estimates mostly due to a higher degree of confounder control, and it failed to explain why the overall set of studies is highly inconsistent.

6.2 Reliable scientific research has not established a plausible biological mechanism for any effects of OCs on venous thrombosis.

Biological plausibility ought to be considered only after a statistically significant association, with appropriate control of bias and confounding, has been demonstrated. Such a valid association (in this instance, a valid difference between the effects of 3rd and 2nd generation OCs on venous thrombosis) has not been established. Nevertheless, Public Citizen proposes that the purported risk of VTE in users of 3rd generation OCs can be explained by a reduction in protein S and increased resistance to APC as measured by the ETP-based assay. Neither of these two hemostatic parameters has a proven association with the risk of VTE. In contrast, other hemostatic parameters, including APC resistance as measured with the APTT-based assay, are associated with an increased risk of VTE; none of these parameters are differentially affected by the use of 3rd and 2nd generation OCs, and none has been reliably shown to be a plausible explanation for VTE in OC users. In summary, Public Citizen fails to present any evidence affecting the approval of 3rd generation OCs and their current package inserts.

6.3 3rd generation OCs confer clinical benefits in addition to those of 2nd generation OCs.

Public Citizen states that 3rd generation OCs do not convey any clinical benefit over 2nd generation OCs. This assertion ignores epidemiologic studies that show 3rd generation OCs are not associated with an increased risk of acute myocardial infarction (AMI), and the reported odds ratios for AMI and 3rd generation OCs are lower than those for 2nd generation OCs. In addition, the much higher fatality rate of AMI than VTE translates into an important clinical and public health benefit of 3rd generation OCs even if the initial 1995 VTE studies were believed to show a valid association.

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6.4 The benefits of 3rd generation OCs on public health outweigh the adverse effects resulting from a ban of these drugs.

Public Citizen's claims, based on a Jick study, that the pill scare in 1995 did not result in an increased rate of unwanted pregnancies and abortions, provide no new evidence not already considered by FDA. Furthermore, Jick's data are in contrast with the official government statistics from various European countries, including the U.K., and studies that show the 1995 pill scare was followed by increased numbers of abortions and pregnancies. Public Citizen is simply wrong that its proposed ban of 3rd generation OCs would not pose substantial potential detrimental effects on public health.

6.5 Conclusion: No reliable scientific basis for the withdrawal of approval of 3rd generation OCs containing desogestrel.

Public Citizen presents no new information or scientific evidence showing 3rd generation OCs are unsafe, ineffective, or unnecessary. The available evidence instead confirms the safety, efficacy, and importance of 3rd generation OCs for the public health of women in and outside the U.S. The current labeling of desogestrel-containing oral contraceptives adequately reflects the substantial scientific evidence available to FDA for assessing the risk of venous thrombosis. There is no reliable scientific basis for the withdrawal of approval of 3rd generation OCs containing desogestrel. For the foregoing reasons, Organon respectfully submits that the Petition should be denied.

Sincerely,

Joe G. Hollingsworth/UKM

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Katharine R. Latimer
C. Robert Manor
Counsel to Organon USA Inc.

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