1. **Objective.** This paper is tabled for discussion at the electronic working group on vibrios established as part of the current trade negotiations between the EU and the USA regarding establishing reciprocal trade of bivalve molluscan shellfish. In preliminary discussion it was identified that the EU should summarise the concern (from an EU perspective) regarding food safety controls for naturally occurring marine vibrio’s in relation to products that might be traded from the USA to the EU.

2. **Scope.** The paper addresses risks associated with the naturally occurring human pathogens *Vibrio parahaemolyticus* and *Vibrio vulnificus*. Raw shellfish produce, especially oysters, are the most common foodborne source of vibriosis (Newton *et al*. 2012). The USA has experienced significant public health problems with these pathogens following consumption of products from at risk areas. Currently Vibrio infection associated with consumption of molluscs produced in the EU is rarely documented. The concern is that health problems associated with marine vibrio’s will arise in the EU if products from at risk areas in the USA are exported to the EU. It is acknowledged that the US has introduced comprehensive control measures for this issue. The question to be considered is the extent to which these measures can be considered to have successfully reduced the risk to an acceptable level. The paper summarises our understanding of the current epidemiological status of bivalve mollusc associated *Vibrio* infections within the USA (annex A and B) which informs discussion on the effectiveness of current controls for products that may be exported to the EU.

3. **Vibrio vulnificus.** The Gram-negative bacterium *V. vulnificus* is a naturally occurring and common inhabitant of estuarine and coastal environments. Globally, *V. vulnificus* is a significant foodborne pathogen capable of causing necrotizing wound infections and primary septicemia, and is a leading cause of seafood-related mortality. This species is present in high numbers in filtering organisms, such as oysters, especially in warmer months (Oliver *et al*. 2006). Human infections typically occur after ingestion of raw or undercooked shellfish, particularly oysters, or through entry via a flesh wound (Oliver 2005). Significantly, *V. vulnificus*-associated primary septicaemia carries the highest fatality rate of any food-borne pathogen (Rippey 1994). Most cases of infection (~95%) occur in males, who are immuno-compromised or who have underlying diseases/syndromes which result in elevated serum iron levels, primarily liver cirrhosis secondary to alcohol abuse/alcoholism (Oliver and Kaper, 2005).

3.1. Annex B summarises our understanding of the current epidemiological status of *V. vulnificus* in the USA. Between 1988-2010, 1,874 *V. vulnificus* cases and 574 associated deaths were reported in the USA (Baker-Austin *et al*. 2013). Mortality was associated most commonly with cases linked to shellfish consumption (42.2% overall fatality rate). Data published by the CDC (Newton *et al*. 2012) indicates an increase in *V. vulnificus* infections reported in the US between 1996-2010.

3.2. To the best of our knowledge, all US States producing oysters have, since the late 1990’s, been required to perform an assessment of *V. vulnificus* risk. Specifically, states that have previously reported two or more confirmed *V. vulnificus* infections are
required to implement a control plans. Control plans essentially limit the time between oyster harvest and the first refrigeration step (FAO/WHO 2006). In general these plans consider epidemiological information on reported cases in States, as well as ambient air temperatures and data on time from harvest to refrigeration during summer months in shellfish harvesting areas. Our understanding is that all relevant States have performed the assessment and, if necessary, have introduced control plans for this pathogen.

3.3. Our concern is over the effectiveness of these control plans for managing the risk to a acceptable level given the apparent continuing level of *V. vulnificus* cases in the USA. From the epidemiological data (Annex B) a decrease in the number of cases commensurate with the introduction of the control plans (3.2) is not readily apparent.

3.4. The state of California apparently has similar reservations on the effectiveness of current controls. In 2003 California, in an effort to reduce *V. vulnificus* shellfish-associated infections, banned the sale of raw Gulf coast oysters during April-October unless the produce was processed using appropriate post harvest processing to reduce numbers of *V. vulnificus* to non-detectable levels, and this ban continues to date. Our understanding is that this has had a marked impact on the number of oyster associated *V. vulnificus* cases occurring in California (Annex B). The success of California in reducing *V. vulnificus* cases through this action in our view tends to support the concern that current controls, as enacted in State management plans, are not sufficiently protective.

3.5. The epidemiological evidence suggests that in Europe the risks associated with *V. vulnificus* are low with the small number of reported cases almost all wound-associated infections rather than shellfish borne (Baker-Austin et al. 2010, Baker-Austin et al. 2013). Considering the potential population size of susceptible individuals in Europe we feel there is a significant risk of human infection, including mortality, if products from high risk areas are exported to the EU. We have a linked concern that clinical cases of *V. vulnificus* potentially occurring through this trade may not be recognised in a timely manner, because of the lack of experience of this pathogen in the EU, thus potentially tending towards more fatal outcomes since rapid administration of life-saving antibiotics, or other clinical interventions, may not occur.

3.6. The concern extends beyond oysters sold live since we are not clear why the risk would not equally apply to shucked oysters and to other bivalve mollusc species which are not commercially processed. Our understanding is that risk assessment and control measures are applied only to whole oysters sold live and not to any other commodity.

3.7. We welcome FDA comments on the above and on the epidemiological data supporting our concerns as set out in Annex B.

4. **Vibrio parahaemolyticus** is a Gram-negative, bacterial pathogen found commonly in temperate and warm estuarine waters. Globally, *V. parahaemolyticus* is the leading cause of bacterial gastroenteritis associated with the consumption of seafood products. While the majority of environmental strains are innocuous members of the marine microbiota, small
subpopulations are opportunistic pathogens of humans (Johnson et al. 2008). An established route of transmission includes the consumption of raw bivalve shellfish species, such as oysters and clams. In general, seawater temperature is regarded as the best overall indicator of *V. parahaemolyticus* abundance, and is a major factor in both the seasonal and geographical distribution of this species.

4.1. CDC data (Scallan et al. 2011) estimates that there are, on average, about 35,000 infections per year in the USA caused by *V. parahaemolyticus* with around 86% of these cases designated as seafood acquired. Recent CDC data (Newton et al. 2012) shows an increasing trend in *V. parahaemolyticus* infections in the USA during the period 1996-2010. Of all bacterial causes of foodborne infection occurring in the USA vibrios appears to be the only group with an increasing trend (CDC, 2008). In summary *V. parahaemolyticus* linked to seafood consumption causes a significant amount of human illness each year in the USA and appears to be on the increase (Annex A).

4.2. Our understanding is that, as with *V. vulniﬁcus*, all US States producing oysters have since the late 1990’s been required to perform an assessment of *V. parahaemolyticus* risk for their coastal waters. Briefly, if a State’s *V. parahaemolyticus* risk evaluation indicates that the risk of illness from the consumption of local oysters is reasonably likely to occur, the State must develop and implement a *V. parahaemolyticus* control plan for that area. This assessment is based on epidemiological criteria (2 or more cases linked to consumption of oysters produced in their coastal waters in the last three years) as well as ambient (daytime) temperature of the harvesting area exceeding given thresholds. The control plan sets out the necessary control measures for that State such as post-harvest time/processing, temperature controls, hours of harvest for tidal and inter-tidal areas, etc.

4.3. Given the significant number of cases of *V. parahaemolyticus* cases linked to bivalve mollusc consumption continuing to occur each year in the USA, and the apparent increasing trend in such cases despite the introduction of comprehensive control measures, our general concern is whether the measures contained in control plans are sufﬁciently effective to contain the risk to acceptable levels. From the epidemiological data (Annex A) a decrease in the number of cases commensurate with the introduction of the control plans in the late 1990’s is not readily apparent. It would seem likely that exported products from at risk areas during high risk periods would pose a risk of infection in EU consumers despite the control measures in place.

4.4. An additional concern is whether newly emerging *V. parahaemolyticus* strains pose additional risks not adequately controlled in current management plans. The at risk area in the USA has traditionally been the Gulf Coast region. However, over recent years an increasing number of outbreaks have been associated with other regions, these include the Pacific Northwest (including Alaska) and recently New York State. These incidents appear to be linked with the emergence of *V. parahaemolyticus* strains with enhanced virulence. These new strains appear to be responsible for increasing numbers of cases. The introduction of enhanced control measures (Annex A) does not appear to have been effective in containing the increase in these cases. The concern is whether the conventional post harvest controls stipulated in *V. parahaemolyticus* risk management plans are effective for controlling the risk from
these newly emergent strains. We are concerned that the available epidemiological data (Annex A) does not provide reassurance that control measures are sufficiently effective.

4.5. As for *V. vulnificus* we are not clear why the risk from *V. parahaemolyticus* is limited only to oysters sold live and not to shucked oysters or other bivalves species sold raw. Our understanding that risk assessment and control measures are applied only to whole oysters sold live and not to any other commodity.

4.6. We welcome FDA comments on the above and on the epidemiological data supporting our concerns as set out in Annex A.

EURL, Weymouth
29th April 2013
Annex A: Vibrio parahaemolyticus

Vibrio parahaemolyticus is a Gram-negative, bacterial pathogen found commonly in temperate and warm estuarine waters. Globally, V. parahaemolyticus is the leading cause of bacterial gastroenteritis associated with the consumption of seafood products. While the majority of environmental strains are innocuous members of the marine microbiota, small subpopulations are opportunistic pathogens of humans (Johnson et al. 2008). An established route of transmission includes the consumption of raw bivalve shellfish species, such as oysters and clams. In general, water temperature is regarded as the best overall indicator of V. parahaemolyticus abundance, and is a major factor in both the seasonal and geographical distribution of this species.

- **General epidemiology.** Overall, there are highly useful epidemiological datasets available for assessing V. parahaemolyticus disease burden in the USA, as two surveillance systems are available: FoodNet (operating from 1996 to present) and COVIS (Cholera and Other Vibrio Illness Surveillance, operating 1988-present). Both systems gather data on reported infections. Recent data published from the CDC (Scallan et al. 2011) indicate that there are on average 34,664 infections each year in the USA caused by this bacterium (range 18,260-58,027 cases/yr). This data is based on scaling up CDC laboratory confirmed cases with adjustments made for under-reporting, misdiagnosis, travel associated infections and proportion of foodborne cases. Around 86% of cases are designated foodborne based on this data. Compared to previous estimates (see: [http://www.cdc.gov/nczved/divisions/dfebmd/diseases/vibriop](http://www.cdc.gov/nczved/divisions/dfebmd/diseases/vibriop)) of around 4,500 cases each year, this data therefore suggests that there are a significant number of cases each year in the USA, with foodborne infections representing a disproportionate percentage of these infections. Data from COVIS and FoodNet (Newton et al. 2012) also indicate that V. parahaemolyticus infections are the most prevalent Vibrio infection reported in the USA compared to the pathogens V. vulnificus and V. alginolyticus. Given exerted efforts in the USA, and particularly during the last decade to reduce risk from these pathogens, a concern is the apparent large number of reported cases, with foodborne infections representing a sizeable component of this disease burden.

- **Increasing rates of infections.** Data recently published by the CDC (Newton et al. 2012) has shown that there has been a clear recent increase in V. parahaemolyticus infections in the USA, using again, COVIS and FoodNet datasets. According to these data, the incidence of V. parahaemolyticus infection increased from 1996-2010, in COVIS from 0.01 to 0.13 cases (per 100,000 population) and in FoodNet from 0.06 to 0.23 cases (per 100,000 population). Of all bacterial foodborne pathogens, data from CDC (FoodNet) indicates that vibrios is the only grouping increasing (CDC, 2008). A concern is that the introduction of controls plans does not seem to have resulted in decreasing cases numbers – calling into question their effectiveness.

- **Changing geographical extent and nature of risk.** Numerous reports have highlighted outbreaks of V. parahaemolyticus occurring outside areas historically associated with annual illness in the USA (e.g. outside the Gulf Coast). These include outbreaks associated with oyster consumption in the Pacific Northwest in 1997 (CDC 1998), Alaska in 2004, (McLaughlin et al. 2005) and more recently linked to shellfish consumption from produce harvested in New York State in 2012, (CDC-FDA & Cefas unpublished data). Such instances appear to have been mediated by unusual ‘Pacific Northwest’ complex clonal strains (PNW strains), which carry a higher virulence potential compared to other toxigenic V. parahaemolyticus strains (Martinez-Urteza et al. 2010). In some instances, it appears that the numbers of infections have increased in such areas over time (e.g. Washington State from 1997-present, Paranjpye et al. 2012). Indeed, elevated V. parahaemolyticus case rates in the PNW region prompted the Washington State Department of Health and the oyster industry to implement strict post-harvest treatment and handling regimens; however, elevated case rates persist despite improved post-harvest control measures (Paranjpye et al. 2012, Turner et al. 2013). It appears that these cases may shown little or no correlation with concentrations of potentially
pathogenic *V. parahaemolyticus* (Paranjpye et al. 2012,). A concern is that strains from these areas may pose a significant additional risk for example outside of ‘at risk’ periods (e.g. summer months).

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**Annex B: *Vibrio vulnificus***

The Gram-negative bacterium *V. vulnificus* is a naturally occurring and common inhabitant of estuarine and coastal environments. Globally, *V. vulnificus* is a significant foodborne pathogen capable of causing necrotizing wound infections and primary septicemia, and is a leading cause of seafood-related mortality. This species is present in high numbers in filtering organisms, such as oysters, especially in warmer months (Oliver et al. 2006). Human infections typically occur after ingestion of raw or undercooked shellfish, particularly oysters, or through entry via a flesh wound (Oliver 2005). Significantly, *V. vulnificus*-associated primary septicema carries the highest fatality rate of any food-borne pathogen (Rippey 1994). Most cases of infection (~95%) occur in males, who are immunocompromised or who have underlying diseases/syndromes which result in elevated serum iron levels, primarily liver cirrhosis secondary to alcohol abuse/alcoholism (Oliver and Kaper, 2005).

- **General epidemiology.** As with *V. parahaemolyticus* (see above) the availability of both FoodNet and COVIS datasets in the US help to provide a highly useful national overview of disease burden associated with *V. vulnificus*. Using *V. vulnificus* data obtained from the CDC (COVIS) from recent collaborative work, between 1988-2010, 1,874 *V. vulnificus* cases and 574 associated deaths were reported in the USA (Baker-Austin et al. 2013). Mortality was associated most commonly with cases linked to shellfish consumption (42.2% overall fatality rate). Data published by the CDC (Newton et al. 2012) indicates increases in *V. vulnificus* infections reported in the US between 1996-2010 in both the COVIS and FoodNet datasets, with a marked increase in the FoodNet data (0.01 infections per 100,000 population in 1996, increasing to 0.05 cases per population in 2010). A concern is the apparent increasing rate of infections over recent years, despite the introduction of control plans, calling into question their effectiveness.

- **Geographical extent of risk.** Using CDC epidemiological data (COVIS), 1138 *V. vulnificus* cases were reported in the Gulf Coast (1988-2010), constituting approximately 68% of the US national total. Gulf Coast states reported an average incidence rate of 0.111 cases per 100,000 compared to 0.018 cases per 100,000 in non-Gulf coast states (Baker-Austin et al. 2013). *V. vulnificus* infections have increased significantly in the last decade, especially in non-Gulf coast states (Fig. 1). Although it is worth noting that state-by-state participation in COVIS has changed over time, a retrospective analysis of data from individual states reporting cases indicates that the geographical spreading of shellfish-associated cases appears to have increased markedly outside of the Gulf Coast (Baker-Austin, unpublished). Given the apparent recent increase in shellfish associated cases, and in states historically not associated with annual illness in the USA, the concern is in relation to the products from both Gulf coast and from other areas i.e. any area with a current FDA *Vibrio vulnificus* risk management plan. We understand a plan is required where 2 or more etiologically confirmed shellfish-borne *Vibrio vulnificus* illnesses since are traced to the consumption of commercially harvested raw or undercooked oysters that originated from the waters of that state.
Figure 1. *Vibrio vulnificus* cases reported in the USA, 1988-2010

- **California.** In an effort to reduce *V. vulnificus* shellfish-associated infections, the state of California banned the sale of raw Gulf coast oysters (April-October) in 2003, unless the produce was processed using appropriate post harvest processing to reduce numbers of *V. vulnificus* to non-detectable levels. Based on CDC epidemiological data (Baker-Austin et al. 2013), it appears that this restriction has had a marked impact on reducing clinical impact. In California, there were on average of 2.68 *V. vulnificus* fatalities each year (1988-2003) which reduced to 0.28 cases per year (2004-2010) after the banning of Gulf Coast produce in California in 2003.

**Literature cited**


