UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

IN RE: NATIONAL HOCKEY LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION	)	No. 0:14-md-02551 (SRN/BRT)
This Document Relates To: ALL ACTIONS.	)	**SUPPLEMENTAL DECLARATION OF CHARLES S. ZIMMERMAN IN SUPPORT OF MOTION FOR CLASS CERTIFICATION AND FOR APPOINTMENT OF CLASS REPRESENTATIVES AND CLASS COUNSEL**

I, Charles S. Zimmerman, declare as follows:

1. My name is Charles S. Zimmerman.

2. I am a partner with the law firm of Zimmerman Reed LLP, and Plaintiffs' Co-Lead Counsel in the above-captioned litigation.

3. I respectfully submit this Supplemental Declaration in further support of Plaintiffs' Motion for Class Certification, and for Appointment of Class Representatives and Class Counsel.

4. Attached hereto are true and correct copies of the following exhibits:

Exhibit 1:	Guskiewicz, K., et al. *Association between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players*, 57 NEUROSURGERY 4 (Oct. 2005)
Exhibit 2:	Excerpts from the deposition of Kevin Guskiewicz, taken January 30, 2018 **[Confidential – Filed Under Seal]**
Exhibit 3:	Nadia Kounang, *It's not concussions that cause CTE. It's repeated hits, a study finds*, CNN.com (Jan. 18, 2018)
Exhibit 4:	21 C.F.R. §§201.57(c)(6)-(7)

Exhibit 5:	*Traumatic Brain Injury: FDA Research and Actions*, U.S. FOOD & DRUG ADMIN.
Exhibit 6:	*What are the Potential Effects of TBI?*, CENTERS FOR DISEASE CONTROL & PREVENTION
Exhibit 7:	M.D. Green, *et al.*, *Reference Manual on Scientific Evidence* 552 (3d ed. 2011)
Exhibit 8:	Excerpts from the deposition of Christopher Randolph, taken January 30, 2018 **[Confidential – Filed Under Seal]**
Exhibit 9:	Excerpts from the deposition of Lili-Naz Hazrati, taken March 2, 2018 **[Confidential – Filed Under Seal]**
Exhibit 10:	Excerpts from the deposition of Colin Campbell, taken June 30, 2015, all of which have been de-classified by the NHL in a letter dated July 31, 2015
Exhibit 11:	Excerpts from the deposition of Gary Bettman, taken July 31, 2015, all of which (other than any redactions) have been de-classified by the NHL in a letter dated September 28, 2015 **[Redacted]**
Exhibit 12:	NHL0120323-NHL0120384 (Ex. 25 to Deposition Transcript of Gary Bettman, taken July 31, 2015) **[Formerly Confidential – De-Designated]**
Exhibit 13:	Excerpts from the deposition of John Rizos, taken August 12, 2016, all of which have been de-classified by the NHL in a letter dated August 29, 2016
Exhibit 14:	Choice of Law Flow Chart
Exhibit 15:	NHL0035193
Exhibit 16:	NHL1826210
Exhibit 17:	NHL2130456 **[Confidential – Filed Under Seal]**

Exhibit 18: NHL1479965
[Confidential – Filed Under Seal]

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Dated: March 7, 2018

Charles S. Zimmerman
Charles S. Zimmerman

EXHIBIT 1

Association between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Pla....

Article *in* Neurosurgery · October 2005

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Association between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players

OBJECTIVE: Cerebral concussion is common in collision sports such as football, yet the chronic neurological effects of recurrent concussion are not well understood. The purpose of our study was to investigate the association between previous head injury and the likelihood of developing mild cognitive impairment (MCI) and Alzheimer's disease in a unique group of retired professional football players with previous head injury exposure.

METHODS: A general health questionnaire was completed by 2552 retired professional football players with an average age of 53.8 (±13.4) years and an average professional football playing career of 6.6 (± 3.6) years. A second questionnaire focusing on memory and issues related to MCI was then completed by a subset of 758 retired professional football players (≥50 yr of age). Results on MCI were then cross-tabulated with results from the original health questionnaire for this subset of older retirees.

RESULTS: Of the former players, 61% sustained at least one concussion during their professional football career, and 24% sustained three or more concussions. Statistical analysis of the data identified an association between recurrent concussion and clinically diagnosed MCI ($\chi^2 = 7.82$, $df = 2$, $P = 0.02$) and self-reported significant memory impairments ($\chi^2 = 19.75$, $df = 2$, $P = 0.001$). Retired players with three or more reported concussions had a fivefold prevalence of MCI diagnosis and a threefold prevalence of reported significant memory problems compared with retirees without a history of concussion. Although there was not an association between recurrent concussion and Alzheimer's disease, we observed an earlier onset of Alzheimer's disease in the retirees than in the general American male population

CONCLUSION: Our findings suggest that the onset of dementia-related syndromes may be initiated by repetitive cerebral concussions in professional football players.

KEY WORDS: Alzheimer, Concussion, Mild cognitive impairment, Retired professional football players

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Traumatic brain injury (TBI) is an important public health concern, as each year more than 1.2 million Americans suffer head injury (26). More than 50,000 head-related injuries result in a fatality each year in the United States, whereas the overwhelming majority of head injuries are classified as mild traumatic brain injuries that can result in significant cognitive, emotional, and functional disabilities (26). TBI has been identified as a potential risk factor for the occurrence (or early expression) of neurodegenerative dementing disorders, including Alzheimer's disease (AD) disease and Parkinson's syndrome, and other psychiatric disorders such as clinical depression (8, 13, 21, 25, 28, 31, 35–37, 40). Still, other research findings have not shown this association between TBI and dementia (1, 3, 6, 7, 17, 19, 33, 42). Guo et al. (9) suggested that the severity of head injury is related to the magnitude of AD risk, and that the risk of AD associated with head injury involving loss of consciousness was approximately double that associated with head injury without loss of consciousness. However, they reported that even head injury without loss of conscious-

ness significantly increased the risk of AD relative to no head injury (9).

Mild cognitive impairment (MCI) is a recently established diagnostic classification typically applied to older individuals who exhibit some evidence of cognitive decline (usually in the domain of memory) and perform below expected levels on formal neurocognitive testing, but who have not exhibited a sufficient degree of impairment and/or functional decline to meet diagnostic criteria for dementia (30). MCI is often conceptualized as a transitional state between the cognitive changes of normal aging and dementia, with most recent studies estimating that 10 to 20% of MCI patients convert to a more advanced stage labeled as "dementia" each year, compared with healthy controls who convert at a rate of 1 to 2% per year (5, 22, 39). The majority of patients with MCI who convert to dementia are subsequently diagnosed with probable AD, although a significant percentage is diagnosed with vascular dementia (23). The identification of risk factors for the onset of MCI, and for the conversion of MCI to dementia, is an important step in developing strategies for the prevention and early treatment of these disorders, especially with the emergence of various dementia treatment agents thought to provide the greatest therapeutic yield earliest in the disease process. Although head trauma has been linked to irreversible cognitive deficits (24, 29, 30), its role in causing eventual MCI or AD is less clear. Mayeux et al. (20) reported a 10-fold increase in the risk of developing AD among those individuals who tested positive for the ApoE e4 gene and had a history of TBI, compared with only a two-fold increase in risk with the ApoE e4 gene alone. Other authors have described a genetic vulnerability and redistribution of neurofilaments after TBI resulting from rotational acceleration of the head in the nonathletic population (12, 27).

The relatively high rate of concussive brain injuries in contact sports affords a unique opportunity for exploring both the immediate and long-term consequences of concussion. More than 300,000 sport-related concussions, many of which are recurrent injuries, occur annually in the United States (38). Unfortunately, the long-term effects of these concussions remain largely unclear. Organized sports, however, provides for a unique laboratory for studying the influence of recurrent mild TBI on dementia-related syndromes such as MCI and AD. The sports literature has connected ApoE e4 with chronic TBI in boxers (16), and other studies have shown that the repeated head trauma experienced by boxers can lead to the development of dementia pugilistica—punch drunk syndrome (32). This literature has also carefully defined the neuropathology of dementia pugilistica as involving numerous neurofibrillary tangles in the absence of plaques, in contrast to the profusion of tangles and plaques seen in AD. Lower cognitive performance has also been found in older football players with the ApoE e4 gene, suggesting that there may be an association between these dementia syndromes and either recurrent TBI or recurrent subconcussive contacts to the head (18). The purpose of our study was to investigate the association between previous head injury and the likelihood of developing MCI and/or AD in a unique group of individuals, namely retired professional football players, who have previous head injury exposure.

PATIENTS AND METHODS

A diverse group of retired professional football players were studied, including recent retirees and those who played professional football before World War II. All participants played a minimum of two seasons of professional football. We studied this group using two self-report questionnaires: a general health survey and a follow-up instrument specifically targeting cognitive decline. It was explained at the beginning of the survey that participants would not be identified and that research records would be kept confidential. By completing and submitting the survey, participants were acknowledging that they agreed to take part in this research study.

General Health Questionnaire

The general health questionnaire was first sent to all living members of the National Football League Retired Player's Association (n = 3683) through the Center for the Study of Retired Athletes. The questionnaire asked a variety of questions about musculoskeletal, cardiovascular, and neurological conditions that the retired player experienced during and after his football career. It included questions about the number of concussions sustained during their professional football career (concussion history) and the prevalence of diagnosed medical conditions such as depression, Parkinson's disease, AD, and schizophrenia. Previous concussion was based on the player's retrospective recall of injury events and was defined on the questionnaire as an injury resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, and difficulty concentrating. Additionally, the questionnaire included the SF-36 Measurement Model for Functional Assessment of Health and Well-Being, which addresses how well the retired athlete functions with activities of daily living (41). From the SF-36, we calculated a physical health composite score, which includes scores of physical functioning, role physical, bodily pain, and general health, as well as a mental health component score, which includes scores of vitality, social functioning, role emotional, and mental health. These scores were compared with age- and gender-specific population-based norms established by previous researchers (41).

We initially mailed the general health questionnaire in May 2001, followed by remailings to nonrespondents in August 2001 and February 2002. We then began telephoning nonrespondents at different times of the day and completed the questionnaire over the telephone. We then conducted a reliability check of the general health questionnaire by readministering the instrument to 25 of the original respondents 18 to

24 months later to establish a high level of agreement between selected responses.

Mild Cognitive Impairment Instrument

Approximately 4 months later, a second questionnaire focusing on memory and issues related to MCI was sent to a subset of 1754 retirees. The subset comprised all respondents from the original health questionnaire who were aged 50 years or older. The same instrument was also sent to an informant (spouse or close relative) to collect data on any cognitive problems exhibited by the retiree that were not reported on the retiree's instrument. Results from the MCI questionnaire were then cross-tabulated with results from the original general health questionnaire. MCI was defined according to the following, outlined in the American Academy of Neurology Practice Parameter (30): memory complaint corroborated by a family member; objective memory impairment as determined by neurocognitive testing; intact activities of daily living; and does not meet accepted diagnostic criteria for probable AD or other forms of dementia.

Statistical Analysis

X^2 tests of association were used to compare proportions in tables; Fisher's exact test was used when 80% of expected cell counts were less than five. Analysis of variance models were used to determine differences among the groups on selected variables. The groups were stratified by concussion history (none, one, two, and three or more). Because of the sample size, some analyses required us to collapse respondents with one and two previous concussions into a single group (one to two previous concussions). We used the Cochran-Armitage trend test to assess linear trends in the proportion of retirees reporting memory impairments and problems across strata of concussion history. Level of significance for all analyses was set a priori at $P < 0.05$. Estimates of the prevalence of AD in the general population of American men, stratified by age, were provided by researchers at the Johns Hopkins University (2).

RESULTS

General Health Questionnaire

Of the original 3683 general health surveys sent to retired players, 2552 (69.3%) were completed. The age of the respondents averaged 53.8 (±13.4) years, with an average professional football playing career of 6.6 (±3.6) years. Respondents reported having played organized football (junior high school, high school, college, armed service, and professional) for an average of 15.1 (± 4.3) years. When considering the prevalence of previous concussions, 1513 (60.8%) of the retired players reported having sustained at least one concussion during their professional playing career, and 597 (24%) reported sustaining three or more concussions. Of those retired players who had sustained a concussion during their professional career, more than half reported experiencing loss of consciousness (n = 817, 54.0%) or memory loss (n = 787, 52.0%) from at least one of their concussive episodes. We asked the retired athletes for their subjective assessment of the long-term consequences of their injuries. Of the retirees who sustained at least one concussion, 266 (17.6%) reported that they perceived the injury to have had a permanent effect on their thinking and memory skills as they have gotten older.

Only 33 (1.3%) retired players reported being diagnosed by a physician as having AD; 15 were undergoing medical treatment for the disease. We observed a higher prevalence of AD in the study population relative to the general American male population (*Fig. 1*). The overall age-adjusted prevalence ratio for AD was 1.37 (95% confidence interval 0.98–1.56), which indicates that the football retirees have higher prevalence than other American men of the same age. The AD prevalence in the football retirees was particularly increased in the younger age groups (≤70 yr), which suggests that this group may have an earlier onset of AD than the general American male population. The average age of the retired players with AD was 71.7 (± 7.62) years (range, 52–83 yr). There was, however, no association between number of concussions sustained as a professional player (none, one, two, and three or more) and a diagnosis of AD (Fisher's exact test, $P = 0.24$).

Mental Component Scale (MCS) scores on the SF-36 were similar between the NFL retirees and population-based normative values for all age groups ($P > 0.05$) (*Fig. 2*); however, retired players with a history of concussion, especially recurrent concussion, scored lower (worse) on the MCS than those without a history of recurrent concussion (F [3,2146] = 19.29, $P = 0.001$). The lowest MCS scores were observed in those with the most reported concussions (*Table 1*). The group who experienced three or more concussions also scored significantly worse than the normative group on the age-matched MCS (50.31 versus 52.42).

Mild Cognitive Impairment Instrument

Results of the follow-up MCI and memory questionnaires were analyzed based on responses from 758 retired players (average age, 62.4 yr) and 641 retired players' spouses or close relatives. Our findings revealed 22 cases of physician-diagnosed MCI and 77 cases of retirees who have significant

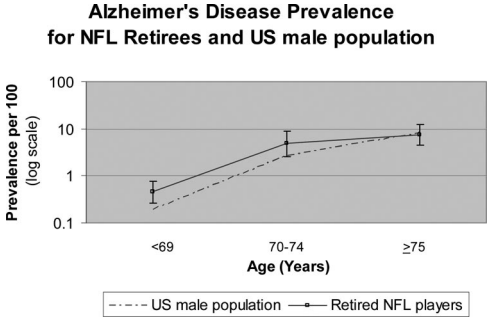

FIGURE 1. *Alzheimer's disease prevalence ratios for the American male population and National Football League (NFL) retirees.* Error bars *indicate 95% confidence intervals.*

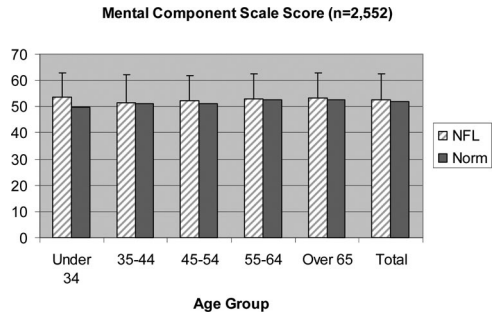

FIGURE 2. *MCS scores for the NFL retirees and population norms by age. "Total" is age-standardized;* error bars *indicate 95% confidence intervals.*

TABLE 1. Mental Component Scale score by concussion history in retired National Football League players aged 50 years or older[a]

No. of previous concussions	Mean MCS score and 95% CI	Standard deviation
0 (n = 814)	54.35 (53.77, 54.94)	(8.50)
1 (n = 429)	52.63 (51.73, 53.52)	(9.47)
2 (n = 374)	52.97 (52.03, 53.91)	(9.22)
3+ (n = 533)	50.31 (49.35, 51.27)	(11.26)

[a] MCS, mental component scale; CI, confidence interval. $P < 0.001$; β -1.51 (0.26).

memory impairment as determined by their spouse or close relative. Further analyses of these data identified an association between recurrent concussion and clinically diagnosed MCI ($\chi^2 = 7.82$, df = 2, $P = 0.02$); self-reported significant memory impairments ($\chi^2 = 19.75$, df = 2, $P = 0.001$); and spouse/relative-reported significant memory impairments ($\chi^2 = 6.05$, df = 2, $P = 0.04$). Retired players with three or more reported concussions had a fivefold prevalence of being diagnosed with MCI and a threefold prevalence of reported significant memory problems compared with those players without a history of concussion (*Fig. 3*). There was no association between MCI and other systemic factors such as coronary heart disease, hypertension, diabetes, or osteoarthritis. Although we found an association between diagnosis of MCI and stroke, this association does not detract from the association between MCI and concussion history. Only three (13.6%) of the 22 MCI cases involved stroke, and we do not know which diagnosis came first.

DISCUSSION

These data suggest that a history of concussion, particularly recurrent concussion, may be a risk factor for the expression of late-life memory impairment, MCI, and AD. Although the

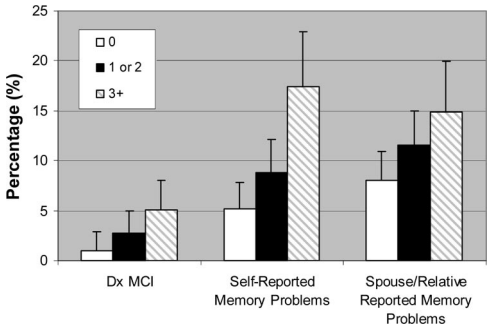

FIGURE 3. *Percentage of retired players aged 50 years or older with a diagnosis of MCI and memory problems (self-reported and reported by a spouse or close relative) by concussion history (none, one, two, and three or more).* Error bars *indicate 95% confidence intervals.* $P < 0.007$.

clinical samples studied are relatively small, retired professional football players were found to have a progressive decline in mental health functioning and a higher rate of memory problems and cognitive decline associated with a history of concussion. Retired players with a history of three or more concussions were at highest risk of being diagnosed by a physician as having MCI and of having significant memory problems based on their own account and the observations of their spouse or caregiver.

Data from a small sample of retired athletes medically diagnosed with probable AD also suggests a trend toward earlier disease onset and higher disease prevalence in younger cohorts relative to the general population (*Fig. 1*). Despite the earlier onset of AD, we failed to find an association between previous concussion and lifetime onset of AD. The cumulative effect of sub-concussive and concussive contacts to the head sustained by professional football players may promote an earlier expression of AD; however, the factor of age eventually overwhelms this factor and prevents it from becoming an independent predictor of lifetime onset of AD. Thus, the lines in *Figure 1* representing the two groups (American male population and retired NFL players) eventually converge.

The number of individuals in the United States with AD was estimated at 2.32 million in 1997, and it is projected that the prevalence will nearly quadruple in the next 50 years, by which time 1 in 45 Americans will be afflicted with the disease (2). As a result, AD is sure to place a large burden on the country's health care system in the decades ahead. For this reason, identification of factors associated with precursor conditions to AD are of interest. The pathology is characterized by cerebral atrophy most severe in frontal, temporal, and parietal lobes resulting in a dramatic reduction of brain weight (normal, 1500–1800 g; AD, 850–1250 g). Microscopic findings include senile plaques, neurofibrillary tangles, and granulovascular degeneration. Biomechanically, there is a 50 to 90% reduction in choline acetyltransferase (5, 15, 17, 23, 36, 37, 39). Clinically, AD presents with a progressive decline in cortical functions principally affecting memory, language, and executive functioning, followed by increasing neurobehavioral and

neuropsychiatric deficits in more advanced stages of the disease (2, 5, 6).

The study of MCI and AD is challenging because of the difficulties in diagnosing the conditions. Both conditions can be evaluated using several measures, but they cannot be diagnosed solely on neuropsychological assessment. Petersen et al. (29, 30) state that the usefulness of any neuropsychological battery for identifying cases of MCI depends on its composition, size, and supporting data. The battery should include measures of new learning, delayed recall, attention, and executive function. Neuroimaging is also considered a powerful tool for the differential diagnosis of cognitive impairment and tracking change (30). Hippocampal atrophy has been identified in amnestic MCI relative to cognitively intact controls, and it is believed that volumetric measurement of this atrophy can predict the rate of conversion from MCI to AD (15).

The human ApoE gene encodes a cholesterol carrier lipoprotein (apolipoprotein E) that is made in the liver and brain and is important in the transport of lipids in the brain. There are three allelic forms (ApoE e2, e3, e4) that give rise to six possible genotype combinations. ApoE plays an important role in the response of the brain to injury. After accelerator forces are imparted to the brain, there is an accumulation of beta amyloid and tau proteins within hours of injury within the neuronal body (12). Possession of the e2 allele is now believed to be underrepresented in AD and may be protective (22). On the other hand, possession of ApoE e4 increases the risk of AD, shifts onset to an earlier age, increases the accumulation of amyloid beta protein in AD and TBI, and decreases recovery after TBI (6, 7, 12, 19, 20).

The sports literature also suggests that possessing the ApoE e4 allele results in greater cognitive impairment after mild repetitive head injury. Older professional football players with the ApoE e4 allele score lower on cognitive tests than players without the allele or less experienced players of any genotype (18). The study clearly suggests that the cognitive status of athletes with repeated head trauma is influenced by age, inherited factors such as ApoE e4, and cumulative exposure to head contact.

Jordan et al. (16) came to similar conclusions in their study of boxers. The boxers with higher exposure (defined by number of bouts) had significantly higher chronic brain injury scores than those with low exposure. Boxers with low exposure had low chronic brain injury scores irrespective of ApoE e4 allele genotype, whereas those with high exposure and the ApoE e4 allele had higher chronic brain injury scores than boxers with high exposure and no ApoE e4 allele. Possession of the ApoE e4 allele was associated with an increased severity of neurological deficits in the high-exposure boxers.

To our knowledge, our study is unique in evaluating the risk of recurrent mild TBI in the development of later-life memory disorders and MCI. These data describe a significant association between recurrent concussion and MCI, as well as with self-reported memory impairments confirmed by a spouse or close relative. Retired professional football players with three or more concussions were twice as likely to be diagnosed with MCI as those with one or two previous concussions, and five times more likely than those with no previous concussions. This trend continued with respect to self-reported significant memory problems. These findings suggest that the clinical features of dementia-related syndromes, such as reductions in synaptic density, loss of neurons, and granulovacuolar degeneration, may be initiated by repetitive cerebral concussions. Other recent peer-reviewed studies of recurrent concussion have identified an acute cumulative effect of concussion as measured by increased symptomatology or slowed recovery on symptom checklists and neuropsychological tests after subsequent injuries in high school and collegiate athletes (4, 10, 11, 14). These acute or short-term consequences of recurrent concussion should be of great interest to the sports medicine community, especially given that they parallel our findings of more chronic consequences after years of playing football.

Our study is influenced by the limitations of any retrospective self-report study. The study is limited by the uncertainty of how well the retired players recalled the concussions sustained during their careers and the accuracy of reporting memory problems and diagnosis of MCI. Recent literature has reported selective preservation of older information in subjects with AD-related dementia, which suggests that recollection of events involving previous injuries is not unlikely in these retired athletes (34). The purpose of the spouse or close relative questionnaire was to confirm the retired players' memory status and any physician-diagnosed MCI. For cases in which there was disagreement in the responses of the retiree and the spouse or relative, phone calls and medical records were used to confirm the diagnosis. When the difference in responses could not be reconciled, the case was eliminated from the analyses. Another limitation of our study is that we do not currently know the ApoE allele form of these retired players, which might help to better understand some of these relationships.

CONCLUSIONS

Despite the limitations, these data suggest some very interesting findings—that a history of recurrent concussions, and probably sub-concussive contacts to the head, may be risk factors for the expression of late-life memory impairment, MCI, and AD. Our findings demonstrate a dose-response relationship between concussion and an increased lifetime burden; however, prospective longitudinal cohort studies are necessary to determine causality. Future prospective studies should implement genetic testing, more rigorous diagnostic criteria, historical documentation, and extensive serial evaluations (e.g., neuropsychological testing, functional neuroimaging) to clarify the direct or mitigating effects of concussion on lifetime risk of dementia or other neurological disorders.

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Acknowledgments

We thank Ron Brookmeyer, Ph.D., of the Johns Hopkins University, for providing data on the projected prevalence of Alzheimer's disease in the general American population.

COMMENTS

The significance of repeated concussions is a question of great interest to all athletes, from players in grade schools to professionals. Anecdotes suggest that repetitive concussions may have a detrimental effect, but more rigorous analyses of this question have been less conclusive. In this report, Dr. Guskiewicz et al. surveyed retired professional football players, first by asking them to complete a general health questionnaire and subsequently by sending them a second questionnaire focusing on memory problems and cognitive impairment. Their data suggest that recurrent concussions seem to be related to mild cognitive impairment diagnosed by a physician and to be related to self-reported memory problems. These associations seemed to be stronger in patients with three or more reported concussions. Alzheimer's disease may have occurred at an earlier age in former National Football League players than in the population as a whole, but the number of patients with this diagnosis was quite small.

Like all retrospective studies that rely upon self-reported medical histories and health problems, this one is subject to bias in the accuracy with which problems were recalled and reported. Nevertheless, these results are of considerable interest. The authors make appropriate recommendations for further prospective studies to include such factors as genetic testing, standardized diagnostic criteria, and more extensive evaluation of players with concussion, perhaps including neuropsychological testing and functional neuroimaging.

Alex B. Valadka
Houston, Texas

The safety of contact sports and likelihood of neurologic impairment occurring after retiring from the sport are of obvious concern to athletes and to parents deciding on which sports they should allow their kids to participate in. Studies such as this have the potential to provide important information in this regard. Unfortunately, this particular study is confounded by a critical design flaw of relying on retired athletes to accurately recall events from decades earlier and relating those events to their current memory problems. The study would have been much stronger had the authors corroborated the frequency and severity of concussions sustained with independent sources.

Donald Marion
Boston, Massachusetts

Thank you for the opportunity to comment on this excellent and extremely important study. The authors have used the tremendous resource of a database of the National Football League Retired Players Association, which contains 3683 individuals who played football at a high level for an average of 15 years (minimum six yrs of professional-level football). Using carefully constructed retrospective questionnaires, they have shown a strong association between three or more concussions sustained during a players' professional football career and mild cognitive impairment.

Although this evidence was the most compelling, they also showed an earlier onset and increased incidence of Alzheimer's disease in this group of professional football players who received concussions frequently than in the general age-matched male population in the United States.

This study has important and far-reaching implications. To my knowledge, this is one of few studies to show a positive association between repetitive concussion and long-term cognitive impairment and Alzheimer's disease (1–4). Therefore, this study documents the dangers of contact sports, such as professional football. As professional football evolves, the speed of the plays appears to be increasing, the prowess, strength, and size of the athletes is measurably increasing, and, therefore, the potential for concussions, especially higher-impact energy concussions, is increasing. It is important to know whether the incidence of multiple concussions per player each year is increasing over time, and this invaluable cohort provides such details by including players with a history as far back as pre-World War II.

What are the implications for the future of the game? Possibly, rules could be tightened to limit the types of dangerous plays, but, in the "heat of the game," this may be unlikely. Helmet design has evolved tremendously in recent years (3), and clearly, studies with kinematic accelerometers of the type used in crash-test dummies by the auto industry should be performed and correlated with the "action replays," which are such an exciting facet of modern televised football. In this way, it may be possible to modify the game in ways that are compatible with increased safety without decreasing the spectator appeal of the game. New types of energy-absorbing foam and plastic are becoming available for football helmets.

However, as with professional boxing, athletes who undertake high-impact sports need to be fully and demonstrably informed of the risks that they undertake in pursuit of their vocation. This important study will provide a basis upon which players' associations and teams can formulate decisions.

Do the implications of these data go further? Many have called for apolipoprotein E genotyping of professional boxers to reduce the risk of precipitating Alzheimer's disease in apolipoprotein E e4 homozygous boxers. Should the same apply to professional football players, ice hockey players, and rugby players?

The authors have demonstrated that they have access to an enormous "data mine" to test the role of long-term physical fitness upon the development of delayed degenerative joint disease, low back disorders, and cardiovascular mortality. Do the cumulative effects of strains, sprains, and fractures, which are the inevitable consequence of professional football, outweigh the beneficial effect of many years of peak physical fitness upon the musculoskeletal system?

M.R. Ross Bullock
Richmond, Virginia

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Dr. Guskiewicz et al. have assessed by questionnaire a large number of retired professional football players to assess the incidence of concussions and more serious head injuries sustained during their playing careers and to determine whether such injuries influenced the subsequent development of Alzheimer's disease or mild cognitive impairment. Their results indicated that football players with repetitive concussion injuries (three or more) have a fivefold prevalence of mild cognitive impairment and a threefold increase in self-reported

memory problems. The authors also suggest a 'soft' association between concussion and Alzheimer's disease.

This is an interesting paper that poses an intriguing hypothesis regarding the consequences of recurrent concussion, not only to create short-term problems, but also to accelerate the decline of cognitive function in later years. While tantalizing, the findings are soft. This data is derived from a questionnaire administered to a group that may have substantial bias, especially considering the recent reports and concerns expressed by physicians and the media. How did the authors pare down the original 2552 respondents to 758 whose memory questionnaires were analyzed? Figure one suggests an earlier onset of Alzheimer's disease in respondents aged less than 69 years, but the trend corrects by the age of 75. If the hypothesis is correct, why shouldn't this early separation persist or widen over time?

As usual, the data in sports medicine is difficult to control. Despite its shortcomings, it is reasonable that this paper should be published, not on the basis of its science, but on its conjecture and the need for neurosurgeons to be more aware of the current information in this area.

Arthur L. Day
Boston, Massachusetts

This latest manuscript on the relationship between cognitive impairment and recurrent concussion focuses on players from the National Football League. As in previous studies, there is an association between the frequency of recurrent concussion, the development of mild cognitive impairment, and the suggestion that Alzheimer's disease develops earlier in such patients. This trend is potentially of interest, but a larger sample is necessary.

One concern with the manuscript is the lack of controls in other sports where aggressive behavior is common but concussion is relatively rare, such as in wrestling. There may be genetic linkage to aggressive behavior and cognitive impairment later in life, which is separate from concussion. Perhaps the link is unlikely, but such controls in future studies would help support the hypothesis. Clearly, this is an area of continuing interest and the authors work is important.

Lawrence F. Marshall
San Diego, California

Unfortunately, this manuscript reflects the low priority our society places on the prevention of head injuries and the major sequelae. It attempts to address the significant concern that repeated head injury leads to brain damage. Injury prevention programs, such as ThinkFirst, confront the lack of accurate studies on the potential damage of head trauma such as those sustained by both amateur and professional athletes.

The present study does not dispel uncertainties regarding the relationship between repeated concussions and subsequent onset of brain disorders, most importantly Alzheimer's disease. The study suffers from lack of professionally obtained prospective data. The glaring deficiency of this study is its reliance on questionnaires from patients and relatives that were obtained retrospectively. Society must provide the author with the necessary funds and incentive to do the study correctly based on professionally obtained prospective data. Regrettably, the questions raised by the authors are of great importance to society and remain unanswered.

Charles H. Tator
Toronto, Ontario, Canada

This is an extremely valuable contribution. Most concussion studies focus on the days and weeks following the injury with the implicit assumption that recovery to preinjury levels is the end of the issue. The present paper provides strong suggestion that some residua of a concussion may not become manifest until decades after the injury. The study also provides a strong rationale for future studies focusing on the effects of concussion on cognitive reserves, rather than simply on performance in the immediate aftermath of injury. Moreover, because the present study demonstrates a dose-response relation between concussion and future cognitive disorder, it highlights the importance of reducing lifetime burden of concussion in athletes.

The authors are to be commended for clearly stating the limitations of their retrospective self-report experimental design. However, the 'gold-standard' methodology would require a multi-decade prospective study. While I think the present findings support the need for a prospective inception-cohort study on this question, this should not overshadow the importance of the present findings and the importance of additional follow-up studies exploring the pathophysiological underpinnings of the present findings.

Joseph Bleiberg
Neuropsychologist
Washington, D.C.

This is an important paper on the relationship between cerebral concussion and subsequent cognitive impairment in retired professional football players. Its major flaw, as the authors acknowledge, is that the history of previous concussion was based on the players' 'retrospective recall of injury events.' Nonetheless, their data strongly suggests there is a cumulative deleterious effect of repeated concussion on later cognitive function. It further emphasizes the need to enhance protective measures that minimize concussion in contact sports and to carefully follow players by documenting the number and severity of concussive events throughout their careers. Finally, given the increasing data concerning the long-term risk of greater cognitive impairment for concussed individuals carrying the apolipoprotein E e4 allele, genetic screening and counseling of individuals about to embark on a potentially long career of contact sports should be considered.

Daniel F. Kelly
Los Angeles, California

EXHIBIT 3

It's not concussions that cause CTE. It's repeated hits, a study finds

CNN.com

January 18, 2018 Thursday 5:32 PM EST

Section: HEALTH

Length: 1015 words

Byline: By Nadia Kounang, CNN

Body

The neurodegenerative disease chronic traumatic encephalopathy can start early and without any signs of concussion, according a study released Thursday.

The Alzheimer's-like disease has been most commonly associated with former professional football players, but has also been detected in military veterans, including many who have been exposed to roadside bombs and other types of military blasts.

Previous studies have shown that repetitive hits to the head -- even without concussion -- can result in CTE, but scientists said this is the most definitive study to date to find this connection.

"Now we have both the scientific proof, the pathologies to support it, and all the evidence to show that concussion is not linked to long-term neurological disease," said Dr. Lee Goldstein, one of the authors on the study, published in the journal Brain.

Goldstein and his colleagues from Boston University evaluated the brains of four deceased athletes, ages 17 and 18 years old. All four had died within a day to four months of receiving some sort of sport-related head injury and had a history of playing football.

Brain changes detected by 24 hours

In all four brains, there were already changes to the brain that could be indicators of CTE, including leaky blood vessels and abnormal buildups of the protein tau.

Some of these changes in the brain occurred as early as 24 hours after injury. Goldstein said one of the cases could be diagnosed as early-stage CTE.

What researchers found under the microscope was striking, said Goldstein. "We're seeing the earliest pathology soon after one of these injuries," he said.

The four specimens were compared to brains from four other athletes of similar age who had not experienced any recent head trauma before death. The brains in this group had no changes in their pathology.

Concussion 'not telling you anything about the brain'

While it seems likely that the recent head injuries could be the source of the brain changes, Goldstein said, "we can infer it, but we can't prove it."

To try and understand the source of the changes, Goldstein and his colleagues mimicked the experiences of the human brains in mouse models, by exposing mice to repeated head trauma, like that in football, and single blast head trauma, similar to military combat.

The researchers found similar pathologies in both the mouse and human brains, regardless of the type of blast exposure they had experienced. Goldstein and his colleagues also measured the mice for concussion-like symptoms by testing their arousal and balance. They found that even without concussion, the mice exposed to the head trauma still exhibited changes in the brain.

Concussion is "not only not correlated, we can decouple it," said Goldstein. He said that concussion itself is not the injury, but rather the symptoms experienced from injury, such as memory impairment or loss of balance.

But not everyone experiences these symptoms, and so "by looking at concussion, it's not telling you anything about the brain or CTE," he added.

Using animal models and computer modeling, Goldstein and his partners were able to see progression of the disease, finding that as tau built up, it began to work its way through the brain.

Currently, the only way to diagnose CTE is with an autopsy after death. Researchers are working on finding biomarkers and other indicators to help detect it in the living, with further hope that such findings can help lead to potential treatments.

Goldstein said that while the new work advanced understanding of the mechanisms underlying CTE, it's not clear how frequently people experience these types of changes in the brain. "We don't know how to weight the information," he said.

But the risk of CTE is worrisome enough that children shouldn't be playing tackle football, said Pro Football Hall of Famer Nick Buoniconti. The legendary Miami Dolphins player suffers from dementia and has been diagnosed with probable CTE.

"Now, CTE has taken my life away. Youth tackle football is all risk with no reward," he said.

Buoniconti and Goldstein joined other former players and researchers to launch the Concussion Legacy Foundation's Flag Football Under 14 initiative on Thursday. The campaign aims to warn parents about the dangers of football's repetitive hits.

'It starts early. It persists'

"I think [this research] really reinforces, as we have suspected, [the idea] that it's not concussion per se, it's the exposure to multiple head impacts," said Dr. Julian Bailes, the director of neurosurgery and co-director of NorthShore University HealthSystem Neurological Institute, who was not involved in the study. Bailes was one of the first researchers to connect repeated head trauma to neurological damage in football players.

A recent evaluation from Boston University's CTE Center found that 110 of 111 former NFL players had been diagnosed with the disease. However, there is a potential bias, as many of the studied brains came from players who experienced clinical CTE symptoms when living, such as memory loss, rage and mood swings.

In addition, scientists are also trying to unravel the role other factors play in the disease -- factors such as genetics, how early someone is exposed to head trauma, and how long they've been exposed to trauma.

While it's not clear how common CTE is, Goldstein said the brains examined in the new study are a warning.

"CTE develops early, soon after injury. It doesn't take years, or decades. It starts early. It persists. And all of our evidence to date shows it's progressive."

Goldstein hopes policy makers, professional players and parents heed the warning that CTE can develop early -- and that focus on concussions doesn't reduce the risk. Instead he said it was important to focus on ways about how to reduce total overall exposure to repeated hits, such as limiting head-to-head contact.

"Most hits to the head are not concussive ... but no one is paying any attention to them," said Goldstein.

But, he remains optimistic for the future of football.

"You can play football differently. There are all sorts of ways to do it more safely," he said.

Load-Date: January 19, 2018

End of Document

EXHIBIT 4

21 C.F.R. § 201.57

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

Effective: June 30, 2015
Currentness

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA–approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) Highlights of prescribing information. The following information must appear in all prescription drug labeling:

(1) Highlights limitation statement. The verbatim statement "These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)."

(2) Drug names, dosage form, route of administration, and controlled substance symbol. The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by § 1302.04 of this chapter.

(3) Initial U.S. approval. The verbatim statement "Initial U.S. Approval" followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on the line immediately beneath the established name or, for biological products, proper name of the product.

(4) Boxed warning. A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately following the heading of the boxed warning: "See full prescribing information for complete boxed warning."

(5) Recent major changes. A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(6) Indications and usage. A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

(7) Dosage and administration. A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information.

(8) Dosage forms and strengths. A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10–milligram tablets) and whether the product is scored.

(9) Contraindications. A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) Warnings and precautions. A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) Adverse reactions.

(i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number and Web address for voluntary reporting of adverse reactions)."

(iii) For vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or VAERS at (insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions)."

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

(12) Drug interactions. A concise summary of the information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(13) Use in specific populations. A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings.

(14) Patient counseling information statement. The verbatim statement "See 17 for Patient Counseling Information" or, if the product has FDA–approved patient labeling, the verbatim statement "See 17 for Patient Counseling Information and (insert either FDA–approved patient labeling or Medication Guide)."

(15) Revision date. The date of the most recent revision of the labeling, identified as such, placed at the end of Highlights.

(b) Full prescribing information: Contents. Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) Full prescribing information. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) 1 Indications and usage. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the "Dosage and Administration" section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(iv) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this

chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(3) 2 Dosage and administration.

(i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

(iii) Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

(iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")

(4) 3 Dosage forms and strengths. This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and

(ii) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

(5) 4 Contraindications. This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section must state "None."

(6) 5 Warnings and precautions.

(i) General. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a)

of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) Other special care precautions. This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

(iii) Monitoring: Laboratory tests. This section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) Interference with laboratory tests. This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

(7) 6 Adverse reactions. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) Listing of adverse reactions. This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) Categorization of adverse reactions. Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) Clinical trials experience. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail

about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) Postmarketing experience. This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

(iii) Comparisons of adverse reactions between drugs. For drug products other than biological products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, any such claim must be based on substantial evidence.

(8) 7 Drug interactions.

(i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the "Contraindications" or "Warnings and Precautions" sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.

(ii) This section must also contain practical guidance on known interference of the drug with laboratory tests.

(9) 8 Use in specific populations. This section must contain the following subsections:

(i) 8.1 Pregnancy. This subsection of the labeling must contain the following information in the following order under the subheadings "Pregnancy Exposure Registry," "Risk Summary," "Clinical Considerations," and "Data":

(A) Pregnancy exposure registry. If there is a scientifically acceptable pregnancy exposure registry for the drug, contact information needed to enroll in the registry or to obtain information about the registry must be provided following the statement: "There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (name of drug) during pregnancy."

(B) Risk summary. The Risk Summary must contain risk statement(s) based on data from all relevant sources (human, animal, and/or pharmacologic) that describe, for the drug, the risk of adverse developmental outcomes (i.e., structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth). When multiple data sources are available, the statements must be presented in the following order: Human, animal, pharmacologic. The source(s) of the data must be stated. The labeling must state the percentage range of live births in the United States with a major birth defect and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug exposure. If such information is available for the population(s) for which the drug is labeled, it must also be included. When use of a

drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary. When applicable, risk statements as described in paragraphs (c)(9)(i)(B)(1) and (2) of this section must include a cross-reference to additional details in the relevant portion of the "Data" subheading in the "Pregnancy" subsection of the labeling. If data demonstrate that a drug is not systemically absorbed following a particular route of administration, the Risk Summary must contain only the following statement: "(Name of drug) is not absorbed systemically following (route of administration), and maternal use is not expected to result in fetal exposure to the drug."

(1) Risk statement based on human data. When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, the Risk Summary must summarize the specific developmental outcome(s); their incidence; and the effects of dose, duration of exposure, and gestational timing of exposure. If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, this risk must be quantitatively compared to the risk for the same outcome in infants born to women who were not exposed to the drug but who have the disease or condition for which the drug is indicated to be used. When risk information is not available for women with the disease or condition for which the drug is indicated, the risk for the specific outcome must be compared to the rate at which the outcome occurs in the general population. The Risk Summary must state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk.

(2) Risk statement based on animal data. When animal data are available, the Risk Summary must summarize the findings in animals and based on these findings, describe, for the drug, the potential risk of any adverse developmental outcome(s) in humans. This statement must include: The number and type(s) of species affected, timing of exposure, animal doses expressed in terms of human dose or exposure equivalents, and outcomes for pregnant animals and offspring. When animal studies do not meet current standards for nonclinical developmental toxicity studies, the Risk Summary must so state. When there are no animal data, the Risk Summary must so state.

(3) Risk statement based on pharmacology. When the drug has a well-understood mechanism of action that may result in adverse developmental outcome(s), the Risk Summary must explain the mechanism of action and the potential associated risks.

(C) Clinical considerations. Under the subheading "Clinical Considerations," the labeling must provide relevant information, to the extent it is available, under the headings "Disease-associated maternal and/or embryo/fetal risk," "Dose adjustments during pregnancy and the postpartum period," "Maternal adverse reactions," "Fetal/Neonatal adverse reactions," and "Labor or delivery":

(1) Disease-associated maternal and/or embryo/fetal risk. If there is a serious known or potential risk to the pregnant woman and/or the embryo/fetus associated with the disease or condition for which the drug is indicated to be used, the labeling must describe the risk.

(2) Dose adjustments during pregnancy and the postpartum period. If there are pharmacokinetic data that support dose adjustment(s) during pregnancy and the postpartum period, a summary of this information must be provided.

(3) Maternal adverse reactions. If use of the drug is associated with a maternal adverse reaction that is unique to pregnancy or if a known adverse reaction occurs with increased frequency or severity in pregnant women, the labeling must describe the adverse reaction and available intervention(s) for monitoring or mitigating the reaction. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk to the pregnant woman of experiencing the adverse reaction.

(4) Fetal/Neonatal adverse reactions. If it is known or anticipated that treatment of the pregnant woman increases or may increase the risk of an adverse reaction in the fetus or neonate, the labeling must describe the adverse reaction, the potential severity and reversibility of the adverse reaction, and available intervention(s) for monitoring or mitigating the reaction. The labeling must describe, if known, the effect of dose, timing, and duration of exposure on the risk.

(5) Labor or delivery. If the drug is expected to affect labor or delivery, the labeling must provide information about the effect of the drug on the pregnant woman and the fetus or neonate; the effect of the drug on the duration of labor and delivery; any increased risk of adverse reactions, including their potential severity and reversibility; and must provide information about available intervention(s) that can mitigate these effects and/or adverse reactions. The information described under this heading is not required for drugs approved for use only during labor and delivery.

(D) Data—

(1) "Data" subheading. Under the subheading "Data," the labeling must describe the data that are the basis for the Risk Summary and Clinical Considerations.

(2) Human and animal data headings. Human and animal data must be presented separately, beneath the headings "Human Data" and "Animal Data," and human data must be presented first.

(3) Description of human data. For human data, the labeling must describe adverse developmental outcomes, adverse reactions, and other adverse effects. To the extent applicable, the labeling must describe the types of studies or reports, number of subjects and the duration of each study, exposure information, and limitations of the data. Both positive and negative study findings must be included.

(4) Description of animal data. For animal data, the labeling must describe the following: Types of studies, animal species, dose, duration and timing of exposure, study findings, presence or absence of maternal toxicity, and limitations of the data. Description of maternal and offspring findings must include dose-response and severity of adverse developmental outcomes. Animal doses or exposures must be described in terms of human dose or exposure equivalents and the basis for those calculations must be included.

(ii) 8.2 Lactation. This subsection of the labeling must contain the following information in the following order under the subheadings "Risk Summary," "Clinical Considerations," and "Data":

(A) Risk summary. When relevant human and/or animal lactation data are available, the Risk Summary must include a cross-reference to the "Data" subheading in the "Lactation" subsection of the labeling. When human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans. When use of a drug is contraindicated during breastfeeding, this information must be stated first in the Risk Summary.

(1) Drug not absorbed systemically. If data demonstrate that the drug is not systemically absorbed by the mother, the Risk Summary must contain only the following statement: "(Name of drug) is not absorbed systemically by the mother following (route of administration), and breastfeeding is not expected to result in exposure of the child to (name of drug)."

(2) Drug absorbed systemically. If the drug is absorbed systemically, the Risk Summary must describe the following to the extent relevant information is available:

(i) Presence of drug in human milk. The Risk Summary must state whether the drug and/or its active metabolite(s) are present in human milk. If there are no data to assess this, the Risk Summary must so state. If studies demonstrate that the drug and/or its active metabolite(s) are not detectable in human milk, the Risk Summary must state the limits of the assay used. If studies demonstrate the presence of the drug and/or its active metabolite(s) in human milk, the Risk Summary must state the concentration of the drug and/or its active metabolite(s) in human milk and the actual or estimated daily dose for an infant fed exclusively with human milk. The actual or estimated amount of the drug and/or its active metabolite(s) ingested by the infant must be compared to the labeled infant or pediatric dose, if available, or to the maternal dose. If studies demonstrate the presence of the drug and/or its active metabolite(s) in human milk but the drug and/or its active metabolite(s) are not expected to be systemically bioavailable to the breast-fed child, the Risk Summary must describe the disposition of the drug and/or its active metabolite(s). If only animal lactation data are available, the Risk Summary must state only whether or not the drug and/or its active metabolite(s) were detected in animal milk and specify the animal species.

(ii) Effects of drug on the breast-fed child. The Risk Summary must include information, on the known or predicted effects on the child from exposure to the drug and/or its active metabolite(s) through human milk or from contact with breast or nipple skin (for topical products). The Risk Summary also must include information on systemic and/or local adverse reactions. If there are no data to assess the effects of the drug and/or its active metabolite(s) on the breast-fed child, the Risk Summary must so state.

(iii) Effects of drug on milk production. The Risk Summary must describe the effects of the drug and/or its active metabolite(s) on milk production. If there are no data to assess the effects of the drug and/or its active metabolite(s) on milk production, the Risk Summary must so state.

(3) Risk and benefit statement. For drugs absorbed systemically, unless breastfeeding is contraindicated during drug therapy, the following risk and benefit statement must appear at the end of the Risk Summary: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breast-fed child from (name of drug) or from the underlying maternal condition."

(B) Clinical considerations. Under "Clinical Considerations," the following information must be provided to the extent it is available and relevant:

(1) Minimizing exposure. The labeling must describe ways to minimize exposure in the breast-fed child if: The drug and/or its active metabolite(s) are present in human milk in clinically relevant concentrations; the drug does not have an established safety profile in infants; and the drug is used either intermittently, in single doses, or for short courses of therapy. When applicable, the labeling must also describe ways to minimize a breast-fed child's oral intake of topical drugs applied to the breast or nipple skin.

(2) Monitoring for adverse reactions. The labeling must describe available intervention(s) for monitoring or mitigating the adverse reaction(s) presented in the Risk Summary.

(C) Data. Under the subheading "Data," the labeling must describe the data that are the basis for the Risk Summary and Clinical Considerations.

(iii) 8.3 Females and males of reproductive potential. When pregnancy testing and/or contraception are required or recommended before, during, or after drug therapy and/or when there are human and/or animal data that suggest drug-associated fertility effects, this subsection of labeling must contain this information under the subheadings "Pregnancy Testing," "Contraception," and "Infertility," in that order.

(iv) 8.4 Pediatric use.

(A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(H) of this section, the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(B) If there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the "Indications and Usage" section, and appropriate pediatric dosage information must be given under the "Dosage and Administration" section. The "Pediatric use" subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information must also be contained in the "Contraindications" and/or "Warnings and Precautions" section(s).

(C) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and Administration" section. The "Pediatric use" subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in

any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the "Contraindications" and/or "Warnings and Precautions" section(s).

(D)(1) When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling must contain either the following statement or a reasonable alternative:

The safety and effectiveness of (drug name) have been established in the age groups ____ to ____ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).

(2) Data summarized in the preceding prescribed statement in this subsection must be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions must be included in the "Dosage and Administration" section. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients must be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings and Precautions," and "Dosage and Administration" sections.

(E) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection must contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (____) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

(F) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection must contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

(G) If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(H) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk must be made, generally in the "Contraindications" or "Warnings and Precautions" section.

(v) 8.5 Geriatric use.

(A) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population must be described under the "Indications and Usage" section, and appropriate geriatric dosage must be stated under the "Dosage and Administration" section. The "Geriatric use" subsection must cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection must pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection must be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information must also be contained in the "Warnings and Precautions" and/or "Contraindications" section(s).

(B) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the "Geriatric use" subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biologics license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection must contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(1) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must include the following statement:

Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

(2) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), ____ percent were 65 and over, while ____ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(3) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection must contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, must refer to more detailed discussions in the "Contraindications," "Warnings and Precautions," "Dosage and Administration," or other sections.

(C)(1) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they must be described briefly in the "Geriatric use" subsection and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" and "Drug Interactions" sections ordinarily contain information on drug/disease and drug/drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to use concomitant drugs.

(2) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection must include the statement:

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

(D) If use of the drug in the elderly appears to cause a specific hazard, the hazard must be described in the "Geriatric use" subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section, and the "Geriatric use" subsection must refer to those sections.

(E) Labeling under paragraphs (c)(9)(v)(A) through (c)(9)(v)(C) of this section may include statements, if they are necessary for safe and effective use of the drug, and reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely.

(F) If the sponsor believes that none of the requirements described in paragraphs (c)(9)(v)(A) through (c)(9)(v)(E) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant

to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(vi) Additional subsections. Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (e.g., renal or hepatic impairment).

(10) 9 Drug abuse and dependence. This section must contain the following information, as appropriate:

(i) 9.1 Controlled substance. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled must be stated.

(ii) 9.2 Abuse. This subsection must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used.

(iii) 9.3 Dependence. This subsection must describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and must identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details must be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state and the principles of treating the effects of abrupt withdrawal must be described.

(11) 10 Overdosage. This section must be based on human data. If human data are unavailable, appropriate animal and in vitro data may be used. The following specific information must be provided:

(i) Signs, symptoms, and laboratory findings associated with an overdosage of the drug;

(ii) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis);

(iii) Concentrations of the drug in biologic fluids associated with toxicity or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the “Clinical Pharmacology” section also may be referenced here, if applicable to overdoses;

(iv) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life threatening;

(v) Whether the drug is dialyzable; and

(vi) Recommended general treatment procedures and specific measures for support of vital functions (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center). Such recommendations must be

based on data available for the specific drug or experience with pharmacologically related drugs. Unqualified recommendations for which data are lacking for the specific drug or class of drugs must not be stated.

(12) 11 Description.

(i) This section must contain:

(A) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug or, for biological products, the proper name (as defined in § 600.3 of this chapter) and any appropriate descriptors;

(B) The type of dosage form(s) and the route(s) of administration to which the labeling applies;

(C) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for drug labels or §§ 610.60 and 610.61 of this chapter for biological product labels;

(D) If the product is sterile, a statement of that fact;

(E) The pharmacological or therapeutic class of the drug;

(F) For drug products other than biological products, the chemical name and structural formula of the drug; and

(G) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(ii) If appropriate, other important chemical or physical information, such as physical constants or pH, must be stated.

(13) 12 Clinical pharmacology.

(i) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

(A) 12.1 Mechanism of action. This subsection must summarize what is known about the established mechanism(s) of the drug's action in humans at various levels (e.g., receptor, membrane, tissue, organ, whole

body). If the mechanism of action is not known, this subsection must contain a statement about the lack of information.

(B) 12.2 Pharmacodynamics. This subsection must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or toxicity. Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack of information. Detailed dosing or monitoring recommendations based on pharmacodynamic information that appear in other sections (e.g., "Warnings and Precautions" or "Dosage and Administration") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(C) 12.3 Pharmacokinetics. This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (C_{min}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), pertinent half-lives ($t_{1/2}$), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (V_d) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data. Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., "Warnings and Precautions," "Dosage and Administration" or "Use in Specific Populations") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(ii) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section only under the following circumstances:

(A) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(B) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled studies, as defined in § 314.126(b) of this chapter, to be necessary for the safe and effective use may be included in this section only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

(14) 13 Nonclinical toxicology. This section must contain the following subsections as appropriate:

(i) 13.1 Carcinogenesis, mutagenesis, impairment of fertility. This subsection must state whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If results from reproduction studies or other data in animals raise concern about mutagenesis or impairment of fertility in either males or females, this must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. Human data suggesting that the drug may be carcinogenic or mutagenic, or suggesting that it impairs fertility, as described in the "Warnings and Precautions" section, must not be included in this subsection of the labeling.

(ii) 13.2 Animal toxicology and/or pharmacology. Significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling must be included in this section (e.g., specifics about studies used to support approval under § 314.600 or § 601.90 of this chapter, the absence of chronic animal toxicity data for a drug that is administered over prolonged periods or is implanted in the body).

(15) 14 Clinical studies. This section must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. If a specific important clinical study is mentioned in any section of the labeling required under §§ 201.56 and 201.57 because the study is essential to an understandable presentation of the information in that section of the labeling, any detailed discussion of the study must appear in this section.

(i) For drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in § 314.126(b) of this chapter and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section. For biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute or contribute to substantial evidence and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section.

(ii) Any discussion of a clinical study that relates to a risk from the use of the drug must also refer to the other sections of the labeling where the risk is identified or discussed.

(16) 15 References. When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

(17) 16 How supplied/storage and handling. This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information must include, as appropriate:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets) and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation;

(ii) The units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100);

(iii) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number; and

(iv) Special handling and storage conditions.

(18) 17 Patient counseling information. This section must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA–approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling. Any FDA–approved patient labeling printed immediately following this section or accompanying the labeling is subject to the type size requirements in paragraph (d)(6) of this section, except for a Medication Guide to be detached and distributed to patients in compliance with § 208.24 of this chapter. Medication Guides for distribution to patients are subject to the type size requirements set forth in § 208.20 of this chapter.

(d) Format requirements. All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter “m” in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2–inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

Credits

[71 FR 3988, Jan. 24, 2006; 79 FR 72101, Dec. 4, 2014]

SOURCE: 40 FR 13998, March 27, 1975; 51 FR 8182, March 7, 1986; 51 FR 43904, Dec. 5, 1986; 52 FR 2111, Jan. 20, 1987; 53 FR 4135, Feb. 12, 1988; 54 FR 39635, Sept. 27, 1989, 57 FR 54300, Nov. 18, 1992; 58 FR 45201, Aug. 26, 1993; 62 FR 51515, Oct. 1, 1997; 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999, unless otherwise noted.

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Notes of Decisions (21)

Current through February 1, 2018; 83 FR 4604.

End of Document

EXHIBIT 5

Traumatic Brain Injury: FDA Actions and Research

fda.gov/forconsumers/consumerupdates/ucm519116.htm

Traumatic brain injury, which includes concussions, can happen in a variety of situations. And everyone is at risk, especially children and older adults.

Español

Subscribe: FDA Consumer Health Information

A car accident. A football tackle. An unfortunate fall. These things—and more—can cause head injuries. Head injuries can happen to anyone, at any age, and they can damage the brain.

Here's how damage can happen: A sudden movement of the head and brain can cause the brain to bounce or twist in the skull, stretching and injuring brain cells and creating chemical changes. This damage is called a traumatic brain injury, or "TBI."

Today, the U.S. Food and Drug Administration continues to research TBI—and encourage the development of new medical devices to help diagnose and treat it.

Causes and Symptoms of TBI

TBI is often caused by a bump, blow, jolt, or explosive blast to the head, or a penetrating head injury that disrupts the brain's normal function. Not all hits to the head result in TBI. But when it happens, TBI can range from "mild" (such as a brief change in mental status or consciousness) to "severe" (such as an extended period of unconsciousness or major problems with thinking and behavior after injury).

In 2013, about 2.8 million TBI-related emergency department (ED) visits, hospitalizations, and deaths occurred in the United States, according to the Centers for Disease Control and Prevention (CDC).

A concussion is a form of mild TBI—and about 75 percent of TBIs that occur each year are this type.

Symptoms of mild TBI include:

- headache

- confusion
- blurred vision, and
- behavioral changes.

Moderate and severe TBI can include those symptoms plus:

- repeated vomiting or nausea,
- slurred speech,
- weakness in the arms or legs, and
- problems with thinking abilities.

You can learn more about symptoms from the National Institute of Neurological Disorders and Stroke (NINDS).

Diagnosis of TBI

A medical exam is the first step in diagnosing potential head injury. Assessment usually includes a neurological exam, a typically painless exam that includes an evaluation of thinking, motor function (movement), sensory function, coordination, and reflexes.

But it can be hard to officially diagnose TBI. No universally accepted “gold standard” for diagnosing TBI has been established, though the CDC, the American College of Rehabilitation Medicine, and some others have published guidelines for diagnosing TBI.

Imaging tests, including computerized tomography scans (“CT” scans) and magnetic resonance imaging (MRI) tests do not diagnose TBI, but they can help doctors rule out a life-threatening injury to the brain (particularly bleeding that resulted from the traumatic injury that can require immediate medical or surgical attention).

How the FDA Supports Getting Medical Devices to Patients in the United States

In 2016, the FDA, which reviews and evaluates medical devices for safety and effectiveness, allowed the marketing of two devices that assess cognitive function following suspected brain injury in adults and children.

In 2018, the FDA also allowed marketing of the first blood test to evaluate concussion (mild TBI) in adults. This test works by measuring levels of proteins (known as UCH-L1 and GFAP) that are released from the brain into blood and measured within 12 hours of a head injury. Levels of these blood proteins after a concussion can help predict which patients may have an injury to the brain that would be visible by CT scan—and which patients won’t. So the test, along with other patient-specific information and testing, helps health care providers determine the need for CT scans, in patients at minimal risk, which can help prevent unnecessary follow-up testing.

The FDA also is working with the research and clinical community to develop better-designed clinical studies so new medical products can be developed.

But the FDA has not yet cleared or approved standalone medical products that are intended to specifically diagnose or treat TBI.

“We’re excited about today’s advances in research and development,” says Christian Shenouda, M.D., a clinician and medical device reviewer in the FDA’s Division of Neurological and Physical Medicine Devices. “We hope these advances will lead to further patient access to additional diagnostics and treatments.”

FDA Research on TBI

More sensitive and objective diagnostic methods to detect mild TBI are needed. Timely diagnosis is important to prevent repetitive injury and to help develop new therapies. So the FDA continues to research diagnostic measures of mild TBI.

“Repetitive injury carries the risk of ‘second impact syndrome.’ If people who have not recovered from a head injury have a second head injury, this can result in more significant injury to the brain and more neurological deficits. And, in some cases, repetitive injury can be fatal,” explains Meijun Ye, Ph.D., a neuroscientist in the FDA's Office of Science and Engineering Laboratories.

FDA scientists are studying biomarkers (measurable, biological indicators of a particular state or condition), such as brain imaging, biofluid (specific proteins in blood), and physical indicators such as eye tracking and electroencephalography (EEG). “EEG is the measurement of electrical activity in the brain along the scalp. It holds promise because it’s fast, portable, and typically less expensive than MRI and CT,” Ye says.

Highlights? After scientists developed a small animal “blast” TBI model with high-intensity focused ultrasound, and checked accuracy (called “validation”), they found EEG can detect mild TBI in this model. “These results, and others by FDA regulatory science labs, contribute to the TBI scientific community and efforts to develop diagnostic devices,” Ye notes.

The FDA is now validating results from other animal models (such as when injuries are produced by a bump or jolt). Scientists also are working with human volunteers with Walter Reed National Military Medical Center in Bethesda, Maryland. And they’re recruiting more adult patients—including those with and without TBI—for continued research.

In addition to EEG, they are investigating using other portable imaging devices to detect mild TBI, such as diffuse correlation spectroscopy that can monitor blood flows in the brain from the scalp

What to Do if You Suspect Traumatic Brain Injury

Anyone with signs of moderate or severe TBI should receive medical attention as soon as possible, advises the National Institute of Neurological Disorders and Stroke.

People who survive TBI can face short- or long-term complications that affect thinking, sensation (including sight or balance), language, or emotions.

People with their first, mild TBI may just need to rest and reduce vigorous activity for a short period of time, while those with moderate to severe TBI may require physical therapy (to help with body movement), occupational therapy (to help with conducting daily activities), or psychiatric therapy and other support.

Little can be done to reverse the initial brain damage caused by trauma, the institute reports. But medical professionals will work to stabilize the patient and try to prevent further harm.

Long-term effects depend on the seriousness of the injury, location of the injury, and the age and general health of the patient.

For any TBI, it’s important to follow up with medical professionals as needed.

Updated: February 14, 2018

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EXHIBIT 6

Potential Effects

What are the Potential Effects of TBI?

The severity of a traumatic brain injury (TBI) may range from “mild” (i.e., a brief change in mental status or consciousness) to “severe” (i.e., an extended period of unconsciousness or amnesia after the injury).

A TBI can cause a wide range of functional short- or long-term changes affecting:

- **Thinking** (i.e., memory and reasoning);
- **Sensation** (i.e., sight and balance);
- **Language** (i.e., communication, expression, and understanding); and
- **Emotion** (i.e., depression, anxiety, personality changes, aggression, acting out, and social inappropriateness).[1]

A TBI can also cause epilepsy and increase the risk for conditions such as Alzheimer’s disease, Parkinson’s disease, and other brain disorders.

About 75% of TBIs that occur each year are concussions or other forms of mild TBI.[2]

Repeated mild TBIs occurring over an extended period of time can result in cumulative neurological and cognitive deficits. Repeated mild TBIs occurring within a short period of time (i.e., hours, days, or weeks) can be catastrophic or fatal.[3]

For information on how to prevent TBI and the potentially serious effects from this injury, please visit our TBI Prevention page(https://www.cdc.gov/traumaticbraininjury/prevention.html).

CDC’s HEADS UP campaign also includes steps to help protect children and teens from concussion and other serious head and brain injuries—both on and off the sports field. Learn more at HEADS UP’s Brain Injury Safety Tips and Prevention page(https://www.cdc.gov/headsup/basics/concussion_prevention.html).

General Tips to Help Aid in Recovery:

- Get lots of rest. Don’t rush back to daily activities such as work or school.
- Avoid doing anything that could cause another blow or jolt to the head.
- Ask your health care professional when it’s safe to drive a car, ride a bike, or use heavy equipment. Your ability to react may be slower after a brain injury.
- Only take medications your health care provider has approved. Don’t drink alcohol until your health care provider says it’s OK.
- Write things down if you have a hard time remembering.

- You may need help to re-learn skills you lost. Your health care professional can help arrange for these services.[4]

Related Pages

References

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3. Centers for Disease Control and Prevention (CDC). Sports-related recurrent brain injuries—United States. *MMWR* 1997;46(10):224–227.
4. Centers for Disease Control and Prevention (CDC). Facts about concussion and brain injury: Where to Get Help. 2010.

Connect with the CDC Injury Center

EXHIBIT 7

Reference Manual on Scientific Evidence

Third Edition

Committee on the Development of the Third Edition of the
Reference Manual on Scientific Evidence

Committee on Science, Technology, and Law
Policy and Global Affairs

FEDERAL JUDICIAL CENTER

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THE FEDERAL JUDICIAL CENTER

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Since its founding, the Center has had nine directors. Judge Barbara J. Rothstein became director of the Federal Judicial Center in 2003

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I. Introduction

Epidemiology is the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations. The purpose of epidemiology is to better understand disease causation and to prevent disease in groups of individuals. Epidemiology assumes that disease is not distributed randomly in a group of individuals and that identifiable subgroups, including those exposed to certain agents, are at increased risk of contracting particular diseases.[1]

Judges and juries are regularly presented with epidemiologic evidence as the basis of an expert's opinion on causation.[2] In the courtroom, epidemiologic research findings are offered to establish or dispute whether exposure to an agent[3]

1. Although epidemiologists may conduct studies of beneficial agents that prevent or cure disease or other medical conditions, this reference guide refers exclusively to outcomes as diseases, because they are the relevant outcomes in most judicial proceedings in which epidemiology is involved.

2. Epidemiologic studies have been well received by courts deciding cases involving toxic substances. *See, e.g.,* Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1356 (N.D. Ga. 2001) ("The existence of relevant epidemiologic studies can be a significant factor in proving general causation in toxic tort cases. Indeed, epidemiologic studies provide 'the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or disease.'" (quoting Conde v. Velsicol Chem. Corp., 804 F. Supp. 972, 1025–26 (S.D. Ohio 1992))), *aff'd,* 295 F.3d 1194 (11th Cir. 2002); Berry v. CSX Transp., Inc., 709 So. 2d 552, 569 (Fla. Dist. Ct. App. 1998). Well-conducted studies are uniformly admitted. 3 Modern Scientific Evidence: The Law and Science of Expert Testimony § 23.1, at 187 (David L. Faigman et al. eds., 2007–08) [hereinafter Modern Scientific Evidence]. Since *Daubert v. Merrell Dow Pharmaceuticals,* 509 U.S. 579 (1993), the predominant use of epidemiologic studies is in connection with motions to exclude the testimony of expert witnesses. Cases deciding such motions routinely address epidemiology and its implications for the admissibility of expert testimony on causation. Often it is not the investigator who conducted the study who is serving as an expert witness in a case in which the study bears on causation. *See, e.g.,* Kennedy v. Collagen Corp., 161 F.3d 1226 (9th Cir. 1998) (physician is permitted to testify about causation); DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 953 (3d Cir. 1990) (a pediatric pharmacologist expert's credentials are sufficient pursuant to Fed. R. Evid. 702 to interpret epidemiologic studies and render an opinion based thereon); Medalen v. Tiger Drylac U.S.A., Inc., 269 F. Supp. 2d 1118, 1129 (D. Minn. 2003) (holding toxicologist could testify to general causation but not specific causation); Burton v. R.J. Reynolds Tobacco Co., 181 F. Supp. 2d 1256, 1267 (D. Kan. 2002) (a vascular surgeon was permitted to testify to general causation); Landrigan v. Celotex Corp., 605 A.2d 1079, 1088 (N.J. 1992) (an epidemiologist was permitted to testify to both general causation and specific causation); Trach v. Fellin, 817 A.2d 1102, 1117–18 (Pa. Super. Ct. 2003) (an expert who was a toxicologist and pathologist was permitted to testify to general and specific causation).

3. We use the term "agent" to refer to any substance external to the human body that potentially causes disease or other health effects. Thus, drugs, devices, chemicals, radiation, and minerals (e.g., asbestos) are all agents whose toxicity an epidemiologist might explore. A single agent or a number of independent agents may cause disease, or the combined presence of two or more agents may be necessary for the development of the disease. Epidemiologists also conduct studies of individual characteristics, such as blood pressure and diet, which might pose risks, but those studies are rarely of interest in judicial proceedings. Epidemiologists also may conduct studies of drugs and other pharmaceutical products to assess their efficacy and safety.

caused a harmful effect or disease.[4] Epidemiologic evidence identifies agents that are associated with an increased risk of disease in groups of individuals, quantifies the amount of excess disease that is associated with an agent, and provides a profile of the type of individual who is likely to contract a disease after being exposed to an agent. Epidemiology focuses on the question of general causation (i.e., is the agent capable of causing disease?) rather than that of specific causation (i.e., did it cause disease in a particular individual?).[5] For example, in the 1950s, Doll and Hill and others published articles about the increased risk of lung cancer in cigarette smokers. Doll and Hill's studies showed that smokers who smoked 10 to 20 cigarettes a day had a lung cancer mortality rate that was about 10 times higher than that for nonsmokers.[6] These studies identified an association between smoking cigarettes and death from lung cancer that contributed to the determination that smoking causes lung cancer.

However, it should be emphasized that *an association is not equivalent to causation*.[7] An association identified in an epidemiologic study may or may not be

4. *E.g.,* Bonner v. ISP Techs., Inc., 259 F.3d 924 (8th Cir. 2001) (a worker exposed to organic solvents allegedly suffered organic brain dysfunction); Burton v. R.J. Reynolds Tobacco Co., 181 F. Supp. 2d 1256 (D. Kan. 2002) (cigarette smoking was alleged to have caused peripheral vascular disease); *In re* Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig., 524 F. Supp. 2d 1166 (N.D. Cal. 2007) (multidistrict litigation over drugs for arthritic pain that caused heart disease); Ruff v. Ensign-Bickford Indus., Inc., 168 F. Supp. 2d 1271 (D. Utah 2001) (chemicals that escaped from an explosives manufacturing site allegedly caused non-Hodgkin's lymphoma in nearby residents); Castillo v. E.I. du Pont De Nemours & Co., 854 So. 2d 1264 (Fla. 2003) (a child born with a birth defect allegedly resulting from mother's exposure to a fungicide).

5. This terminology and the distinction between general causation and specific causation are widely recognized in court opinions. *See, e.g.,* Norris v. Baxter Healthcare Corp., 397 F.3d 878 (10th Cir. 2005); *In re* Hanford Nuclear Reservation Litig., 292 F.3d 1124, 1129 (9th Cir. 2002) ("'Generic causation' has typically been understood to mean the capacity of a toxic agent . . . to cause the illnesses complained of by plaintiffs. If such capacity is established, 'individual causation' answers whether that toxic agent actually caused a particular plaintiff's illness."); *In re* Rezulin Prods. Liab. Litig., 369 F. Supp. 2d 398, 402 (S.D.N.Y. 2005); Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 524–25 (W.D. Pa. 2003); Burton v. R.J. Reynolds Tobacco Co., 181 F. Supp. 2d 1256, 1266–67 (D. Kan. 2002). For a discussion of specific causation, see *infra* Section VII.

6. Richard Doll & A. Bradford Hill, *Lung Cancer and Other Causes of Death in Relation to Smoking: A Second Report on the Mortality of British Doctors,* 2 Brit. Med. J. 1071 (1956).

7. *See* Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 461 (W.D. Pa. 2003) (Hill criteria [see *infra* Section V] developed to assess whether an association is causal); Miller v. Pfizer, Inc., 196 F. Supp. 2d 1062, 1079–80 (D. Kan. 2002); Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 591 (D.N.J. 2002) ("[A]n association is not equivalent to causation." (quoting the second edition of this reference guide)); Zandi v. Wyeth a/k/a Wyeth, Inc., No. 27-CV-06-6744, 2007 WL 3224242, at *11 (D. Minn. Oct. 15, 2007).

Association is more fully discussed *infra* Section III. The term is used to describe the relationship between two events (e.g., exposure to a chemical agent and development of disease) that occur more frequently together than one would expect by chance. Association does not necessarily imply a causal effect. Causation is used to describe the association between two events when one event is a necessary link in a chain of events that results in the effect. Of course, alternative causal chains may exist that do not include the agent but that result in the same effect. For general treatment of causation in tort law

causal.[8] Assessing whether an association is causal requires an understanding of the strengths and weaknesses of the study's design and implementation, as well as a judgment about how the study findings fit with other scientific knowledge. It is important to emphasize that all studies have "flaws" in the sense of limitations that add uncertainty about the proper interpretation of the results.[9] Some flaws are inevitable given the limits of technology, resources, the ability and willingness of persons to participate in a study, and ethical constraints. In evaluating epidemiologic evidence, the key questions, then, are the extent to which a study's limitations compromise its findings and permit inferences about causation.

A final caveat is that employing the results of group-based studies of risk to make a causal determination for an individual plaintiff is beyond the limits of epidemiology. Nevertheless, a substantial body of legal precedent has developed that addresses the use of epidemiologic evidence to prove causation for an individual litigant through probabilistic means, and the law developed in these cases is discussed later in this reference guide.[10]

The following sections of this reference guide address a number of critical issues that arise in considering the admissibility of, and weight to be accorded to, epidemiologic research findings. Over the past several decades, courts frequently have confronted the use of epidemiologic studies as evidence and have recognized their utility in proving causation. As the Third Circuit observed in *DeLuca v. Merrell Dow Pharmaceuticals, Inc.*: "The reliability of expert testimony founded on reasoning from epidemiologic data is generally a fit subject for judicial notice; epidemiology is a well-established branch of science and medicine, and epidemiologic evidence has been accepted in numerous cases."[11] Indeed,

and that for factual causation to exist an agent must be a necessary link in a causal chain sufficient for the outcome, see Restatement (Third) of Torts: Liability for Physical Harm § 26 (2010). Epidemiologic methods cannot deductively prove causation; indeed, all empirically based science cannot affirmatively prove a causal relation. *See, e.g.,* Stephan F. Lanes, *The Logic of Causal Inference in Medicine,* in Causal Inference 59 (Kenneth J. Rothman ed., 1988). However, epidemiologic evidence can justify an inference that an agent causes a disease. See *infra* Section V.

8. *See infra* Section IV.

9. *See In re* Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1240 (W.D. Wash. 2003) (quoting this reference guide and criticizing defendant's "ex post facto dissection" of a study); *In re* Orthopedic Bone Screw Prods. Liab. Litig., MDL No. 1014, 1997 U.S. Dist. LEXIS 6441, at *26–*27 (E.D. Pa. May 5, 1997) (holding that despite potential for several biases in a study that "may . . . render its conclusions inaccurate," the study was sufficiently reliable to be admissible); Joseph L. Gastwirth, *Reference Guide on Survey Research,* 36 Jurimetrics J. 181, 185 (1996) (review essay) ("One can always point to a potential flaw in a statistical analysis.").

10. *See infra* Section VII.

11. 911 F.2d 941, 954 (3d Cir. 1990); *see also* Norris v. Baxter Healthcare Corp., 397 F.3d 878, 882 (10th Cir. 2005) (an extensive body of exonerative epidemiologic evidence must be confronted and the plaintiff must provide scientifically reliable contrary evidence); *In re* Meridia Prods. Liab. Litig., 328 F. Supp. 2d 791, 800 (N.D. Ohio 2004) ("Epidemiologic studies are the primary generally accepted methodology for demonstrating a causal relation between the chemical compound and a set of symptoms or a disease. . . ." (quoting Conde v. Velsicol Chem. Corp., 804 F. Supp. 972,

much more difficult problems arise for courts when there is a paucity of epidemiologic evidence.[12]

Three basic issues arise when epidemiology is used in legal disputes, and the methodological soundness of a study and its implications for resolution of the question of causation must be assessed:

1. Do the results of an epidemiologic study or studies reveal an association between an agent and disease?
2. Could this association have resulted from limitations of the study (bias, confounding, or sampling error), and, if so, from which?
3. Based on the analysis of limitations in Item 2, above, and on other evidence, how plausible is a causal interpretation of the association?

Section II explains the different kinds of epidemiologic studies, and Section III addresses the meaning of their outcomes. Section IV examines concerns about the methodological validity of a study, including the problem of sampling error.[13] Section V discusses general causation, considering whether an agent is capable of causing disease. Section VI deals with methods for combining the results of multiple epidemiologic studies and the difficulties entailed in extracting a single global measure of risk from multiple studies. Additional legal questions that arise in most toxic substances cases are whether population-based epidemiologic evidence can be used to infer specific causation, and, if so, how. Section VII addresses specific causation—the matter of whether a specific agent caused the disease in a given plaintiff.

1025–26 (S.D. Ohio 1992))); Brasher v. Sandoz Pharms. Corp., 160 F. Supp. 2d 1291, 1296 (N.D. Ala. 2001) ("Unquestionably, epidemiologic studies provide the best proof of the general association of a particular substance with particular effects, but it is not the only scientific basis on which those effects can be predicted.").

12. *See infra* note 181.

13. For a more in-depth discussion of the statistical basis of epidemiology, see David H. Kaye & David A. Freedman, Reference Guide on Statistics, Section II.A, in this manual, and two case studies: Joseph Sanders, *The Bendectin Litigation: A Case Study in the Life Cycle of Mass Torts,* 43 Hastings L.J. 301 (1992); Devra L. Davis et al., *Assessing the Power and Quality of Epidemiologic Studies of Asbestos-Exposed Populations,* 1 Toxicological & Indus. Health 93 (1985). *See also* References on Epidemiology and References on Law and Epidemiology at the end of this reference guide.

EXHIBIT 10

UNITED STATES DISTRICT COURT

DISTRICT OF MINNESOTA

IN RE: NATIONAL HOCKEY LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION

MDL No. 14-2551 (SRN/JSM)

*** TRANSCRIPT IS DEEMED PROTECTED UNDER THE PROTECTIVE ORDER***

--- This is the Videotaped Deposition of COLIN CAMPBELL, taken at the offices of Skadden, Arps, Meaher & Flom, 222 Bay Street, Suite 1750, Toronto, Ontario, on the 30th day of day of June, 2015.

Reported By: Helen Martineau, CSR (Ont.)

Videographer: James Neeson

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A P P E A R A N C E S: (continued)

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you said. Let's?

BY MR GRYGIEL:

Q. You'll end up seeing the document but I'm trying to cut ahead here. You've heard somebody say that?

A. Someone said that. What is ban all hits? Like, ban the puck hitting the guy in the head? Ban an incidental knee to the head? How do you ban that?

Q. I'm sorry. Ban all body contact to the head. No elbows to the head. No shoulders to the head. No hands to the head. No torso to the head. No knees to the head. No hitting the head

A. Well, the OHL banned a hit to the head.

Q. 2006.

A. And my discussion with Dave Branch, who is Commissioner of the CHL and president of his League, the OHL, I said, "What does hits to the head mean, Dave?" Because there will be contact, accidental contact with a player's head. How can you avoid accidental contact in a fast-skating game when you have ten skater on the ice?

And we were never -- I was never in favor of that. I was in favor of making adjustments that you could adjust, as we did when we had rule 48. So players expect that -- maybe the single largest change we've made was -- to hitting was a shoulder to the head. That was always considered legal in our game since the beginning of the

game, if there was nothing illegal to it.

Q. The player didn't jump?

A. Late, early, jump. I've gone through that with you.

Q. Right.

A. If it was a shoulder that hit the head, because it was always expected by all players. I expected it, my teammates expected it, the opposition expected it, the coaches expected it that you had to be aware of where you were on the ice if you had the puck and that you could be hit legally.

Q. Did anyone, ever, in the NHL executive offices propose an experiment at the preseason games, "Let's try telling the players all hits to the head with any part of their bodies to another player are going to be called a penalty and see what happens"?

MR. GOLDFEIN: Object to the form of the question.

THE DEPONENT: First of all I don't recall that. Secondly, I have always disliked any experiments, trials, in preseason because that is not a fair time to practice or try new rules, even though we've done it in the past. I've never really liked it because all your players don't play in every game, the pace of the game, the results. No one cares about the results of the game. The game does

A. As I said, what we do is we do the best job we can do, I think it's a good job. We've taken any plays on the ice that could result in concussion. We've made the game of hockey as safe as we can regarding blows to the head.

Q. With respect, my answer -- my question was a little different. You haven't heard those words, that there a link between repeated head hits and long-term brain disease, from Ruben Echemendia?

MR. GOLDFEIN: Objection to the form of the question.

THE DEPONENT: I haven't talked to Ruben.

BY MR GRYGIEL:

Q. You haven't heard those words from Julie Grand have you?

MR. GOLDFEIN: Object to the form of the question.

THE DEPONENT: I haven't heard what words? The link? We know that concussions are not good. We haven't taken a -- I haven't heard from her that there's a definitive link to long -- if there was then we would let all our players know. And they're part of the concussion working group so they should know. It's not that they're in a silo. They're part of this.

EXHIBIT 12

Hits to the Head Analysis
General Managers' Meeting
March 8, 2010

Evolution of Hits to the Head

"Stick swinging in our game continues to be the single greatest risk to the careers of our players and jeopardizes the entire conduct of the sport. If players cannot control themselves to refrain from doing it, then the only alternative is to bar such players temporarily or even permanently. They are not worth the risk they involve."

- NHL President Clarence Campbell, 1958

Evolution of Hits to the Head

- Hits to the head have been around as long as the NHL – have evolved (for the most part) from stick swinging in the NHL's early years through the 1960's; to slashes and crosschecks to the head in the 1970's and 1980's to elbows in the 1990's – all illegal and dealt with by supplemental discipline;

- In the NHL's first season, 1917-18, the Canadiens' Joe Hall and Toronto's Alf Skinner got into a stick swinging that left both players bruised and bloodied. They both were given match penalties, fined $15 by the League and charged by the Toronto police for disorderly conduct.

- In the modern era, 13 players have been charged under the criminal code as a result of striking another player in the head in a game.

Hits to the Head/Concussions - In the News

OCTOBER 2009 – FEBRUARY 2010

- NHL has been blamed/targeted/lumped in with hits to the head and concussion issues that other hockey leagues and sports have faced over the last five months.

- February 4, 2010 – **Marco Scandella** (Val D'Or, QMJHL) 15-game suspension for head hit on Alexandre Durette (Rimouski).

- February 2, 2010 – **Independent Canadian Fan Poll** - 80% of fans say that hits to the head in pro hockey are getting out of hand. Six out of 10 Canadians think those guilty of hits to the head should be punished with longer or even life-time suspensions for repeat offenders.

Hits to the Head/Concussions - In the News

- January 27, 2010 – **Hockey Canada** announces plans for a **summit to address hits to the head**.

  "Somehow, we have to get rid of hits to the head at all levels. When you start to talk to the doctors on concussions, it's not just there in a few players. It's there in too big a percentage of players at all levels."
  - Hockey Canada President Bob Nicholson

- January 17, 2010 – **Patrice Cormier** (Rouyn-Noranda, QMJHL) suspended for remainder of season and playoffs for elbow to the head of Mikael Tam (Quebec).

- January 14, 2010 - **Zack Kassian** (Peterborough, OHL) 20-game suspension for head hit on Matt Kennedy (Barrie).

Hits to the Head/Concussions - In the News

- December 20, 2009 – **Former NHL'er Reggie Fleming** found to have had brain damage associated with repeated head trauma, connecting hockey for the first time to health risks linked to boxers and, most recently, football players. Fleming, who died in July, was found by Boston University researchers to have chronic traumatic encephalopathy, a neurodegenerative disease known to cause cognitive decline, behavioral abnormalities and ultimately dementia.

- December 18, 2009 - **Zero tolerance for hits to the head during the Vancouver Olympic Games** - IIHF announces that it will crack down on all hits to the head and neck area, enforcing a rule that was adopted in 2002.

Hits to the Head/Concussions - In the News

- December 5, 2009 - Neurosurgeon Charles Tator announces that he is leading a team of researchers who are asking NHL'ers to donate their brains after their deaths for a new research project aimed at understanding the long-term effects of concussions.
- October 30, 2009 – OHL incident that saw **Michael Liambas** suspended for the remainder of the year for a hit on Ben Fanelli.
- October 28, 2009 – **U.S. House Judiciary Committee** hearing conducted to discuss the long-term effects of head injuries in the NFL.
- October 24, 2009 – Mike Richards hit on David Booth.

Headlines Following Cormier Decision

AP Associated Press

Heads-up! NHL Could Make Rule to Ban High Hits

- January 24

Newsday

NHL Must Take Stand on Hits to the Head

- January 24

NHL SHOULD STOP HEAD SHOTS

- January 26

NATIONAL POST

Headlines Following Cormier Decision

OTTAWA CITIZEN

NHL's duty to stop head shots; Dangerous hits won't stop until the big league gets serious

- January 26

THE GLOBE AND MAIL

CANADA'S NATIONAL NEWSPAPER • FOUNDED 1844

Will the NHL ever learn? Cormier hit shows head shots have no place in hockey; Player's suspension shouldn't end debate

- January 26

OTTAWA SUN

ottawasun.com

NHL SETS STANDARDS FOR GAME; Whether it likes it or not, the league should take a leadership position on head shots

- January 30

Hits to the Head – Factors to Consider

HITS PER SEASON	
Season	**Hits**
2003-04	38,831
2005-06	39,248
2006-07	44,050
2007-08	46,764
2008-09	51,561
2009-10	54,000*

AVG HITS PER GAME	
Season	**Avg Per Game**
2003-04	31
2005-06	32
2006-07	36
2007-08	38
2008-09	42
2009-10	44*

* Projected

Hits to the Head – Factors to Consider

- 40% more hitting in the game this season as compared to year prior to work stoppage;
- We are tracking to set an all-time League record for hits in a season;

Hits leaders this season:

1.	Cal Clutterbuck	5'11, 213 lbs
2.	Ryan Callahan	5'11, 190 lbs
3.	Dustin Brown	6'0, 207 lbs
4.	Stephane Robidas	5'11, 190 lbs
5.	Steve Ott	6'0, 193 lbs
	Avg. 5'11, 199 lbs	NHL avg. 6'1, 204 lbs

Average Size of Players

SEASON	HGT.	WGT	6.0 +	200 LBS +
1961-62	5.11	176.5	45%	15%
1971-72	5.11	184.2	50%	20%
1981-82	6.0	188.1	58%	25%
1991-92	6.0	194.3	68%	38%
2001-02	6.1	202.1	78%	60%
2009-10	6.1	204.2	81%	62%

- Every 10 years, players have been getting bigger by between 2% and 5%;
- 63% increase in players 200 lbs.+ in last 20 years;

Regular Season Concussions (Game Related)

SEASON	NUMBER	TOTAL MAN-GAMES	CONCUSSION PER MAN-GAMES
1997-98	56	40,508	1/723
1998-99	88	42,066	1/478
1999-00	66	43,624	1/708
2000-01	109	46,740	1/428
2001-02	96	46,740	1/486
2002-03	72	46,740	1/649
2003-04	72	46,740	1/649
2005-06	No data		
2006-07	72	46,740	1/649
2007-08	74	46,740	1/631
2008-09	73	46,740	1/640
2009-10	54*	31,388*	1/581

Regular Season Concussions (Game Related)

- Despite having 40% more hitting in our game today as compared to pre-work stoppage (2003-04), the number of concussions per-man games played has only increased by about 10% this season as compared to 2003-04;

- While the # of concussions per-man games played is up by 10% from a year ago, the # is down by 35% from the 2000-01 season.

Career Ending Concussions: Last 15 Years

- **Jamie Heward** – Legal check by Alex Oveckin into glass, Jan.1/09.
- **Steve Rucchin** – Legal hit to the head by Ben Guite, Feb. 8/07.
- **Matthew Barnaby** – In a fight with Josh Gratton, Jan. 9/07.
- **Rob Dimaio** – Hit to the head by G. Latendresse, Sept. 26/06.
- **Keith Primeau** – Elbow by Alexander Perezhogin, Oct. 25/05.
- **Steve Moore** – Sucker punch by Todd Bertuzzi, Mar. 8/04.
- **Steve Heinze** – Hit to the head against Pittsburgh, Dec. 14/02.
- **Adam Deadmarsh** – Legal check by Aki Berg, Nov. 12/02.
- **Mike Richter** - Knee to the head by Todd Marchant, Nov. 5/02.
- **Gino Odjick** - Struck by puck in off-season workout, Aug/02.
- **Cam Stewart** - Legal check by Scott Ferguson, Sept. 25/01.
- **Brad Werenka** - Legal check by Vancouver player, Dec. 29/01.

Career Ending Concussions: Last 15 Years

- **Stu Grimson** – In a fight with Georges Laraque, Dec. 8/01.
- **Petr Svoboda** – Legal check by Shane Doan on Dec. 14, 2000 - Svoboda's own stick came back and struck him.
- **Jeff Beukeboom** – Legal check to the head by Martin Gelinas on Feb. 12/99. Concussion was his third of the season, including sucker punch by Matt Johnson on Nov. 19/98 (12-game suspension).
- **Geoff Courtnall** – Elbow to the head by Bryan Berard (two-game suspension) on Oct. 16, 1999. Also, sucker punch by Owen Nolan on Nov. 27/98.
- **Warren Luhning** – Crosscheck by Randy McKay on Oct. 22/99.
- **Trevor Halverson** – In a fight with Remi Royer, Sept. 25/99.
- **Jeff Kealty** – Suffered his first-ever concussion on an elbow by Atlanta's Mike Stapleton in his first ever NHL game, Sept. 11/99.
- **Pat LaFontaine** – Collided with teammate Mike Keane, Mar. 16/98.

Career Ending Concussions: Last 15 Years

- **Steven Rice** – Suffered his second concussion in two weeks when he went into boards on his own, Sept. 23/98.
- **Jayson More** – Hit to the head against San Jose on Dec. 10/98.
- **Dennis Vaske** – Took a hit to the head against Tampa Bay, suffering his third concussion in three years on Nov. 14/97 (played 3 games in 98-99 with Boston).
- **Jim Johnson** – Took a check to the jaw against Tampa Bay Lightning, Nov. 11/97.
- **Nick Kypreos** – In a fight with Ryan Vandenbussche, Sept. 15/97.
- **Brett Lindros** – Took a legal check to the head by Brent Hughes on Nov. 24, 1995, suffering his second concussion in eight days.

Career Ending Concussions: Last 15 Years

SUMMARY

- 26 players careers ended out of 2743 total players during this period -- 0.9% of total number of players since 1995-96.

Check to the Head:	14
Elbow:	3
Puck:	1
Stick:	1
Fight	4
Collision/Boards	2
Sucker Punch	1

Head Shot Rules in Other Leagues

- **IIHF** – In **2002**, Checking to the Head & Neck Area rule adopted. Any player who directs a check or blow, with any part of his body to the head and neck area of an opposing player or "drives" or "forces" the head of an opposing player into the protective glass or boards will be penalized (either minor and misconduct or, in the case of injury, major and game misconduct).

Head Shot Rules in Other Leagues

- **NCAA** – In **2003**, minor or major penalty adopted for contact to an opposing player's head or neck area in any manner. An emphasis was added later to note the illegality of using the shoulder to make direct contact to the head or neck.

- November, **2009** – NCAA issues a reminder directive on hits to the head: that the responsibility remains with the player approaching an opponent from the blind side. As well, players must refrain from hitting the head of an opposing player directly with their shoulder.

Head Shot Rules in Other Leagues

- **OHL Rule (2006) -** A minor penalty shall be assessed to any player who checks an opponent to the head area.
- **Major plus Game Misconduct Penalty** – At the discretion of the referee and based on the degree of impact a major penalty and a game misconduct can be assessed any player who checks an opponent to the head area.

  Match Penalty – A match penalty shall be assessed to any player who deliberately attempts to injure an opponent by checking to the head area.

  Note: A hit to the head with a shoulder shall be considered an illegal check and shall be penalized as checking to the head.

Hits To The Head Timeline: 1995-2010

1995-96 – SEAMLESS GLASS INTRODUCED

- Seamless Glass systems introduced in NHL building for the first time – GM Place in Vancouver. A dozen new NHL buildings follow suit over the next two years.

November 1997 – GENERAL MANAGERS' MEETING

- Concern about injuries (head & shoulder) caused by seamless glass raised for first time at GM's meeting. One GM: "There's absolutely zero give so you may as well run into a cement wall. We've had two real serious head injuries in the last two years."

Hits To The Head Timeline: 1995-2010

November 1998 – GENERAL MANAGERS' MEETING

- General Managers approved the creation of an Injury Analysis Panel (comprised of team physicians, independent doctors, trainers, head of the injury reporting surveillance system and NHL Hockey Operations staff) on a trial basis for one year.

1999-00 – CLUBS MOVE TO FLEXIBLE GLASS/BOARDS

- In the wake of an increase in player injuries caused by the rigid, seamless glass systems, a handful of clubs begin process of retrofitting with Checkflex board and glass system.

Hits To The Head Timeline: 1995-2010

August 2000 – GENERAL MANAGERS' MEETING

Background: There were a number of high profile supplemental discipline incidents (elbows to the head, sticks to the head and hits from behind) that received considerable negative coverage during the 1998-99 and 1999-00 seasons.

Hits To The Head Timeline: 1995-2010

August 2000 – GENERAL MANAGERS' MEETING

Action: Changes were proposed to the supplementary discipline standards, focusing on 'hits to the head' and paying particular attention to 'hits from behind'.

- The League intended to impose more severe discipline for:
  - Any blow to the head by forceful use of the stick
  - Any blow to the head delivered forcefully by a deliberately raised elbow or forearm
  - Any 'hit from behind' or any act which warrants a major boarding penalty

Result: The total number of Supplemental Discipline suspensions for blows to the head and hits from behind was reduced by 30% in 2000-01 as compared to 1999-00.

Hits To The Head Timeline: 1995-2010

September 2000 – INJURY ANALYSIS PANEL CREATED

- League created Injury Analysis Panel to address issues involving player safety. The Panel was chaired by Dave Dryden, and included representatives from the players, NHLPA, NHL Hockey Operations and Legal, Club doctors, trainers, equipment managers, arena managers, equipment manufacturers, NHL referees and linesmen, General Managers, and coaches.

- The incidence and causes of concussion were a major focus of the Panel, as were steps that could be taken to improve player and Club awareness regarding concussions, and steps that could be taken to reduce the incidence and severity of concussions.

Hits To The Head Timeline: 1995-2010

June 2001 – GENERAL MANAGERS & BOARD MEETING

Background: With a 65% increase in the number of concussions in 2000-01 as compared to 1999-00, the Injury Analysis Panel made a number of recommendations to both the GM's and Board of Governors.

Action:

- *Helmets*: A new rule was adopted requiring that each player be issued a new CERTIFIED helmet at the beginning of each season.

Hits To The Head Timeline: 1995-2010

June 2001 – GENERAL MANAGERS & BOARD MEETING

Action Cont'd:

- *Education of players*: Injury Analysis Panel develops fact sheet for players, educating them on effectiveness of proper fitting chin straps; the effects of modifying foam in helmets; the benefits of visors and mouthguards.

- *"Head Check" Rule* – While not adopted, the Injury Analysis Panel suggested discussion on a new "head checking" rule if it could be implemented as to be: i) fair to all size of players; ii) consistently applied by the referees; iii) explainable to players and the public; iv) instituted and implemented without changing the historic "body contact" nature of pro hockey.

Hits To The Head Timeline: 1995-2010

June 2003 – GENERAL MANAGERS' MEETING

Background: In reaction to the concern that the design of elbow pads (ie. the hard plastic covering) is causing a significant number of injuries, GM's recommended a new rule.

Action: Rule 12.3: All elbow pads which do not have a soft protective outer covering of sponge rubber or similar material at least one-half inch (1/2") thick shall be considered dangerous equipment.

Hits To The Head Timeline: 1995-2010

July 2002 – BOARD OF GOVERNORS MEETING

- *Seamless glass*: The League imposed a mandate that all clubs install a sufficiently flexible glass and boards system.

Hits To The Head Timeline: 1995-2010

February 2004 – GENERAL MANAGERS MEETING

- Injury Analysis Panel reported that, while head injuries were slightly up from the previous season the increase was mostly due to an increase in facial injuries.

- The topic of hits to the head was discussed as a result, including the possibility of harsher penalties for fouls committed on hits to an opponent's head.

Hits To The Head Timeline: 1995-2010

June 2006 – GENERAL MANAGERS MEETING

Background: With the increased speed in the game in the first season with the rule changes, a discussion took place regarding a view that there was an increase in hits to a player's head, and whether or not these types of hits should be penalized.

Topics of discussion:

- Retaliation and head hunting – should it be illegal?
- Majority of the video examples were deemed clean hits and should not be penalized.
- Rules governing amount of time after a player releases a puck when he can still be legally hit.

Hits To The Head Timeline: 1995-2010

June 2007 – GENERAL MANAGERS' MEETING

Background: A couple of high profile incidents in 2006-07 keyed an in-depth discussion on: i) "head-hunting"; ii) players in vulnerable positions; and, iii) where the responsibility lies.

- A vote was conducted to determine whether the GM's felt that Neil's hit on Drury was legal – 21 GM's felt it was legal; 9 felt it was illegal.

Hits To The Head Timeline: 1995-2010

June 2007 – GENERAL MANAGERS' MEETING

Topics of Discussion:

- Timing of the hits
- Size of shoulder pads
- Intentional targeting of the head
- Proposal that all hits to the head be penalized
- Whether or not the focus by the media on a few select hits was disproportionate to the overall number of hits to the head
- Vulnerable players (having just passed the puck)
- Players leaving their feet
- Definition of what a 'legal' hit was.

Hits To The Head Timeline: 1995-2010

June 2007 – GENERAL MANAGERS' MEETING

Action: The following factors were identified for the 2007-08 season as being relevant to whether a player should be subject to supplemental discipline when a hit to an opponent's head is involved:

- When a player targets an opponent's head
- When a player launches himself by leaving his feet to hit a player in the head area
- When the hit to the head is delivered to an unsuspecting opponent
- The timing (lateness) of the hit.
- An additional factor in considering whether discipline is appropriate is whether the player is a repeat offender.

Hits To The Head Timeline: 1995-2010

March 2009 – GENERAL MANAGERS' MEETING

- **Background:** NHL Players' Association reported to GM's on the players' view of head hits. NHLPA showed video of head hits and mutual respect plays to the players during their fall tour and that this was the biggest issue for the players.

- NHLPA suggested that the majority of players supported the implementation of a penalty for "targeted" head hits, but that they were not in favor of a blanket penalty for contact with the head.

Hits To The Head Timeline: 1995-2010

March 2009 – GENERAL MANAGERS' MEETING

Topics of discussion:

- Difference between players coming up into a hit and players launching themselves into a hit
- Hits that show a lack of respect
- Player awareness
- A minimum supplemental discipline penalty
- Whether or not there should be stiffer suspensions for head hits
- Predatory hits and players with a history of such hits.

Action: Agreement that more analysis was needed. The GM's supported continuing to refine the standard while improving and increasing the education to players.

Hits To The Head Timeline: 1995-2010

June 2009 – GENERAL MANAGERS' MEETING

- Discussion by GM's on supplemental discipline regarding hits to the head. There was no indication the process should change.

Hits To The Head Timeline: 1995-2010

November 2009 – GENERAL MANAGERS MEETING

- Consensus among the General Managers that blind side hits on unsuspecting players, currently a legal hit, need to be re-examined. The Managers believe that, given the size of today's players and the speed in the game, these hits have the potential to put players' careers in jeopardy.

- It was agreed that the General Managers would study and debate the issue in more detail at the March, 2010 meeting.

Contact With The Head in Today's Game

- NHL Hockey Ops put 21 regular–season games under the video microscope this season to identify all contact to the head that occurs in a typical game.

Game 796		Location		Contact Made With				Secondary				
Per.	Time	Open Ice	Glass/Boards	Shoulder	Elbow	Hands	Stick	Glass	Boards	Ice	Injury	Penalty
1	19:01	X				X						
1	17:50		X		X							
1	17:27		X			X		X				
1	15:07		X			X						
1	14:12		X	X				X				
1	8:37		X			X		X				
1	3:26		X				X					
1	2:28		X		X							
2	18:00		X	X								
2	15:44		X			X						
2	15:28	X			X							
2	12:28		X	X				X	X			
2	12:05			X				X				
2	9:13		X	X								
2	7:00		X			X						
2	2:27		X	X				X		X		
3	17:58	X		X								
3	9:45		X		X			X				
3	8:43		X			X		X				
3	7:53		X	X				X				
3	7:14		X	X						X		

Contact With The Head in Today's Game

Analysis identified the following:

- Each NHL games contains, on average, 22 instances of contact to the head between players. The vast majority of this contact is incidental in nature and goes unnoticed;

- 62% of the contact to the head occurred along the boards; 38% took place in open ice;
  - 40% of the contact to the head involved the hands;
  - 30% of the contact was shoulder to head;
  - 15% of the contact was elbow to head (incidental);
  - 13% of the contact was stick to head;
  - 2% of the contact came from helmets, knees etc.

Contact With The Head in Today's Game

- 40% of the contact resulted in the "victim's" head having secondary contact with the ice, glass or boards;
- Evidence of the incidental nature of the vast majority of this contact can be found in the fact that only 5% result in a penalty (approximately one per game);
- We average 43 hits per-game this season. In the games put under the microscope, there were five hits to the head included in this total. Therefore, 17 of the 22 instances of 'contact to the head' were not classified as a hit.

Contact With The Head in Today's Game

Conclusion: In an average game, there are 60 instances of contact between players (i.e. a hit or incidental contact with the head). Projected over an entire season: 73,800 incidents of contact between players.

2009-10 Supplemental Discipline

The following standard is used for determining supplemental discipline for hits to the head:

- Any blow to the head delivered by forceful use of the stick (either by cross-check, high stick, or slash);
- Any blow to the head delivered forcefully by a deliberately raised elbow or forearm;

2009-10 Supplemental Discipline

- Any blow to the head delivered to an unsuspecting and vulnerable player, where the player delivering the hit launches himself, targets the head, hits the player late and injures the player. As well, if the player is a repeat offender, all or any of these factors will be considered when imposing Supplementary Discipline.

- Any "hit from behind" or any act which warrants a major boarding penalty.

Supplemental Discipline Hits to the Head: 10-Season Analysis

- A comparison was conducted for all supplemental discipline involving contact with the head for suspensions between the five seasons prior to the work stoppage (1999-00 to 2003-04) and the five seasons since (2005-06 to 2009-10).

Supplemental Discipline Hits to the Head: 10-Season Analysis

'Hit to the Head' Suspensions	1999 - 2004	2005 - 2010
Total Suspensions	95	48
Total Games Suspended	320	202
Average Suspensions/Season	19	10
Average Suspension Length	3.4	4.2
Percent that Cause Injury	26.3%	41.7%
Total Games Lost	139 (+3 Career)	109
Total Cost for Suspensions	$1,353,141.03	$5,009,756.12

- The average number of 'contact to the head' incidents per-season requiring suspensions was 19 between 1999 and 2004; has been reduced to 10 between 2005 and 2010.

Supplemental Discipline Hits to the Head: 10-Season Analysis

'Hit to the Head' Suspensions	1999 - 2004	2005 - 2010
Total Suspensions	95	48
Total Games Suspended	320	202
Average Suspensions/Season	19	10
Average Suspension Length	3.4	4.2
Percent that Cause Injury	26.3%	41.7%
Total Games Lost	139 (+3 Career)	109
Total Cost for Suspensions	$1,353,141.03	$5,009,756.12

- The total number of suspensions has decreased by 49% (95 to 48) for 2005-2010 as compared to 1999-2004.

Supplemental Discipline Hits to the Head: 10-Season Analysis

'Hit to the Head' Suspensions	1999 - 2004	2005 - 2010
Total Suspensions	95	48
Total Games Suspended	320	202
Average Suspensions/Season	19	10
Average Suspension Length	3.4	4.2
Percent that Cause Injury	26.3%	41.7%
Total Games Lost	139 (+3 Career)	109
Total Cost for Suspensions	$1,353,141.03	$5,009,756.12

- The length of an average suspension has increased by 24% (3.4 to 4.2) for the five seasons 2005-2010 as compared to 1999-2004.

Supplemental Discipline Hits to the Head: 10-Season Analysis

'Hit to the Head' Suspensions	1999 - 2004	2005 - 2010
Total Suspensions	95	48
Total Games Suspended	320	202
Average Suspensions/Season	19	10
Average Suspension Length	3.4	4.2
Percent that Cause Injury	26.3%	41.7%
Total Games Lost	139 (+3 Career)	109
Total Cost for Suspensions	$1,353,141.03	$5,009,756.12

- The percentage of suspensions involving contact to the head that cause injury (i.e. man games lost) has increased 60% from 26.3% for 1999- 2004 to 42% causing injury between 2005 and 2010.

Supplemental Discipline Hits to the Head: 10-Season Analysis

Categories 'Hit to the Head' Suspensions	1999 - 2004	2005 - 2010
Elbow/Forearm	27	19
Shoulder	0	11
Stick	58	13
Sucker Punch	10	5

- 61% of the suspensions for hits to the head for 1999-2004 were for stick infractions; only 27% of the suspensions for 2005-10 have been for stick infractions;
- 64% of suspensions for hits to the head for 2005-2010 have been as the result of elbow/forearm or shoulder.

Repeat Offenders: Contact to the Head

PLAYER	INCIDENT	DATE	SUSPENSION	COST
	Crosscheck	11/13/03	3	$365,853.63
Keith	Crosscheck	2/23/03	4	$487,804.84
Tkachuk	High Stick	3/24/02	1	$42,783.51
	Crosscheck	3/23/00	2	$57,986.10
Ed	Elbow	1/9/10	2	$158,536.59
Jovanovski	Elbow	12/7/09	2	$67,357.52
	Elbow	11/28/07	1	$34,759.36
Brad	Sucker Punch	4/17/07	3 (Playoff)	n/a
May	Crosscheck	10/20/03	1	$5,555.56
	Slash	11/11/00	20	$117,647.05
Scott	Crosscheck	12/1/07	5	$45,731.70
Nichol	Sucker Punch	12/21/06	9	$25,267.41
	High Stick	12/19/02	5	$22,865.85

Repeat Offenders: Contact to the Head

PLAYER	INCIDENT	DATE	SUSPENSION	COST
Chris	Forearm	6/2/07	1 (Playoff)	n/a
Pronger	Elbow	5/15/07	1 (Playoff)	n/a
	Crosscheck	4/3/02	2	$231,707.32
Chris	Stick Swinging	3/8/07	25	$80,213.90
Simon	Crosscheck	1/11/04	2	$16,666.66
	Elbow	4/5/01	2	$56,097.56
Joe	Crosscheck	2/28/02	3	$67,073.16
Thornton	Crosscheck	2/1/01	2	$43,495.94
	Crosscheck	12/16/00	2	$19,073.08
Donald	Punch	3/11/01	2	$48,780.49
Audette	Crosscheck	1/12/01	4	$42,780.75
Wade	High Stick	3/20/04	6 + 2 playoff	$67,682.94
Belak	Elbow	11/26/02	2	$8,555.56

Repeat Offenders: Contact to the Head

PLAYER	INCIDENT	DATE	SUSPENSION	COST
Matt	Shoulder	11/28/09	2	$29,268.30
Cooke	Shoulder	1/20/09	2	$12,903.23
Tie	Punch	3/4/03	3	$31,388.88
Domi	Elbow	5/3/01	3 (Playoff) + 8	n/a
Dallas	Forearm	12/7/06	2	$26,829.26
Drake	Crosscheck	10/28/05	2	$12,408.16
Denis	Elbow	1/31/09	5	$56,451.61
Gauthier	Elbow	12/6/99	2	$6,336.80
Eric	Punch	1/6/06	2	$4,639.18
Godard	High Stick	4/9/03	1 (Playoff)	n/a
Darian	Elbow	5/3/04	3	n/a
Hatcher	Elbow	3/25/01	2	$39,786.08
Cam	Shoulder	2/13/10	5	$14,248.70
Janssen	Shoulder	3/2/07	3	$7,220.16

Repeat Offenders: Contact to the Head

PLAYER	INCIDENT	DATE	SUSPENSION	COST
Gino	Elbow	12/13/00	1	$9,585.37
Odjick	Sucker Punch	12/30/99	8	$30,867
Krzysztof	Crosscheck	11/20/03	2	$12,195.12
Oliwa	Crosscheck	11/9/02	5	$24,305.55
Jody	Sucker Punch	3/24/04	3	$21,036.60
Shelley	Sucker Punch	2/21/03	2	$14,024.39
Todd	High Stick	12/26/02	2	$35,365.85
Simpson	High Stick	11/25/02	3	$24,166.68
Marty	High Stick	3/24/04	4	$195,121.96
Turco	High Stick	1/20/03	1	$3,564.81
Igor	Crosscheck	10/10/01	7	$170,731.68
Ulanov	Crosscheck	12/13/00	2	$11,764.70
Alexei	High Stick	4/18/00	1 (Playoff)	n/a
Zhitnik	High Stick	10/17/00	4	$121,951.22

Questions In Need of Answers

- Almost 75 percent of players in our League today have come up through developmental leagues that have automatic penalties for any blow to the head of an opponent. What additional steps should we take to educate these players on the issues of awareness and vulnerability? Should your coaches play a role in educating the players during training camp?

- Hockey traditionalists would say that the responsibility falls on the player being hit rather than the player doing the hitting for a legal check. At what point, if any, should the line of responsibility shift from the "hittee" to the "hitter"?

Questions In Need of Answers

- What risk do we take in changing the fabric of the game if we make changes to the existing rules on what constitutes a legal shoulder check when it makes contact with an opponent's head?
- How do we reduce the incidence of injuries to players for legal hits to the head?
- Should we consider longer supplemental discipline suspensions for illegal hits to the head? Should repeat offenders be hit with longer suspensions? What is the definition of a "repeat offender"?

Questions In Need of Answers

- What is a blindside hit?
- What is an unsuspecting player?
- Currently, we consider any hit that is later than ½ a second to ¾ of a second after a player releases the puck as being in the danger zone as to what constitutes being late. Should our definition of "late" be re-defined?

Questions In Need of Answers

What is charging?

- Charging rule language has been further defined only ONCE since rule first adopted in 1937-38:
- 1937-38: "A minor penalty shall be imposed on a player who runs (now we use the word "skates") or jumps into or charges an opponent. If more than two steps are taken, it shall be considered a charge."
- 1996-97: Additional wording: "Charging shall mean the actions of a player who, as a result of distance travelled, shall violently check an opponent in any manner. A charge may be the result of a check into the boards, into the goal frame or in open ice."

Questions In Need of Answers

What is boarding?

- 1937-38: "A major penalty shall be imposed on a player who jumps at or charges a player from behind. A minor or major penalty shall be imposed on a player who body-checks in a manner that causes an opponent to be violently thrown into the fence."
- 1965-66: Additional wording: "Any unnecessary contact on an obvious icing or offside which results in that player being knocked into the boards is 'boarding'".
- 2006-07: Additional wording: "There is an enormous amount of judgment involved in the application of this rule by the Referees. The onus is on the player applying the check to ensure his opponent is not in a vulnerable position and if so, he must avoid the contact. However, there is also a responsibility on the player with the puck to avoid placing himself in a dangerous and vulnerable position. This balance must be considered by the Referees when applying this rule.

Questions In Need of Answers

- Should hits to the head along the boards be treated differently than those in open ice?
- Should a player coming out of the penalty box NOT be permitted to initiate contact with an opponent for a period of three seconds?
- Should a player either exiting or entering play NOT be permitted to initiate contact with an opponent within five feet of the player's bench?
- Should a player who challenges an opponent to a fight after a legal hit (either on him or a teammate) be assessed an automatic instigator penalty?
- Is it possible to determine that a player targets an opponent's head when delivering a hit?

EXHIBIT 13

UNITED STATES DISTRICT COURT

DISTRICT OF MINNESOTA

IN RE: NATIONAL HOCKEY LEAGUE)
PLAYERS' CONCUSSION INJURY) MDL No. 14-2551
LITIGATION) (SRN/JSM)
---)

CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER

--- This is the Videotaped Deposition of Dr. John Rizos, taken at the offices of Skadden, Arps, Slate, Meagher & Flom, 222 Bay Street, Suite 1750, Toronto, Ontario, on the 12th day of August, 2016.

Reported By: Deana Santedicola, CSR (Ont.), RPR, CRR

DIGITAL EVIDENCE GROUP

1730 M Street NW, Suite 812

Washington, DC 20036

(202) 232-0646

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well.

THE WITNESS: So --

BY MR. CASHMAN:

Q. You can answer now.

A. I can answer? Yes, I did not have authority within the context of the Concussion Working Group.

Q. The Concussion Working Group is pretty much run by the NHL?

MR. KEYTE: Again, objection, foundation.

THE WITNESS: I would say that is true.

BY MR. CASHMAN:

Q. So would it be fair to say that the Concussion Working Group being run by the NHL, the NHL pretty much decides what studies are going to happen; is that fair to say?

MR. KEYTE: Again, objection, complete lack of foundation.

THE WITNESS: Yes.

BY MR. CASHMAN:

Q. Mr. Keyte asked you some questions

about the Fall Tours and the summer tours, you remember generally he showed you some of your presentations?

A. Yes.

Q. Would you put those all in the category of providing information, educational information?

A. Yes.

Q. Would you agree you were not attempting or intending to be providing warnings?

MR. KEYTE: Objection, over-broad.

THE WITNESS: Yes.

BY MR. CASHMAN:

Q. Would you agree that your view was that the NHL controls player safety?

MR. KEYTE: Well, objection, foundation.

BY MR. CASHMAN:

Q. Well, let me put it this way. Would you agree that it was your view that it was the NHL's responsibility to provide any warnings?

MR. KEYTE: Objection, foundation.

THE WITNESS: I believe that they had the greatest influence on the ground rules of the game, the rules that governed it, and, as such, on safety matters. But we also had the opportunity to provide our opinions and our impressions.

BY MR. CASHMAN:

Q. Right, but at the end of the day, the NHL controlled those things, they could take your opinion or not?

MR. KEYTE: Objection, foundation, which means he has no basis to ask this. Go ahead.

MR. KEELING: If you understand the question.

THE WITNESS: I believe in the end it was the -- that the greatest influence was from the Leagues and its owners.

MR. KEYTE: Move to strike as non-responsive.

BY MR. CASHMAN:

Q. Would it be correct you did not ever give a warning in the fall or summer tours that repeated brain trauma was associated with

EXHIBIT 14

Choice of Law

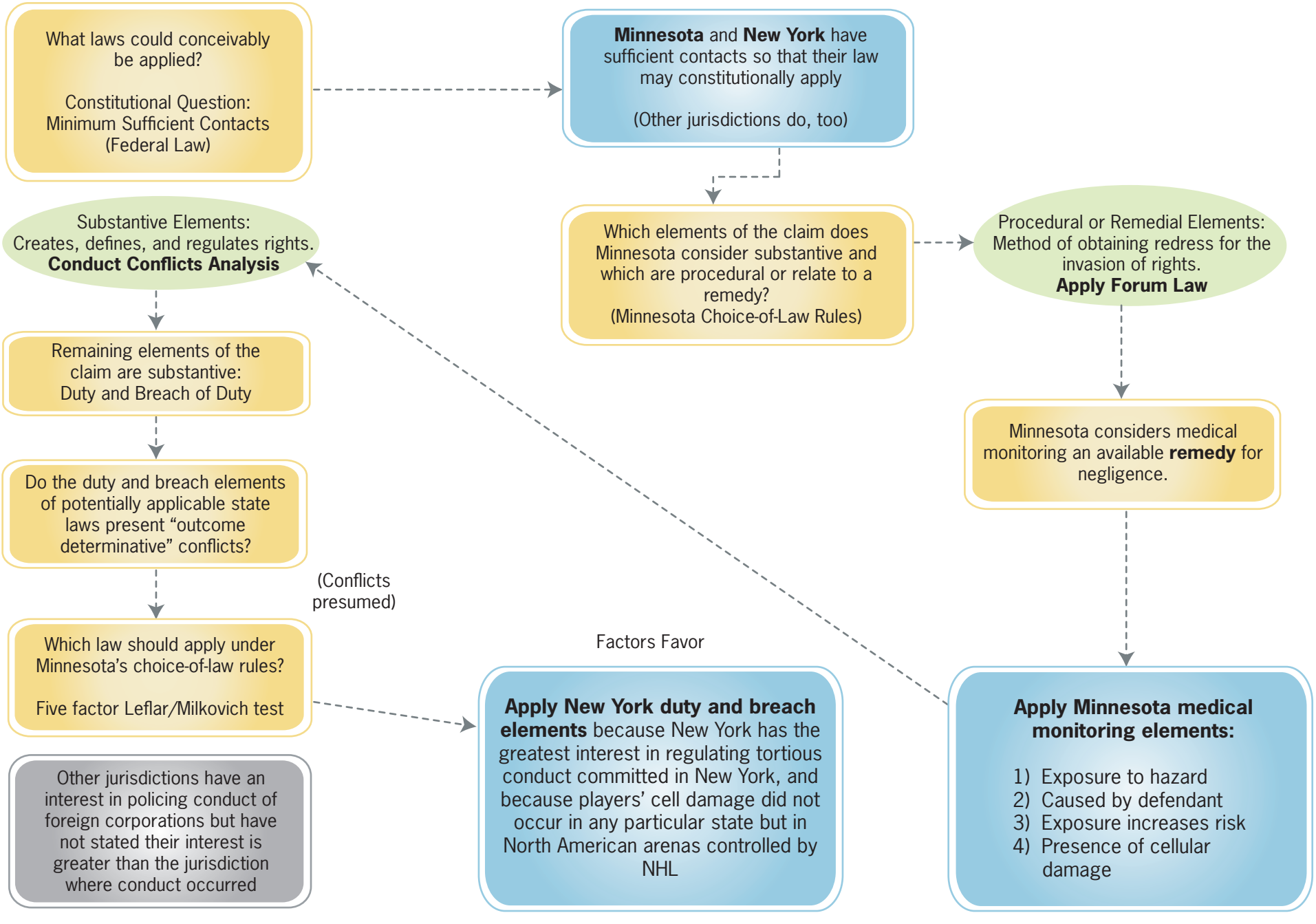

EXHIBIT 15

Re: Concussions
Julie Grand to: Bill Daly, Gary Bettman 11/10/2011 11:41 AM
Cc: Kris King, Colin Campbell, Brendan Shanahan, Gary Meagher

Right point re the underreporting. I will check re Reimer.

From: Bill Daly
Sent: 11/10/2011 11:38 AM EST
To: Julie Grand; Gary Bettman
Cc: Kris King; Colin Campbell; Brendan Shanahan; Gary Meagher
Subject: Re: Concussions

But this doesn't take into account the "under-reporting" of concussions that Kinger thinks our Clubs are engaged in. BTW, has Reimer been reported as a "concussion" by Toronto?

From: Julie Grand
Sent: 11/10/2011 10:09 AM EST
To: Gary Bettman
Cc: Bill Daly; Kris King; Colin Campbell; Brendan Shanahan; Gary Meagher
Subject: Re: Concussions

Below are the numbers for regular season concussions up to and including Nov 7th. We are at 10 this season compared to 26 last season. It is obviously early in the season to forecast trends.

Note that the MGL are for the season in which they were injured only, and the ones from this year have not had any time to accumulate MGL. This season, of the 10 concussions, 4 have returned to play, and 6 are still accumulating MGL.

Season	Count	total MGL
2006-2007	6	28
2007-2008	11	150
2008-2009	9	48
2009-2010	22	132
2010-2011	26	377
2011-2012	10	46*

Julie Grand
National Hockey League
1185 Avenue of the Americas
New York, NY 10036
Phone: (212) 789-2043
Fax: (212) 789-2050

From: Gary Bettman/NYC/NHL
To: "Julie Grand" <jgrand@nhl.com>

Date: 11/10/2011 09:07 AM
Subject: Concussions

How are we doing so far this season?
Sent from my Blackberry
Gary B Bettman

EXHIBIT 16

Re: For CR
Julie Grand to: Kris King 10/31/2011 01:31 PM
Cc: Gary Meagher

ok
Julie Grand
National Hockey League
1185 Avenue of the Americas
New York, NY 10036
Phone: (212) 789-2043
Fax: (212) 789-2050

Kris King Let's not ask yet. I will follow up to see how long... 10/31/2011 12:49:51 PM

From: Kris King/TOR/NHL
To: Julie Grand/NYC/NHL@NHL
Cc: Gary Meagher/TOR/NHL@NHL
Date: 10/31/2011 12:49 PM
Subject: Re: For CR

Let's not ask yet. I will follow up to see how long these guys are out.

Kris King
Vice President
Hockey Operations
National Hockey League
50 Bay Street, Suite 1100
Toronto, ON, Canada
M5J 2X8
Office: (416)359-7922
Cell: (647)224-9990
E-mail: kking@nhl.com

Julie Grand ok; if you share that list with me and brett send... 10/31/2011 12:48 PM EDT

From: Julie Grand
To: Kris King
Cc: Gary Meagher
Date: 10/31/2011 12:48 PM EDT
Subject: Re: For CR

ok; if you share that list with me and brett sends me the clips i will follow up with clubs and ask.

Julie Grand
National Hockey League
1185 Avenue of the Americas
New York, NY 10036
Phone: (212) 789-2043
Fax: (212) 789-2050

Kris King For this small group only. I really feel teams are... 10/31/2011 12:47:07 PM

From: Kris King/TOR/NHL
To: Julie Grand/NYC/NHL@NHL, Gary Meagher/TOR/NHL
Date: 10/31/2011 12:47 PM
Subject: Re: For CR

For this small group only. I really feel teams are not reporting concussions. We hear they are out with "concussion like" symptoms but only have 1 player official on IR with concussion this week. I thought we had 3 on Saturday alone. I am keeping a log of the players that show these symptoms in a game and actually leave the game, miss their next game but don't show up on our tracking.

Kris King
Vice President
Hockey Operations
National Hockey League
50 Bay Street, Suite 1100
Toronto, ON, Canada
M5J 2X8
Office: (416)359-7922
Cell: (647)224-9990
E-mail: kking@nhl.com

Julie Grand for conversion to player name pls Julie Grand... 10/31/2011 12:40 PM EDT

From: Julie Grand
To: Sonya Goel
Cc: Winne Meeuwisse <sportmd@me.com>; Kris King; Brett Leonhardt
Date: 10/31/2011 12:40 PM EDT
Subject: Fw: For CR

for conversion to player name pls

Julie Grand
National Hockey League
1185 Avenue of the Americas
New York, NY 10036
Phone: (212) 789-2043
Fax: (212) 789-2050

----- Forwarded by Julie Grand/NYC/NHL on 10/31/2011 12:40 PM -----

From: Willem Meeuwisse <sportmd@me.com>
To: Julie Grand <JGrand@nhl.com>
Cc: Kris King <KKing@nhl.com>
Date: 10/31/2011 11:23 AM
Subject: For CR

Hi Julie:
Here is the separate file for CR that has just the new concussion. I don't have Sonja's email address
Winne

[attachment "Oct31 Concussions.xlsx" deleted by Kris King/TOR/NHL]