the legislation provided no new resources, no new authority for postmarketing safety, and little new flexibility for the agency in the review process.

Soon after the law's passage, the FDA released a proposed decision to reject all eight pending ingredients, citing multiple gaps in data, including key safety studies and reports of adverse events in countries where relevant products are marketed.

The agency's proposal provoked a swift and angry response. In a press release, the PASS coalition stated that the agency "demonstrates clear disregard for increased rates of melanoma and the public's demand for latest sunscreen technology."[3] The *Wall Street Journal* editorial board stated that "the agency's willful culture of control and delay is the real public-health menace. . . . The only solution is to strip the sunscreen police of all powers over the stuff."[4]

An audio interview with Dr. Sharfstein is available at NEJM.org

These attacks missed their mark. It's no surprise that the FDA would act cautiously given the scientific advice it's received and a legal structure that essentially provides it with just one tool: authorizing extensive marketing of multiple products and formulations. Understanding the FDA means recognizing that the framework for over-the-counter products is not designed to promote innovation, even innovation with potential public health benefits.

In my view, Congress should try again and pass legislation establishing an alternative approval pathway that combines the flexibility of the new drug pathway with the ability to simultaneously approve multiple formulations and concentrations. The FDA should be able to negotiate with sponsors to get the right data without years of rulemaking, establish postmarketing data requirements, consult with other countries' regulators to establish consistent standards where possible, and move quickly in the event that safety concerns emerge. Congress should provide additional resources to facilitate timely analysis and review. That this path is viable is evidenced by the fact that the one approval of a product with a new sunscreen ingredient in the past decade came through the new drug pathway.

More timely and flexible review can expand sunscreen options for consumers and complement other measures to reduce melanoma prevalence. Promising steps include FDA efforts to discourage use of tanning beds and initiatives by the Centers for Disease Control and Prevention to promote prevention measures. The federal government should also reconsider whether it makes sense to continue allowing some products to be marketed as sunscreen without evidence of protection against cancer. After all, the ultimate goal is to make meaningful progress against this public health problem.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. National Cancer Institute. A snapshot of melanoma (http://www.cancer.gov/researchandfunding/snapshots/melanoma).
2. Tucker ME. FDA advisory panel calls for sunscreen safety testing. Medscape Medical News. September 8, 2014 (http://www.medscape.com/viewarticle/831359).
3. Public Access to SunScreens Coalition (PASS). FDA's announcement on ecamsule and enzacamene applications demonstrates clear disregard for increased rates of melanoma, public's demand for latest sunscreen technology. February 24, 2015 (http://www.passcoalition.com/index.php/media-info/173-fda-s-announcement-on-ecamsule-and-enzacamene-applications-demonstrates-clear-disregard-for-increased-rates-of-melanoma-public-s-demand-for-latest-sunscreen-technology).
4. Washington's skin cancer hostages: the FDA is defying Congress and Obama on better sunscreens. Wall Street Journal. March 13, 2015 (http://www.wsj.com/articles/washingtons-skin-cancer-hostages-1426287044).

DOI: 10.1056/NEJMp1504912

Synthetic Cannabinoid–Related Illnesses and Deaths

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Synthetic cannabinoids (SCs) were first created in the 1980s as laboratory research tools (ligands) for studying human endocannabinoid receptor systems. SC-containing products supplied by illicit manufacturers were then marketed throughout Europe as herbal incense, before arriving in the United States in November 2008. The prevalence and variety of SCs on the illicit market have steadily increased over the past 6 years, as manufacturers and distributors of SCs and dealers of SC-containing products have attempted to circumvent federal, state, and local laws.

Since 2011, through actions on four separate occasions, the U.S. Drug Enforcement Administration (DEA) has placed a total of 15 SCs in Schedule I of the Controlled Substances Act (CSA). In 2012 the Synthetic Drug Abuse Prevention Act permanently placed 26 synthetic compounds including 10 additional SCs in Schedule I. States have taken similar actions to regulate SCs, yet manufacturers continue to rapidly synthesize new compounds that fall outside such regulations.

After being shipped to the United States from foreign chemical suppliers, the psychoactive substances are typically either mixed with plant material, dissolved in liquid and then applied to plant material, dissolved in liquid for use in e-cigarettes, or dissolved in liquid that users can ingest or mix with another substance (such as energy drinks or tobacco) and consume. SC-containing products are sold in varied packaging, from nondescript plastic baggies to colorfully labeled packets containing intriguing brand names and claims such as "legal alternative to marijuana" and "legal high."[1,2] The products are distributed for sale in gas stations, convenience stores, or head shops or through Internet vendors.

Despite warnings ("not for human consumption") and reassurances ("does not contain [any regulated] compounds") on packages, widespread recreational use of these products by a broad demographic, but particularly by younger and inexperienced users, has led to multiple clusters of cases of adverse health effects and deaths.[1,2] As reported in the table,

Clusters of Cases of Adverse Health Effects or Severe Toxic Effects and Deaths Associated with Synthetic Cannabinoid (SC) Product Use.*

Location	Date	No. of Cases	No. of Cases Resulting in Death	Substance Identified
Clusters of illness involving SCs				
Casper, WY	March 2012	4	0	XLR11†
Portland, OR	May–Oct. 2012	6	0	XLR11†
Brunswick, GA	Aug.–Sept. 2013	22	0	ADB-PINACA†
Denver, CO	Aug.–Sept. 2013	>220	0	ADB-PINACA
Austin, TX	May 2014	>20	0	XLR11, AB-FUBINACA‡
Dallas, TX	May 2014	>100	0	XLR11, AB-FUBINACA‡
Gainesville, FL	May–June 2014	>29	0	AB-CHMINACA†
St. Louis, MO	Aug. 2014	3	0	AB-CHMINACA, AB-PINACA
Manchester, NH	Aug. 2014	>44	0	AM2201 N-(3-chloropentyl) isomer, AB-PINACA, ADB-PINACA, UR-144†
Fort Wayne, IN	Aug. 2014	7	0	AB-CHMINACA
Westland, MI	Sept. 2014	6	0	AB-PINACA
Baton Rouge, LA	Oct. 2014	>120	0	MAB-CHMINACA
Bryan, TX	Nov. 2014	>41	2	MAB-CHMINACA†
Beaumont, TX	Dec. 2014–Jan. 2015	>62	0	MAB-CHMINACA, AB-PINACA, ADB-PINACA‡
Salina, KS	Dec. 2014–Jan. 2015	3	0	MAB-CHMINACA†
Santa Ana, CA	Jan. 2015	>40	0	JWH-122, MAM-2201
Middletown, CT	Feb. 2015	11	0	AB-FUBINACA
Austin, TX	April 2015	4	0	AB-CHMINACA†
Philadelphia, MS	April 2015	6	0	MAB-CHMINACA†
Hampton, VA	April 2015	7	0	MAB-CHMINACA†
Hagerstown, MD	April 2015	9	0	MAB-CHMINACA†
Jackson, MS	April 2015	19	0	MAB-CHMINACA†

(Continued.)

Location	Date	No. of Cases	No. of Cases Resulting in Death	Substance Identified
Additional cases of severe toxic effects involving SCs				
Washington County, AR	Aug. 2011	1	1	AM2201
Anderson, SC	Oct. 2011	1	1	JWH-018
Athens, GA	Feb. 2012	1	1	AM2201, JWH-122, JWH-210
Fayetteville, GA	March 2012	1	1	AM2201
Benton County, MN	Dec. 2012	1	1	UR-144, XLR11
Oakland, CA	April 2013	1	0	XLR11
Davenport, IA	July 2013	1	1	5F-PB-22
Aurora, CO	Aug. 2013	1	1	AB-FUBINACA
Waverly, NE	Oct. 2013	1	1	5F-PB-22
Lafayette, LA	April 2014	1	1	AB-CHMINACA
Bay Minette, AL	April 2014	1	1	AB-CHMINACA
Baton Rouge, LA	May 2014	1	1	ADB-FUBINACA
Corvallis, OR	May 2014	1	1	AB-CHMINACA†
New Orleans, LA	June 2014	1	0	AB-CHMINACA†
Irving, TX	June 2014	1	0	AB-CHMINACA†
Atlantic City, NJ	June 2014	2	0	AB-FUBINACA, AB-PINACA
Newport Beach, CA	July 2014	1	1	AB-CHMINACA
Shreveport, LA	July 2014	1	0	AB-CHMINACA†
Austin, TX	Aug. 2014	1	1	THJ-2201, AB-PINACA†
Holdrege, NE	Oct. 2014	1	0	AB-PINACA†
Austin, TX	Oct. 2014	1	1	AB-CHMINACA, AB-PINACA, ADB-PINACA MAB-CHMINACA†
Springfield, MO	Nov. 2014	1	1	AB-CHMINACA†
Salina, KS	Dec. 2014	2	0	MAB-CHMINACA†
Boyle, KY	Jan. 2015	1	1	AB-CHMINACA
Killeen, TX	Jan. 2015	1	1	AB-CHMINACA, AKB48, XLR11

* SC compounds were identified on the basis of analysis of clinical samples from patients, when available. 5F-PB-22 denotes 1-(5-fluoropentyl)-1*H*-indole-3-carboxylic acid 8-quinolinyl ester, AB-CHMINACA *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-*1H*-indazole-3-carboxamide, AB-FUBINACA *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide, AB-PINACA *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide, ADB-FUBINACA *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide, ADB-PINACA *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide, AKB48 *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide, AM2201 1-(5-fluoropentyl)-3-(1-naphthoyl)indole, AM2201 N-(3-chloropentyl) isomer, (1-(3-chloropentyl)-1*H*-indol-3-yl)(naphthalen-1-yl)methanone, JWH-018 1-pentyl-3-(1-naphthoyl)indole, JWH-122 1-pentyl-3-(4-methyl-1-naphthoyl)indole, JWH-210 1-pentyl-3-(4-ethyl-1-naphthoyl)indole, MAB-CHMINACA *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide, MAM-2201 1-(5-fluoropentyl)-4-methyl-3-(1-naphthoyl)indole, THJ-2201 (1-[5-fluoropentyl]-1*H*-indazol-3-yl)(naphthalene-1-yl)methanone, UR-144 1-pentyl-3-(2,2,3,3-tetramethycyclopropoyl)indole, and XLR11 1-(5-fluoro-pentyl)-3-(2,2,3,3-tetramethylcyclopropoyl)indole.

† Substance identified by the Clinical Toxicology and Environmental Biomonitoring Laboratory, University of California, San Francisco.

‡ Substance identified on the basis of information about local law-enforcement seizures during the same period.

deaths from SC use have ranged from 13 to 56 years of age (seven were 13 to 19 years of age; five, 20 to 29; three, 30 to 39; three, 40 to 49; and two, 50 to 56).

A recent study examined the prevalence and motives for SC use among patients undergoing treatment for substance use dis-

order. Some 38% of these patients reported using an SC, most commonly by smoking (91%); 27% also took SCs by other methods, including using a vaporizer and e-cigarettes. Cited motives for use included curiosity or experimentation (91%) and a desire to feel good or get high (89%), to relax (71%), and to get high without risking a positive drug test (71%).[3]

SC use has repeatedly been reported to produce serious adverse health effects, including but not limited to excited delirium, acute kidney injury, seizures, psychosis, hallucinations, cardiotoxic effects, coma, and death — with some users dying before they could reach an emergency department.[1,2] Unlike opioid drugs such as heroin and morphine, SCs have no available antidote, and treatment of the often unpredictable and severe adverse health effects is largely supportive. Moreover, there is no clear toxidrome that signals the cause of intoxication in someone without a history of SC-product use. Severe signs and symptoms exhibited in users are also commonly seen with many other classes of recreational stimulant or hallucinogenic drugs.

Adding to the challenge of recognizing SC intoxication is the lack of rapid laboratory tests to confirm exposure. SCs are not detected by routine urine immunoassay screens for drugs of abuse, and confirmatory clinical testing is available only through sophisticated analysis at reference or research laboratories. When a new SC is encountered on the illicit market, the compound must first be identified, through either testing of products seized by police or laboratory analysis of clinical samples from an intoxicated person. After preliminary identification of a potentially new compound, an analytical standard must be synthesized to confirm the presence of the new SC by repeated analysis. If the compound was previously unknown, collaboration between a legitimate manufacturer of the analytical standard and the toxicology laboratory analyzing the clinical samples may identify predicted metabolites. If these putative metabolites are synthesized as analytical standards, reanalysis of biologic samples from patients in a cluster of SC-associated illness may provide a means of determining which predicted metabolites are valid targets for analysis in subsequent cases.

Once both the parent compound and metabolites have been identified, it takes time for other toxicology reference laboratories to obtain the standards and validate their own analytical methods. Thus, many months may elapse before confirmatory testing for the new compound is widely available. By that time, clandestine illicit laboratories have moved on to a newer compound. As a result, cases of SC intoxication, fatalities from SC misuse, and outbreaks of severe illness associated with new or particularly toxic compounds are most likely underrecognized.[1,2]

As the table documents, we have recently observed an increase in the incidence of clusters of SC intoxication resulting in severe illness and death. (The information presented here does not represent all SC-associated cases of severe toxic effects.) In the past, such clusters occurred less frequently: multiple cases of acute kidney injury in SC users occurred in Wyoming and Oregon in 2012, after use of products containing XLR-11.[4] The following year, two outbreaks of agitated delirium linked to the same previously unknown SC (ADB-PINACA) and product ("Crazy Clown" or "10X") occurred in Brunswick, Georgia, and Denver[2]; and Gainesville, Florida, saw a large outbreak in May 2014, linked to the novel compound AB-CHMINACA. After the Florida outbreak, we identified a trend of a rapidly increasing number and size of clusters throughout 2014 and into 2015. Between mid-March and May 2015, an unprecedented outbreak resulting from SC use affected at least 12 states.[5] The Mississippi State Department of Health reported more than 1200 SC-related emergency visits and 17 deaths potentially related to SC use during this period, while the Alabama Department of Public Health reported more than 1000 such emergency visits and 5 such deaths.

Possible explanations for this trend include better reporting of suspected clusters by health care facilities and local public health entities, enhanced media attention to and reporting of recreational-drug-associated clusters of illness, and improved collaboration between public health and law-enforcement agencies. Alternatively, the increase may be related to the SC compounds themselves. Whereas we had at least some pharmacologic and pharmacokinetic data on earlier generations of SC compounds from their use as experimental cannabinoid-receptor ligands, more recent products contain novel SC compounds that are rapidly synthesized and marketed in response to regulatory actions. These compounds often have unknown receptor-binding affinity and selectivity, which may result in unexpectedly severe or idiosyncratic toxicity. Individual pharmacoge-

netic differences among users may affect the length of time that the active form of the drug remains in the body and at what concentration. Illicit manufacturing of SC compounds or SC-containing products may lead to the presence of impurities, contaminants, or variability in SC content within products.

Challenges to defining the scope of the public health threat posed by SCs include underreporting by clinicians and public health practitioners, limited availability of laboratory testing to confirm exposures, delays in the availability of analytical laboratory standards for the newest compounds, and frequent product changes. To address these challenges, clusters of adverse health effects potentially related to SC-product use can be reported to either local poison centers or local public health departments. Cases of severe SC intoxication, unusual toxic effects, death, or multiple patients presenting with SC intoxication clustered in time and space may reflect the appearance of a novel SC compound or toxicity of a contaminated or poorly manufactured product; rapid identification of these events will allow public health officials to better support local practitioners. Collaboration between forensic and toxicology laboratories and legitimate suppliers of analytical standards may result in better preparation and a more timely response to future outbreaks. Increased recognition and reporting by clinicians and public health personnel may aid federal and state regulatory efforts in combating this ongoing SC epidemic.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, the Agency for Toxic Substances and Disease Registry, the Department of Health and Human Services, the Drug Enforcement Administration, the Department of Justice, or any other office of the U.S. government.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. van Amsterdam J, Brunt T, van den Brink W. The adverse health effects of synthetic cannabinoids with emphasis on psychosis-like effects. J Psychopharmacol 2015;29:254-63.
2. Schwartz MD, Trecki J, Edison LA, Steck AR, Arnold JK, Gerona RR. A common source outbreak of severe delirium associated with exposure to the novel synthetic cannabinoid ADB-PINACA. J Emerg Med 2015;48:573-80.
3. Bonar EE, Ashrafioun L, Ilgen MA. Synthetic cannabinoid use among patients in residential substance use disorder treatment: prevalence, motives, and correlates. Drug Alcohol Depend 2014;143:268-71.
4. Acute kidney injury associated with synthetic cannabinoid use — multiple states, 2012. MMWR Morb Mortal Wkly Rep 2013;62:93-8.
5. Notes from the field: increase in reported adverse health effects related to synthetic cannabinoid use — United States, January–May 2015. MMWR Morb Mortal Wkly Rep 2015;64:618-9.

DOI: 10.1056NEJMp1505328

BECOMING A PHYSICIAN

Breaking Up Is Hard to Do

Geoffrey A. Rubin, M.D.

"It's not you — it's me."

I blushed in bewilderment at hearing myself say it. The conversation leading up to it had been jumbled and unintentionally hurtful to both parties. I had been totally unprepared. After 20 more minutes and a packet of tissues, the encounter ended. It was not productive.

But the breakup aftermath didn't involve untagging of Facebook photos, remorseful late-night text messages, or venting sessions with friends. Instead, it meant the end of faxing recertifications for the visiting nurse service and refilling prescriptions: I was ending a relationship not with a girlfriend but with a patient from my resident internal medicine clinic.

Despite all the oversight of today's residents — the electronic fail-safes and hard stops, the hour logging, the quality-improvement committees, the personal advisor meetings — a key aspect of residency has been largely overlooked: ending it. In medical school, we do subinternships to prepare for the start of clinical training. As interns, we perform procedures and run treatment plans with supervision to solidify our skills. But we receive little guidance on leaving residency.

One of the oddest aspects of concluding residency is the obligatory termination of all our patient relationships. Just when these relationships are comfortably established, most residents at academic medical centers break ties and pursue career development —