Biogen International GmbH et al. v. Mylan Pharmaceuticals Inc.:

Another hurdle for Pharmaceutical Patents

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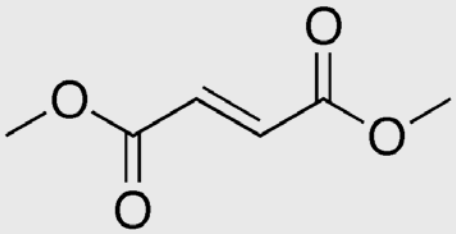
November 2, 2022

Biogen's TECFIDERA drug product

- Biogen is the New Drug Application (NDA) holder; TECFIDERA (dimethyl fumarate or "DMF") was approved in 2013 by the FDA as a treatment for adults with relapsing multiple sclerosis ("MS")



Dimethyl fumarate

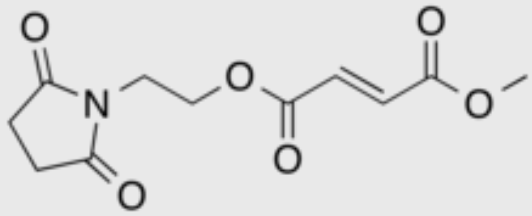
- Biogen lists U.S. Patent No. 8,399,514 ("the '514 patent") in the Orange Book
  - Covers methods of treating MS using DMF

TECFIDERA (dimethyl fumarate)

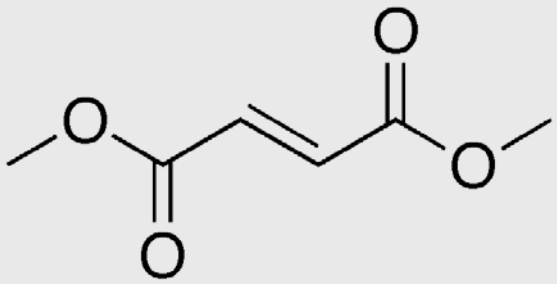
- 1959: a topical formulation for psoriasis
- 1994: dimethyl fumarate combined with three other fumaric acid esters is (in Germany) an oral therapy for psoriasis (FUMADERM)
- 2017: in the UK, it is available as a pure oral formulation (SKILARENCE) for moderate-to-severe plaque psoriasis

DMF is a Prodrug

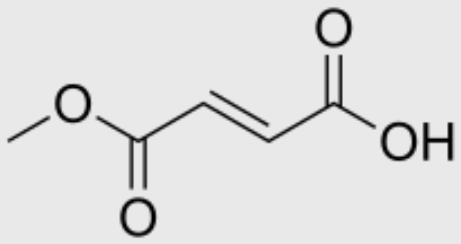
- Biogen also has diroximel fumarate (brand name VUMERITY), approved by the FDA in October 2019



- Monomethyl fumarate, sold under the brand name BAFIERTAM



Dimethyl fumarate



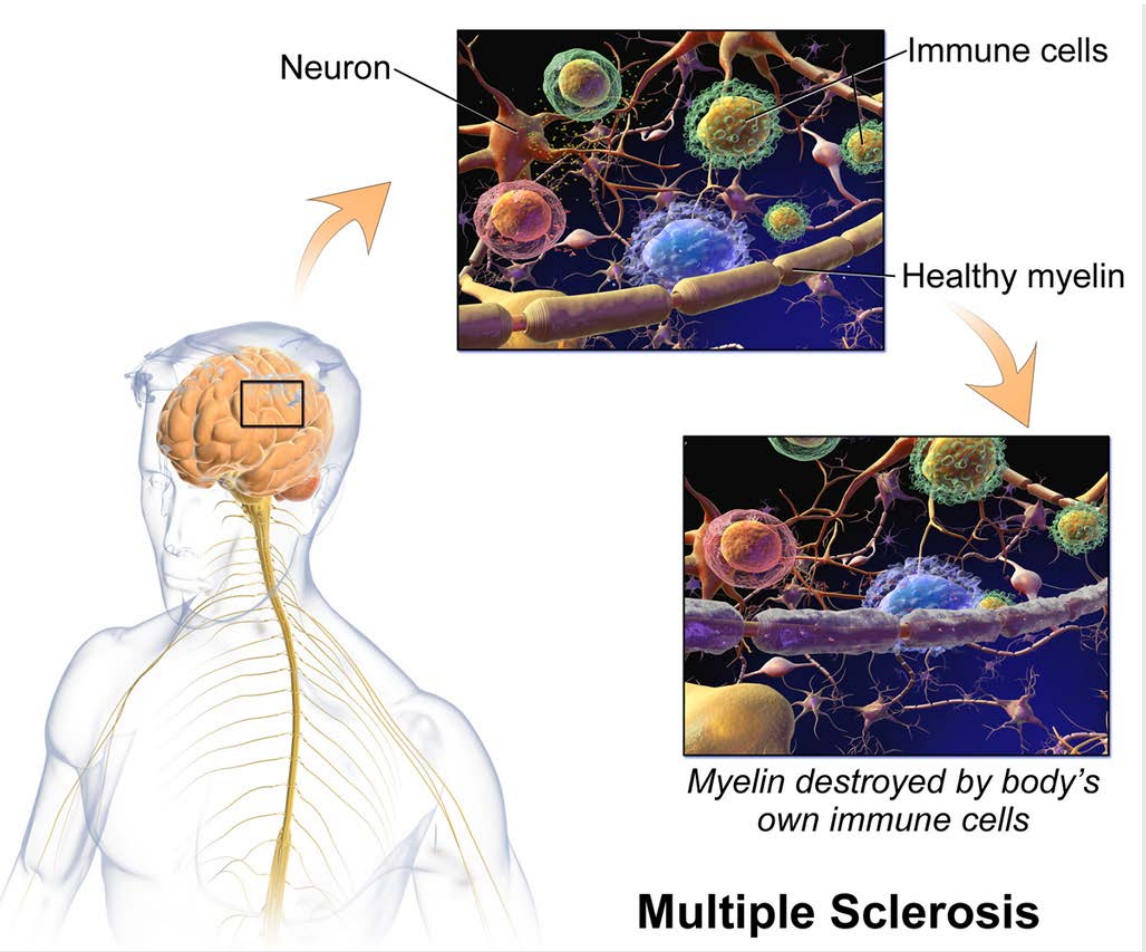
Monomethyl fumarate

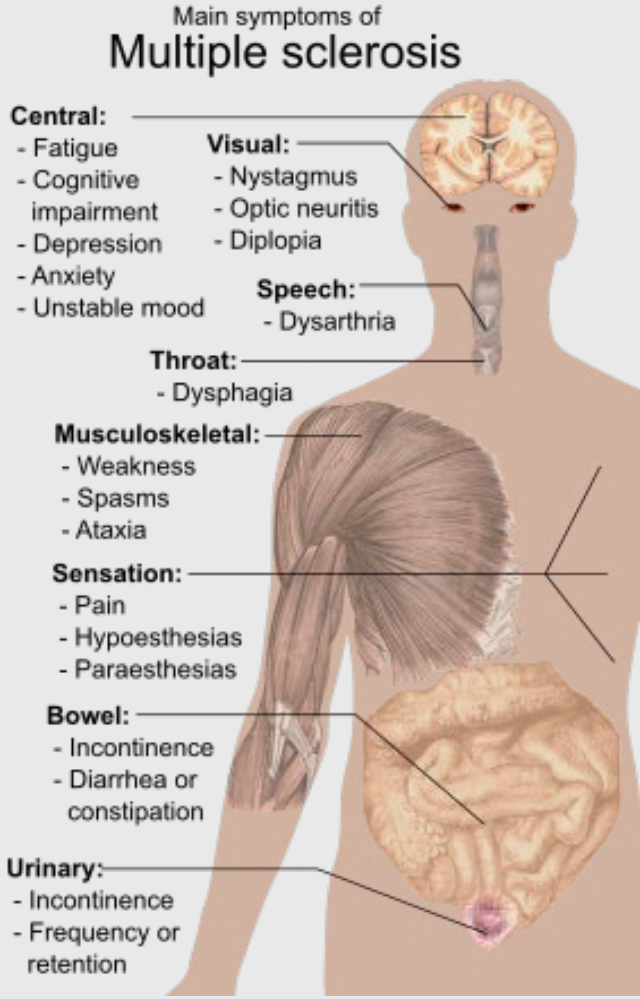
How does DMF work to treat MS?

The way DMF works to treat MS is not fully understood, but studies suggest that it may work in two ways:

- **reduces the inflammation** caused when the immune system attacks myelin, resulting in less damage to myelin
- **protects nerve cells** from damage caused by chemicals released during the immune attack

See https://mstrust.org.uk/a-z/tecfidera-dimethyl-fumarate#:~:text=The%20way%20Tecfidera%20works%20is,released%20during%20the%20immune%20attack





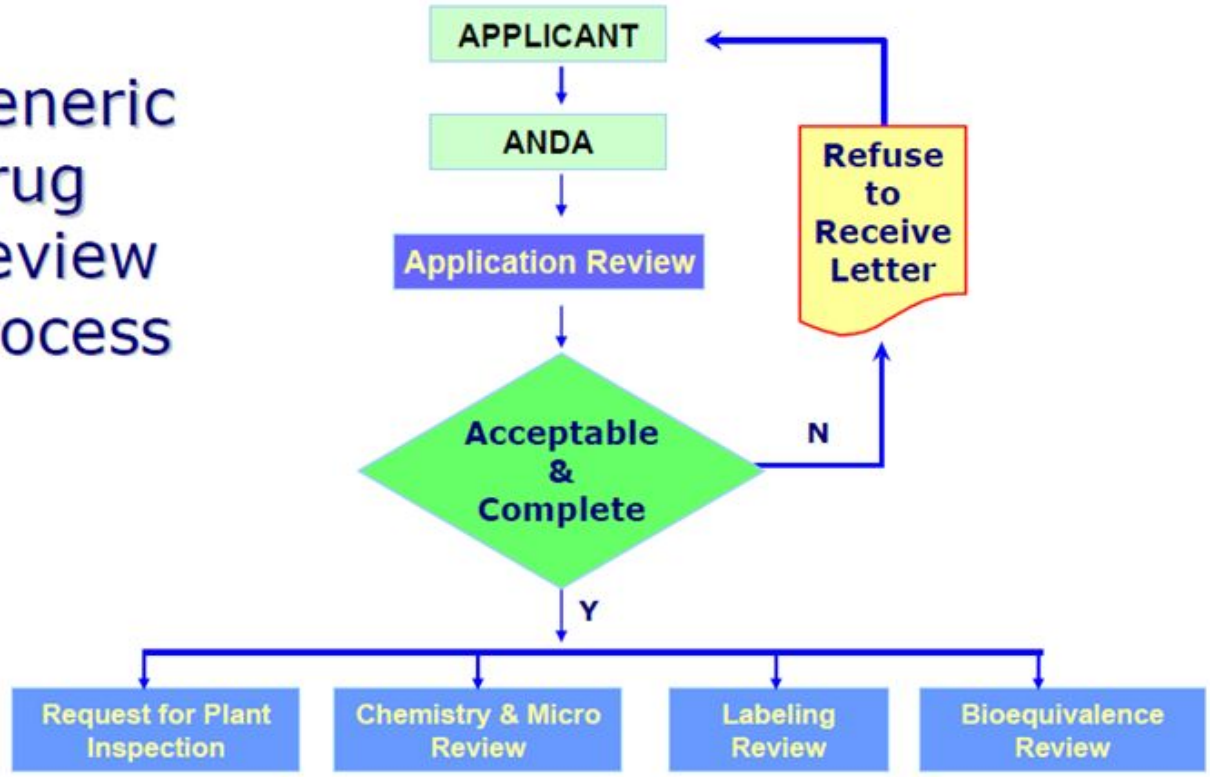
Images from:
https://en.wikipedia.org/wiki/Multiple_sclerosis

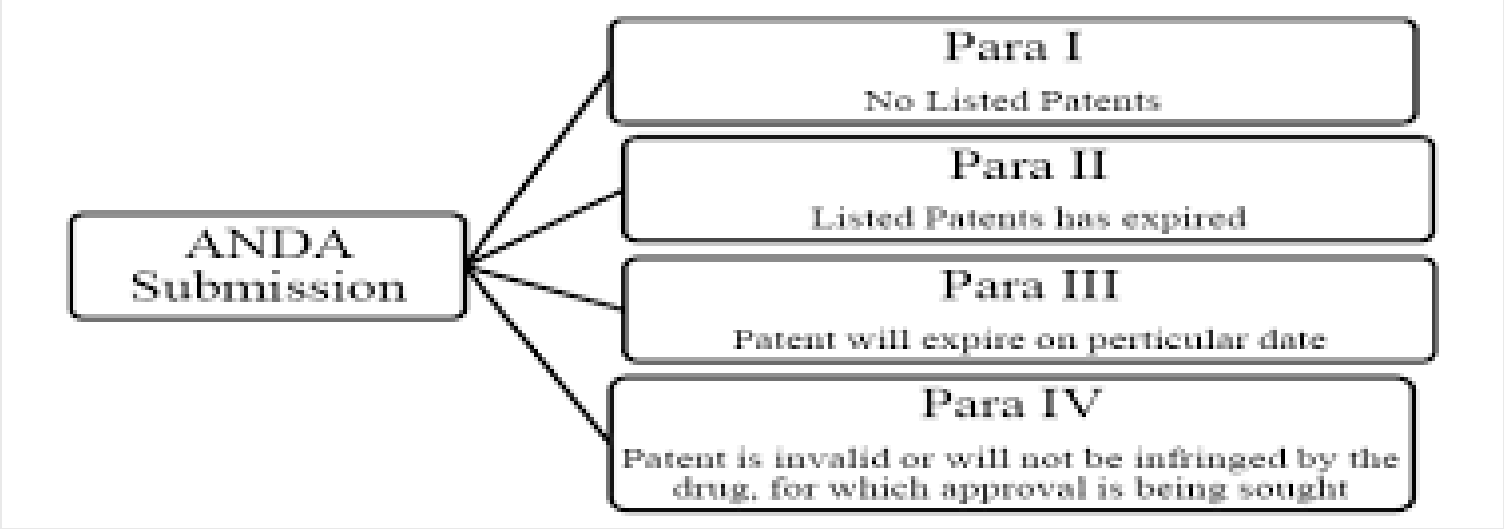
ANDA case

- Mylan (now Viatris) applied for an Abbreviated New Drug Application (ANDA)

ANDA Filing Process

Generic Drug Review Process




ANDA Submission
Para I
No Listed Patents
Para II
Listed Patents has expired
Para III
Patent will expire on perticular date
Para IV
Patent is invalid or will not be infringed by the drug, for which approval is being sought

ANDA case

- Mylan filed a paragraph IV certification w/rt U.S. Patent No. 8,399,514 (“the ’514 patent”)

- Biogen sued Mylan (now Viatris) in West Virginia in June 2017, alleging Mylan's proposed generic of Tecfidera would infringe its patents.

- District Court ruled in 2000 that ’514 patent is invalid for failing to meet the written description requirement
  - *Mylan launches generic*

- November 30, 2021: Federal Circuit upheld the judge’s ruling in favor of Mylan

- March 16, 2022: CAFC denies Biogen’s petition for *en banc* review

- October 3, 2022: the Supreme Court denies cert

Biogen's '514 Patent

- The claims at issue in Biogen's '514 patent recite a method of administering a **therapeutically effective amount** of **about 480 mg** of dimethyl fumarate ("DMF") per day **to treat multiple sclerosis.**

Claim 1 of the ’514 Patent

1. A method of treating a subject in need of treatment for **multiple sclerosis** comprising **orally administering** to the subject in need thereof a pharmaceutical composition consisting essentially of

(a) **a therapeutically effective amount of dimethyl fumarate,** monomethyl fumarate, or a combination thereof, and

(b) one or more pharmaceutically acceptable excipients,

wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is **about 480 mg per day**.

the ’514 Patent

- Specification is primarily about drug discovery/screening
- But the ’514 patent does contain some general language regarding treatment methods, including specific description of MS

the ’514 Patent

- “Also provided are methods of **treating a neurological disease** by administering to the subject in need thereof at least one compound that is at least partially structurally similar to DMF and/or MMF.”
- “In some embodiments of method 4, a method of **treating a mammal who has or is at risk for a neurological disease** is provided. The methods comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound which has Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF).”

the ’514 Patent

- “In some embodiments of method 4, a method of **slowing or preventing neurodegeneration (more specifically, e.g., demyelination, axonal loss, and/or neuronal death)** in a subject in need thereof, by administering the at least one compound in an amount and for a period of time sufficient to do at least one of slow or prevent demyelination, slow or prevent axonal loss, and slow or prevent neuronal death, e.g., by at least 30%, 50%, 100% or higher over a control over a period of at least 5, 10, 12, 20, 40, 52, 100, or 200 weeks, or more.”

the ’514 Patent

- “The terms ‘therapeutically effective dose’ and ‘therapeutically effective amount’ refer to that amount of a compound which results in at least one of **prevention or delay of onset or amelioration of symptoms of a neurological disorder in a subject or an attainment of a desired biological outcome,** such as reduced neurodegeneration (e.g., demyelination, axonal loss, and neuronal death) or reduced inflammation of the cells of the CNS.”

the ’514 Patent

There is only one paragraph regarding the DMF-dosage (not linked to any specific disease):

“For DMF or MMF, an effective amount can range from 1 mg/kg to 50 mg/kg (e.g., from 2.5 mg/kg to 20 mg/kg or from 2.5 mg/kg to 15 mg/kg). Effective doses will also vary, as recognized by those skilled in the art, dependent on route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments including use of other therapeutic agents. For example, an effective dose of DMF or MMR to be administered to a subject orally can be from about 0.1 g to 1 g per pay, 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or **from about 480 mg to about 720 mg per day**; or about 720 mg per day). For example, the 720 mg per day may be administered in separate administrations of 2, 3, 4, or 6 equal doses.”

Biogen's Phase II and III clinical trials

- Between 2004-2006, Biogen tested efficacy of DMF

at 120, 360, and 720 mg/day concentrations

  - The Phase II results showed DMF720 was effective in treating MS, but the DMF120 and DMF360 were not effective
- FDA recommended Biogen add a DMF480 dosing regimen for Phase III trials because the lower dosage "might improve patient compliance and/or minimize dropouts from adverse effects during the study"
  - The Phase III results showed efficacy for DMF480 and DMF720

Inventor testimony

- Title of the ’514 patent was only amended to “Treatment for Multiple Sclerosis” in 2011 after Phase III clinical data on the use of DMF480 in treating MS
- The Phase II lead scientist (Dr. O’Neill) suggested DMF480 and advocated testing at this dose; he was added as an inventor after the claims were refocused on treatment
- O’Neill had not been involved in any of the work relating to the original Nrf2 research

Inventor testimony

- The original inventor (Dr. Lukashev) testified that he did not know why O'Neill was added as an inventor
- Lukashev described the original application as focused on drug discovery and exploration; he "denied that his research could be extrapolated to a clinical dose of DMF"; it "was never the focus of [his] work to inform the clinical dosing of [DMF]."

District Court

- The ’514 patent was invalid for lack of written description
  - Biogen’s attempt to cobble together a few selected disclosures
  - Testimony at trial, the prosecution history, and “significant omissions from the specification”

35 U.S.C. § 112

- *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.*

Current Written Description Test (*Ariad*)

- Under ***Ariad***, **"possession as shown in the disclosure"** is the test
- This test requires an objective inquiry into the 'four corners' of the specification from the perspective of a person of ordinary skill in the art.
- Based on that inquiry, the specification must describe an invention understandable to a skilled artisan and show that the inventor actually invented the invention claimed.

Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co., 598 F.3d 1336, 1341 (Fed. Cir. 2010)

Current Written Description Test (*Ariad*)

- The test for adequate written description "is **whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date**." *Ariad Pharms*., 598 F.3d at 1351.

- "A 'mere wish or plan' for obtaining the claimed invention is not adequate written description." *Centocor Ortho Biotech, Inc. v. Abbott Labs*., 636 F.3d 1341, 1348 (Fed. Cir. 2011).

Current Written Description Test

- *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, No. 20-1758 (Fed. Cir. 2021) states:

  What is required to meet the written description requirement "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005); *see also Ariad*, 598 F.3d at 1351.

Current Written Description Test

- Whether a claim satisfies the written description requirement is a question of fact in litigation:
  - Existing knowledge in the field
  - Extent/content of the prior art
  - Maturity of the science or technology
  - Predictability of the aspect at issue
  - For genus claim: "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."

See Ariad, 598 F.3d at 1350-1351.

Written Description Test

How do you show that the inventor actually invented the claimed invention?

- By a reduction to practice, drawings and structures (showing invention is complete), and/or distinguishing characteristics.
- However, usually the claims encompass more than just the disclosed species. The court/Examiner will look to the extrinsic evidence to see if the specification is sufficient to support the scope of the claimed invention.
- Therefore, take a good look at the art when drafting an application to gauge the level of description needed for the public to understand the essential or critical features of the claimed invention.

Federal Circuit review of the ’514 patent

- Core issue: whether the specification Biogen originally filed on February 8, 2007 supports the claims that ultimately issued in the ’514 patent
  - Does it describe “possession” of the claimed therapeutically effective DMF480-dose limitation for treating MS

Federal Circuit review

- The specification covers a broad array of nearly three dozen neurological disorders, including MS
- DMF appears more than two dozen times, and in three examples
- The prior art demonstrates the link between DMF-mediated activation of the Nrf2 pathway, and the neuroprotective effects, which could be used to treat MS
- The CAFC seemed to agree there was written description that DMF was therapeutically linked to MS treatment

Federal Circuit review

- The DMF480 dose is listed once in the entire specification
- The 480 mg dose appears at one end of a range
  - Meanwhile, DMF720 is referenced independently
- Inventor testimony
- The paragraph containing the only DMF480 reference fails to link an effective dose of DMF to treatment of MS
- At the time of filing, a skilled artisan could not deduce from the specification that DMF480 would be a therapeutically effective treatment for MS

Federal Circuit review

- “Regardless of whether O’Neill had in fact hypothesized or even conceived the idea of treating MS with a DMF480 dose as early as 2003…the law is clear that a patent cannot be awarded for mere theoretical research without more….”

Judge O’Malley’s dissent

Argued that the district court had abused its discretion:

- (i) The ’514 patent had survived IPR (non-obvious, unexpected results); district court estopped Biogen from arguing that the written description requirement should be directed to **therapeutic efficacy** and not **clinical efficacy**; and

- (ii) invalidating Biogen’s patent because it included no Phase III clinical trial data in its specification.

Judge O’Malley’s dissent

Argued that the majority conflates therapeutic efficacy with the results of a higher bar required to show efficacy via clinical trials:

“[I]t is clear on its face of the ‘514 patent that the claimed ‘therapeutically effective amount’ refers to DMF’s ability to mitigate MS symptoms vis-à-vis its modulation of Nrf2 expression; it has nothing to do with whether DMF480 outperforms the standard of care for MS (Rebif®) in a Phase III clinical trial.”

- District Court ruled in 2000 that ’514 patent is invalid for failing to meet the written description requirement

- November 30, 2021: Federal Circuit upheld the ruling in favor of Mylan

- **March 16, 2022: CAFC denies Biogen’s petition for *en banc* review**

- October 3, 2022: the Supreme Court denies cert

CAFC denies Biogen's petition for *en banc* review by 6-3 vote

- Dissent (Lourie, Moore, Newman) said this case is an "outlier" and remarked, "this case, in which every claim limitation is expressly described in the disclosure of the patent specification, is at the farthest end of the spectrum of cases where written description has not been found."

Dissent (con’t)

- “In this case, where the claimed species—i.e., ‘multiple sclerosis’ within the genus ‘neurological diseases’—is expressly described in the specification, the written description requirement is satisfied regardless of the specification’s additional disclosure of other unclaimed neurological diseases….”

Dissent (con't)

- "Written description support for the claimed 480 mg per day dose is not undermined by the fact that it only appears one time in the specification or by the fact that the patent also discloses unclaimed dose ranges…. Once is enough."

Dissent (con’t)

- “[b]y focusing on whether the patentee **proved** that 480 mg per day is an effective amount to treat multiple sclerosis—as distinct from whether the ’514 patent specification **discloses** that 480 mg per day is an effective amount to treat multiple sclerosis—**the panel majority and the district court erroneously imported operability considerations into the written description analysis**.”

- TECFIDERA is Biogen's best-selling drug
  - Biogen priced the drug at $54,000 per year in the US
  - Biogen's revenues dropped from over $3 billion to $1 billion in 2020 after generic entered the market.

VUMERITY®
(diroximel fumarate) delayed-release capsules 231 mg

Learn about another treatment option.

EXPLORE VUMERITY ›

Continue to TECFIDERAHCP.com

Please see **Important Safety Information** and full **Prescribing Information** for VUMERITY.

Biogen

What takeaways?

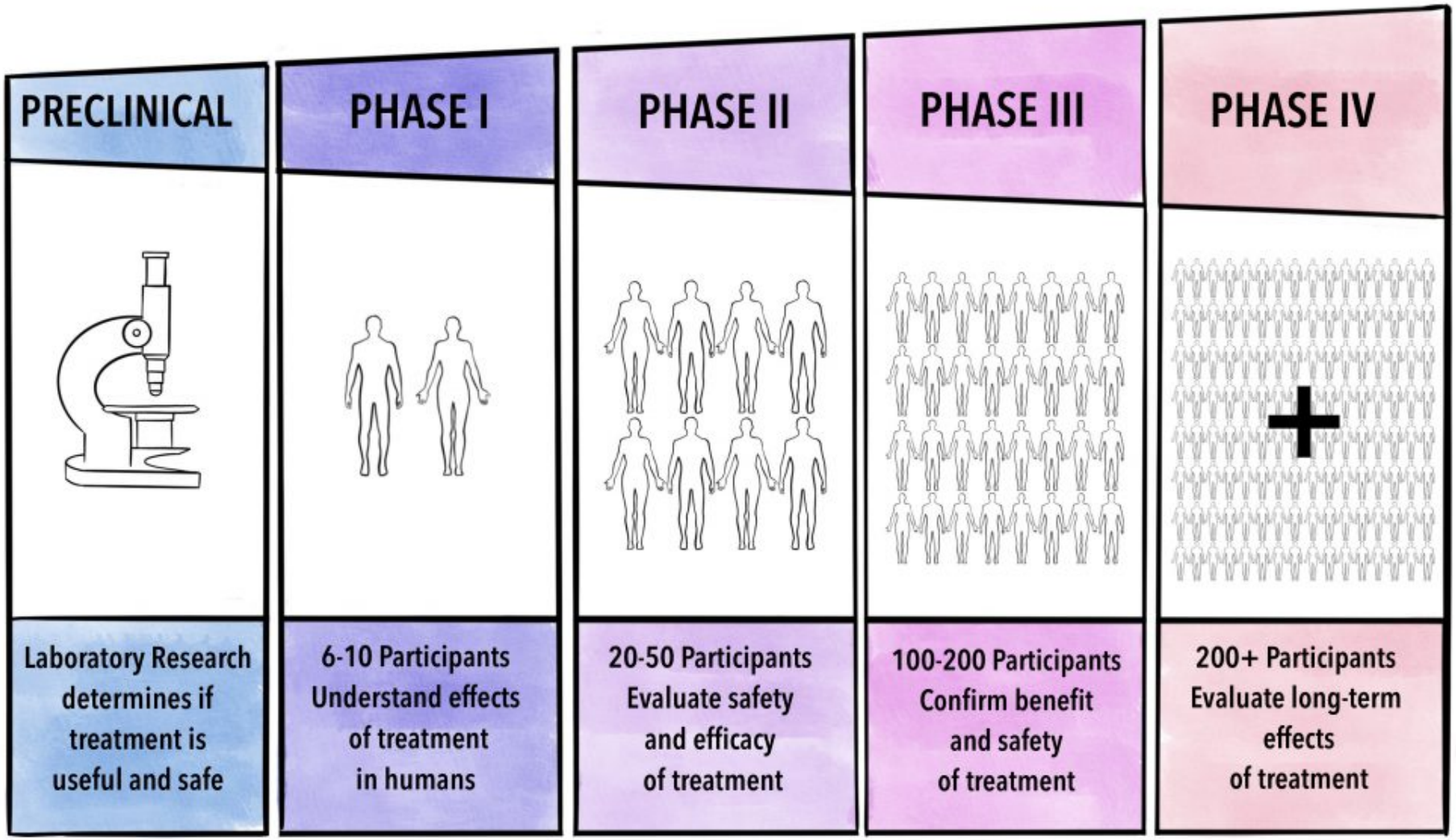
- Is this case an outlier?
  - The written description requirement has never required an inventor to actually reduce the invention to practice, or provide working examples (or clinical data)
  - The 480 mg/day dose was disclosed but somehow not described

What takeaways?

- In this case, the invention described in the specification from 2007 “bears no resemblance to the invention claimed in 2011” (the continuation)
  - Biogen “grafted the ’514 claims onto a specification written to cover a different set of inventions, conceived of by an entirely different inventor, and filed more than four years before Biogen’s 2011 Phase III trial results demonstrated the effectiveness” of DM480

What takeaways?

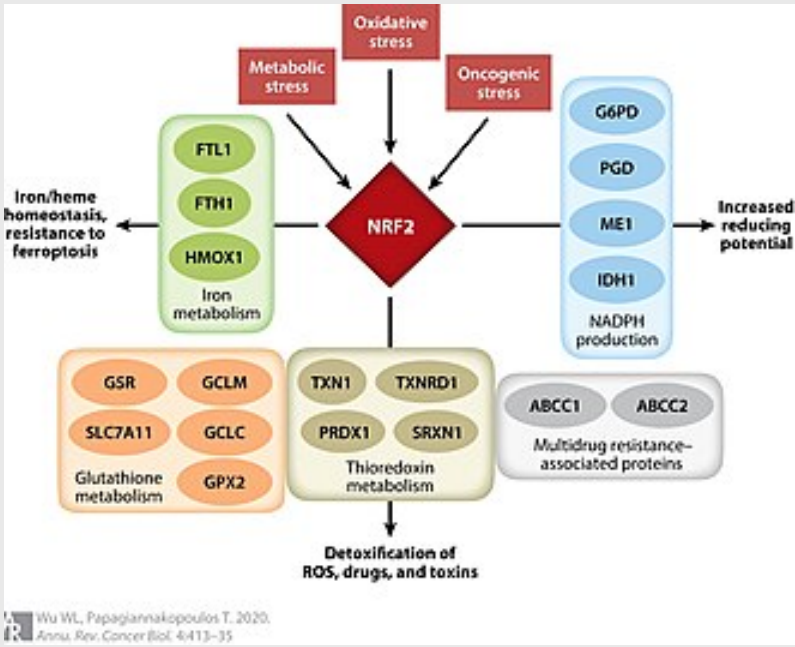
- Scientist desire to publish/share their work; want to file application as early as possible and before competitors
- But filing too soon risks not adequately describing invention; creates Applicant's own prior art
- Do we change how we file or draft applications?
  - Providing "blaze marks" or individual doses?
- Do we need to file CIPs when we get clinical data?


PRECLINICAL
PHASE I
PHASE II
PHASE III
PHASE IV
Laboratory Research determines if treatment is useful and safe
6-10 Participants Understand effects of treatment in humans
20-50 Participants Evaluate safety and efficacy of treatment
100-200 Participants Confirm benefit and safety of treatment
200+ Participants Evaluate long-term effects of treatment

NRF2 pathway

- Nuclear factor erythroid 2-related factor 2 (NRF2), also known as nuclear factor erythroid-derived 2-like 2, is a transcription factor that in humans is encoded by the NFE2L2 gene.

- Activation of NRF2 induces the transcription of genes encoding cytoprotective proteins.



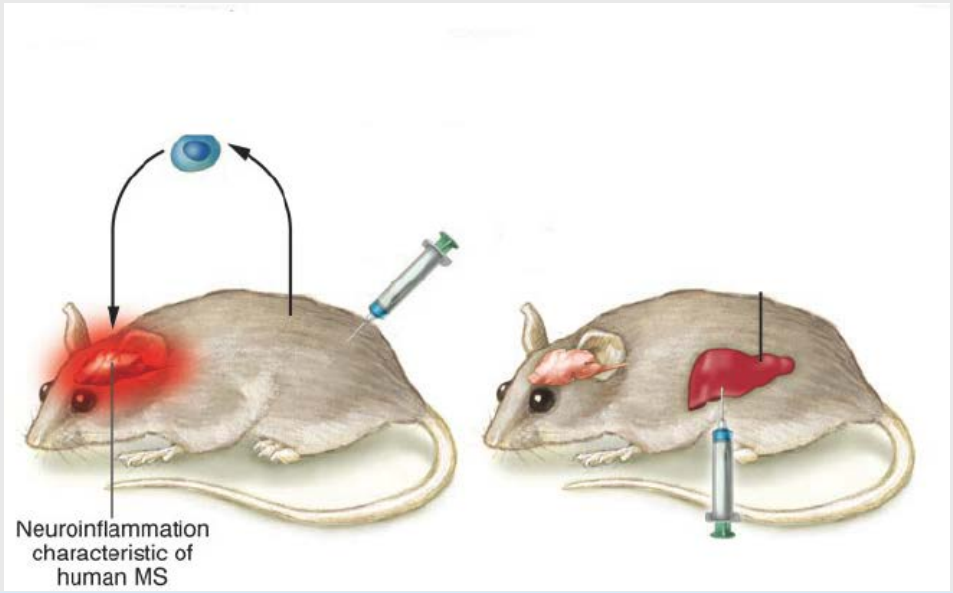
See https://en.wikipedia.org/wiki/NFE2L2

the ’514 Patent states that:

- “Phase 2 enzymes” serve as a protection mechanism in mammalian cells against oxygen/nitrogen species (ROS/RNS), electrophiles and xenobiotics.
- Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor responsible for the induction of a variety of important antioxidant and detoxification enzymes that coordinate a protective cellular response to metabolic and toxic stress.
- To date, more than 10 different chemical classes of inducers of Nrf2 pathway have been identified…

Animal testing

- Experimental autoimmune encephalomyelitis, sometimes experimental allergic encephalomyelitis (EAE), is an animal model of brain inflammation



https://www.jci.org/articles/view/37079/figure/1

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TECFIDERA safely and effectively. See full prescribing information for TECFIDERA.

TECFIDERA® (dimethyl fumarate) delayed-release capsules, for oral use

Initial U.S. Approval: 2013

INDICATIONS AND USAGE

TECFIDERA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)

DOSAGE AND ADMINISTRATION

- Starting dose: 120 mg twice a day, orally, for 7 days (2.1)
- Maintenance dose after 7 days: 240 mg twice a day, orally (2.1)
- Swallow TECFIDERA capsules whole and intact. Do not crush, chew, or sprinkle capsule contents on food (2.1)
- Take TECFIDERA with or without food (2.1)

DOSAGE FORMS AND STRENGTHS

Delayed-release capsules: 120 mg and 240 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. (4)

Birch
Stewart
Kolasch
Birch LLP

Thank you for your attention!